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Technical Notes

Evaluation of a new transperineal ultrasound probe for inter-fraction image-guidance for definitive and post-operative prostate cancer radiotherapy

Marie Fargier-Voiron [a], Benoît Presles [a], Pascal Pommier [b], Alexandre Munoz [b], Simon Rit [a], David Sarrut [a,b], Marie-Claude Biston [a,b,*]

[a] CREATIS, INSA, Université de Lyon, CNRS UMR5220, Inserm U1044, Lyon F-69622, France
[b] Léon Bérard Cancer Center, University of Lyon, Lyon F-69373, France

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ABSTRACT

Purpose: The aim of this study was to evaluate a new system based on transperineal ultrasound (TP-US) acquisitions for prostate and post-prostatectomy pre-treatment positioning by comparing this device to cone-beam computed tomography (CBCT).
Methods: The differences between CBCT/CT and TP-US/TP-US registrations were analyzed on 427 and 453 sessions for 13 prostate and 14 post-prostatectomy patients, respectively. The inter-operator variability (IOV) of the registration process, and the impact and variability of the probe pressure were also evaluated.
Results: CBCT and TP-US shift agreements at ± 5 mm were 76.6%, 95.1%, 96.3% and 90.3%, 85.0%, 97.6% in anterior-posterior, superior-inferior and left-right directions, for prostate and post-prostatectomy patients, respectively. IOV values were similar between the 2 modalities. Displacements above 5 mm due to strong pressures were observed on both localizations, but such pressures were rarely reproduced during treatment courses.
Conclusions: High concordance between CBCT/CT and TP-US/TP-US localization of prostates or prostatic beds was found in this study. TP-US based prepositioning is a feasible method to ensure accurate treatment delivery, and represents an attractive alternative to invasive and/or irradiating imaging modalities.

Introduction

Compared to invasive and/or irradiating modalities, US imaging appears to be an interesting image-guided radiotherapy (IGRT) strategy for prostate cancer treatment since it offers a 3D visualization of pelvic organs without any additional dose or surrogate implants [1]. Until recently, US-IGRT relied on a transabdominal (TA) acquisition followed by either an inter-modality registration [2,3] (daily US image registered on the reference CT image) or an intra-modality registration [4–7] (daily US image registered on a reference US image). Numerous discrepancies between the target volume localization observed with the US modality and other IGRT devices were reported [4–7]. An intra-modality registration improves accuracy [7] because it removes uncertainties due to differences in prostate delineation between CT and US [8] but does not impact other sources of uncertainties such as the operator variability, the impact of probe pressure [9] and speed of sound aberrations [10]. Furthermore, the acquisition is made with the probe manually placed above the abdomen, which prevents target monitoring during irradiation.

To overcome the previous issues, a new system based on acquisitions with a transperineal ultrasound (TP-US) probe and an intra-modality registration (Clarity, Elekta, Stockholm, Sweden) has recently been proposed [11]. It is made of a 2D US probe with an internal automated sweeping inside a casing. This device is a promising alternative to other US imaging systems since it is fixed on a base plate and it does not interfere with the treatment beam, which enables monitoring of intrafraction motions; it is likely to be less operator-dependent due to this base plate and to the automated sweeping and it should avoid the quality image issues encountered with TA-US probes linked to the bladder filling.

The objective of this study was to perform an evaluation of the system for pre-treatment positioning on definitive and post-operative prostate cancer patient irradiations. To our knowledge, this is the first study investigating the performances of this TP probe in clinical conditions. The performances of the system were compared to soft-tissue CBCT registration by quantifying the registration

* Corresponding author. Department of Radiation Oncology, Centre Léon Bérard, 28 rue Laennec, Lyon 69008, France. Tel.: + 33 4 78 78 26 75; fax: +33 4 78 78 59 98.
E-mail address: marie-claude.biston@lyon.unicancer.fr (M.-C. Biston).

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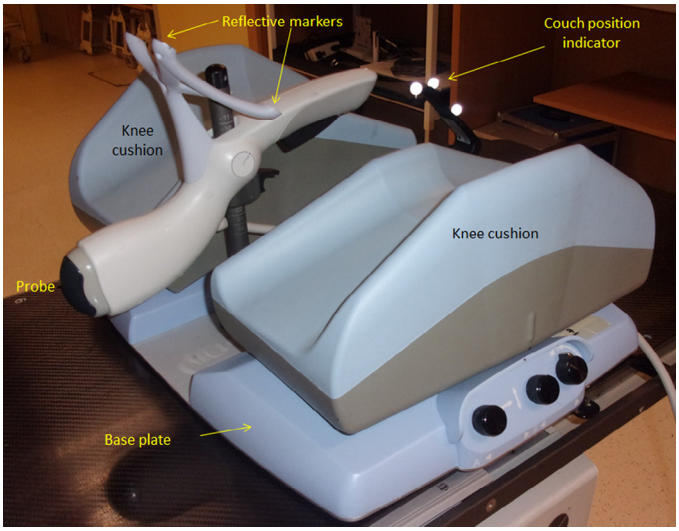

Figure 1. Clarity® Autoscan device.

discrepancies obtained with these 2 modalities for pre-treatment target localization and by evaluating the inter-operator variability (IOV) specific to each technique. The impact of probe pressure on target localization was also investigated.

Material and methods

TP-US system

The TP-US system (Clarity®, Elekta, Stockholm, Sweden) is based on a 2D TP-US probe. The TP-US probe is located in the room coordinates thanks to 4 reflectors fixed on the top of the probe which are tracked by an infrared camera fixed on the ceiling (Fig. 1). For each acquisition, several hundreds of 2D US slices are acquired during an automated probe sweep performed by a step-by-step motor and merged into a 3D image [11]. The sweep time is 2.5 seconds which gives a resolution of 0.35 mm (for a voxel size of 0.58^3 mm^3) in the middle of the prostate, assuming a typical prostate depth of 5 cm [11]. For patients' acquisitions, a specific immobilization device made of a base plate and 2 cushions for the knees enables the TP-US probe to be fixed between the patient legs (Fig. 1). During the planning CT session, a reference US image (US_{ref}) is acquired with the same patient set-up as during the CT acquisition. The US_{ref} image is superimposed to the CT image through a room calibration process, allowing a visualization of the US_{ref} and CT images in the same coordinates system. A reference positioning volume (RPV) is then manually delineated on the US_{ref} image (Fig. 2). Over the treatment course, a daily US image (US_{daily}) is acquired at the beginning of each fraction, and manually registered on the US_{ref} image by RPV projection. The accuracy of the system is checked daily by performing a quality control to warrant an uncertainty inferior to 1 mm and 2 mm for the reference and the daily US systems, respectively [11].

Patient data

Thirteen patients receiving a definitive irradiation of the intact prostate (cohort A) and 14 patients irradiated after prostatectomy (cohort B) were included in this study, which was approved by the hospital ethics committee. During the CT session, patients were immobilized using the above-described device and the reference US acquisition was performed just before the CT acquisition. The probe position of each patient was marked on the base plate to minimize the probe position variability between fractions during the treatment phase. Patients were scanned in supine position, with

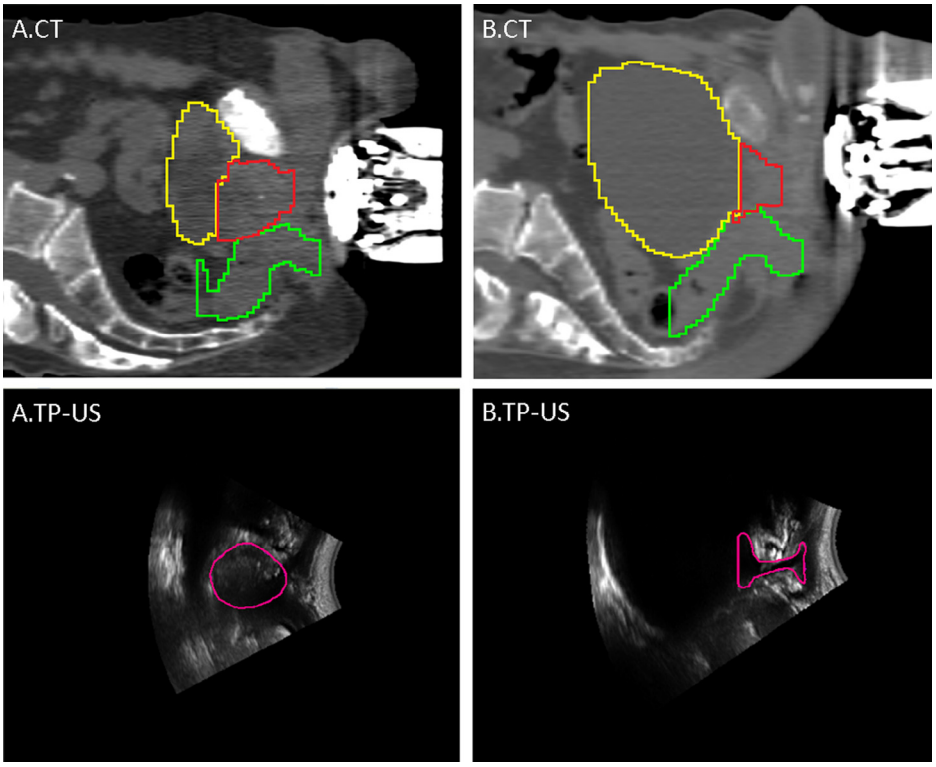

Figure 2. Sagittal slices of CT and TP-US images of prostate patients (respectively A.CT and A.TP-US) and of post-prostatectomy patients (respectively B.CT and B.TP-US). Red, yellow and green contours correspond to the CTV, bladder and rectum volumes, respectively, delineated on the CT image; pink contour corresponds to the RPV volume, delineated on the TP-US image.

3 mm slice thickness and standard prostate protocol of the Brilliance CT Big Bore scanner (Philips medical systems, Best, the Netherlands). For cohort A, the RPV was the prostate itself whereas for cohort B, the RPV corresponded to the bladder neck plus the inferior part of the urethra since these 2 volumes are included in the clinical target volume according to the EORTC guidelines [12] (Fig. 2).

Image and data processing

In this study, US acquisitions were performed for data collection only. Patient repositioning was always carried out based on CBCT/CT registration results, which is our reference modality. At each treatment session, the US_{daily} acquisition and registration on the US_{ref} image was performed after aligning the patient on the lasers. A CBCT image of submillimeter spatial resolution (voxel size 1 mm^3) was acquired directly after US_{daily} imaging in order to minimize patient motion [13]. Registration of CBCT images on the reference CT was done semi-automatically. First, an automatic bony alignment was performed with the XVI® software (Elekta, Stockholm, Sweden). Then, a manual adjustment was done on the soft-tissue target volume, i.e. the prostate for prostate patients and the prostatic bed for post-prostatectomy patients. For TP-US/TP-US registrations the observed shifts correspond to the displacement of the barycenter of the RPV, whereas CBCT/CT registrations correspond to the displacement of the treatment isocenter. US and CBCT registrations were performed by trained radiation therapists (RTs). A total of 427 and 453 paired US and CBCT translational shifts were collected for cohorts A and B, respectively. All US images were of sufficient quality to be analyzed. Rotations were not considered in this study. For subcohorts of 12 patients of each group, the shifts observed with the TP-US monitoring system during CBCT acquisitions were manually recorded and subtracted to the initial TP-US shifts. This represented 357 sessions for prostate patients and 336 sessions for post-prostatectomy patients. This process was not possible during CT image acquisitions because the infra-red camera cannot track the probe in the CT bore.

The required times for US and CBCT acquisition and registration were estimated to 2 and 5 minutes for US and CBCT modalities, respectively.

For patient p and session s, the obtained shifts were denoted $T_{CBCT,p,s}$ and $T_{US,p,s}$ for CBCT and US modalities, respectively. For each session and left-right (LR), superior-inferior (SI) and antero-posterior (AP) directions, the difference between CBCT and US shifts was calculated as follows: $\delta_{CBCT-US,p,s} = T_{CBCT,p,s} - T_{US,p,s}$. Means and standard deviations of the differences were calculated over all patients. The mean differences Δ_p of the $\delta_{CBCT-US,p,s}$ values over all sessions of each patient p, and the standard deviation $\sigma_{patients}$ over all patients on the Δ_p distribution were calculated. Paired samples t-tests were performed on the Δ_p distributions. A value of $p < 0.05$ was considered statistically significant.

To determine whether CBCT and US imaging were localizing the target at the same position without considering any of the 2 as a gold standard, the 95% limits of agreement (LOA) were calculated using the Bland–Altman method [14] for each localization and each direction as follows: LOA = *b* +/− 1.96*SD, where *b* is the bias, i.e. the mean of the differences between CBCT and US measurements and SD the standard deviation of the differences between CBCT and US measurements. It corresponds to the range over which 95% of differences lie if the differences are normally distributed. If LOAs are above a predefined tolerance, the 2 modalities cannot be interchanged without causing a relevant difference. Shift agreements at +/− 5 mm, i.e. the number of sessions for which the difference between the 2 modalities is below 5 mm, were also calculated.

Inter-operator variability

The IOV was evaluated for CBCT and TP-US modalities. Regarding the CBCT modality, 74 images of 4 prostate patients and 62 images of 7 post-prostatectomy patients were retrospectively registered by one expert and 3 well-trained RTs. The same process was repeated on 117 and 129 TP-US images of 4 patients of cohorts A and B, respectively. The standard deviation $\sigma_{p,s}$ for each session s of the patient p was calculated over the 4 operators. The IOV was calculated for each direction as follows: $IOV=RMS_p(RMS_s(\sigma_{p,s}))$, with RMS_p and RMS_s being the root mean square over all patients and the root mean square over all sessions of the same patient, respectively.

Impact and variability of the probe pressure

To investigate the impact of the probe pressure, 3 acquisitions with 3 pressure levels were performed on subsets of cohorts A (8 patients) and B (7 patients) during one of their treatment sessions. The first, second and third images were acquired by applying a soft, moderate and strong pressure, respectively. This was done by moving the probe on the base plate towards the head of the patient. The probe displacement between each acquisition was measured and served to quantify the applied pressure. The target volume delineated on the first image was registered on the second and third images to quantify the volume displacement due to the pressure. For sub-cohort A, the volume corresponded to the RPV. For sub-cohort B, the RPV was divided in 2 parts corresponding to the bladder neck and to the inferior part of the urethra.

To investigate the variability of the probe pressure during treatments, CBCT/CT registrations were performed for each treatment session using a region of interest including only the visible part of the probe. Bony registration results were taken into account in order to get rid of interfraction motion. Correlation tests were carried out between means or standard deviations of probe pressure distributions and the body mass index (BMI) of each patient. Finally, an ANOVA test with 2 factors (patients and operators) was performed on pressure values to investigate the influence of these 2 parameters.

Results

CBCT and TP-US shifts comparison

The differences observed between CBCT and US measurements of target localization are shown in Fig. 3 for cohorts A and B, respectively. The largest discrepancies were observed in the AP direction for cohort A, with larger shifts in the posterior direction for US compared to CBCT. Contrary to cohort A, the largest shifts were observed in the inferior direction for cohort B. These results were confirmed by statistical data given in Table 1. The largest systematic differences were found for cohort A in the AP direction (2.6 ± 3.3 mm) and for cohort B in the SI direction (−1.6 ± 3.2 mm). Shift agreements ranged between 76.6% and 97.6%, the best agreement (≥96.3%) being in the LR direction for both localizations. The maximum LOA value (8.6 mm) was observed on cohort A in the AP direction. When patient movements between US-TP and CBCT imaging were taken into account, the shift agreement was increased by more than 7% in the AP direction for prostate patients (82.6% against 75.4% without correction). Post-prostatectomy data as well as other directions for prostate patients were much less impacted (±2%) (Table 2).

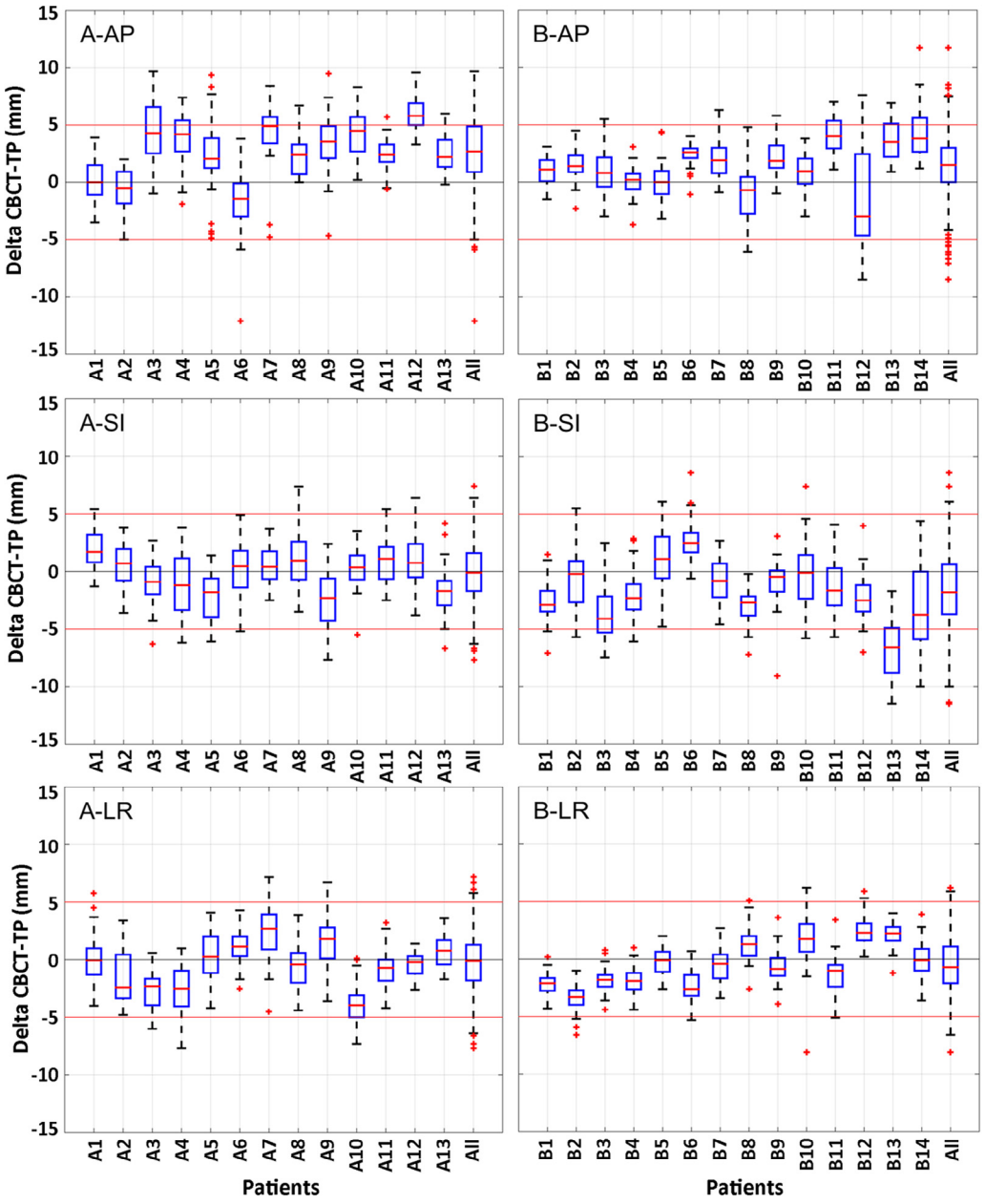

Figure 3. Distributions of the differences between CBCT and US shifts from the raw dataset for each patient of cohorts A and B, in AP, SI and LR directions. Box-and-whisker plots represent the median difference (red dash) observed during the treatment courses, the 25th (q_1) and 75th (q_3) percentiles (edges of the box), and total range (extent of whiskers). Outliers are defined as values outside the range defined by $q_1 \pm 2.7^{*}\sigma$ (q_3–q_1) with σ the standard deviation of the considered distribution, and are represented by a red cross. The red lines represent the +/– 5 mm range. The average of CBCT and US differences is represented for each patient by a red asterisk.

Table 1
Comparison between CBCT and TP-US shifts for cohort A and B.

	Cohort A			Cohort B		
	AP	SI	LR	AP	SI	LR
Mean ± std (mm)	2.6 ± 3.3	–0.1 ± 2.5	–0.2 ± 2.5	1.5 ± 2.6	–1.6 ± 3.2	–0.5 ± 2.3
P Value	<0.001	0.66	0.39	0.01	0.02	0.34
$\sigma_{patients}$	2.2	1.4	1.8	1.8	2.2	1.8
Shift agreements (%)	76.6	95.1	96.3	90.3	85.0	97.6
LOA (mm)	[–3.4 ; 8.6]	[–5.1 ; 4.8]	[–5.1 ; 4.6]	[–3.6 ; 6.6]	[–7.9 ; 4.7]	[–4.9 ; 3.9]

Abbreviations: AP: Anterior-posterior, SI: superior-inferior, LR: left-right, std: standard deviation.

Table 2
Comparison between CBCT and TP-US shifts on 12 patients (357 sessions) of cohort A (357 sessions) and B (336 sessions) with or without considering intrafraction motions occurring between CBCT and US acquisitions.

	Cohort A					
	With intrafraction motion			Without intrafraction motion		
	AP	SI	LR	AP	SI	LR
Mean ± std (mm)	1.9 ± 3.2	0.7 ± 2.6	0.2 ± 2.6	2.8 ± 3	−0.3 ± 2.5	−0.1 ± 2.5
Shift agreements (%)	82.6	93.6	94.7	75.4	95	96.1
LOA (mm)	[−4.3 ; 8.1]	[−4.4 ; 5.8]	[−4.9 ; 5.3]	[−3.2 ; 8.8]	[−5.1 ; 4.6]	[−5 ; 4.7]
	Cohort B					
	With intrafraction motion			Without intrafraction motion		
	AP	SI	LR	AP	SI	LR
Mean ± std (mm)	1.2 ± 2.6	−1.7 ± 3.2	0.3 ± 2.3	1.7 ± 2.7	−1.9 ± 3.3	−0.1 ± 2.2
Shift agreements (%)	91.4	85.4	97.6	88.4	83.0	97.6
LOA (mm)	[−3.9 ; 6.3]	[−7.9 ; 4.5]	[−4.7 ; 4.2]	[−3.5 ; 6.9]	[−8.3 ; 4.5]	[−4.5 ; 4.3]

Abbreviations: AP: Anterior-posterior, SI: superior-inferior, LR: left-right, std: standard deviation.

Inter-operator variability

Table 3 shows the inter-operator variability for both localizations. The IOV values ranges 0.6–2.0 mm and 0.6–1.9 mm for CBCT and US, respectively. Maximum values were observed in the AP direction for the 2 modalities during prostate localization.

Impact and variability of the probe pressure

Displacements of the prostate and of the bladder neck plus the urethra for sub-cohorts A and B, respectively, are shown in Fig. 4 for the SI direction only, since negligible movements were noticed in other directions. The variability of the probe pressure in the SI direction over the treatment course is presented in Fig. 5 for each patient.

Table 3
Inter-operator variability of registration of CT/CBCT and US/US images for prostate and post-prostatectomy localizations.

(mm)	AP		SI		LR	
	Cohort A	Cohort B	Cohort A	Cohort B	Cohort A	Cohort B
CBCT	2.0	1.1	1.8	0.9	1.1	0.6
US	1.9	1.1	1.0	0.9	1.3	0.6

Abbreviations: AP: Anterior-posterior, SI: superior-inferior, LR: left-right.

For both cohorts, shifts were only observed in the superior direction and were found larger with increased pressure (Fig. 4). For cohort A, strong pressure led to displacements above 5 mm for 4 prostate patients. However these probe pressure levels were never reached during the treatment course of these patients (Fig. 5). For other patients, even if strong pressures occurred during the treatment, it induced minimal prostate displacement (Fig. 4A).

For cohort B, large differences were observed between bladder neck and urethra shifts which clearly demonstrated that the initial RPV was deformed with increased pressure (Fig. 4B). Furthermore, displacements above 5 mm were systematically observed when a strong pressure was applied, except for patient B1 (4.6 mm). Note that these pressure levels occurred during the treatments of patients B5 and B1 (Fig. 5).

No statistically significant correlations were found between BMI and averages of the pressure distributions ($R = 0.08$, $p = 0.79$) and between BMI and standard deviations of these distributions ($R = 0.14$, $p = 0.61$). However, the distributions of the applied probe pressures were found to depend on the patient ($p < 0.001$) and the operator ($p < 0.001$).

Discussion

Numerous studies comparing US-IGRT to other commonly used IGRT modalities were carried out with intermodality or intramodality US systems, all based on TA-US acquisitions. Some of them showed

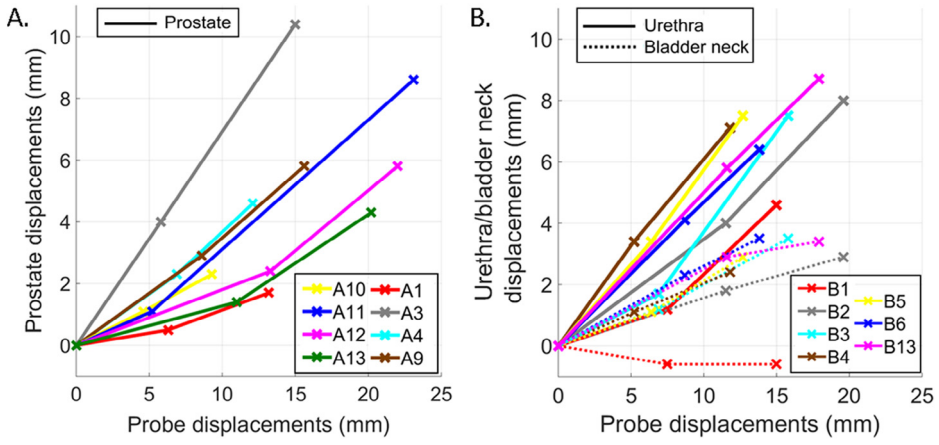

Figure 4. A. Prostate displacements due to moderate and strong pressures, relatively to the soft pressure. B. Bladder neck and urethra displacements observed on post-prostatectomy patients due to moderate and strong pressures, relatively to the soft pressure.

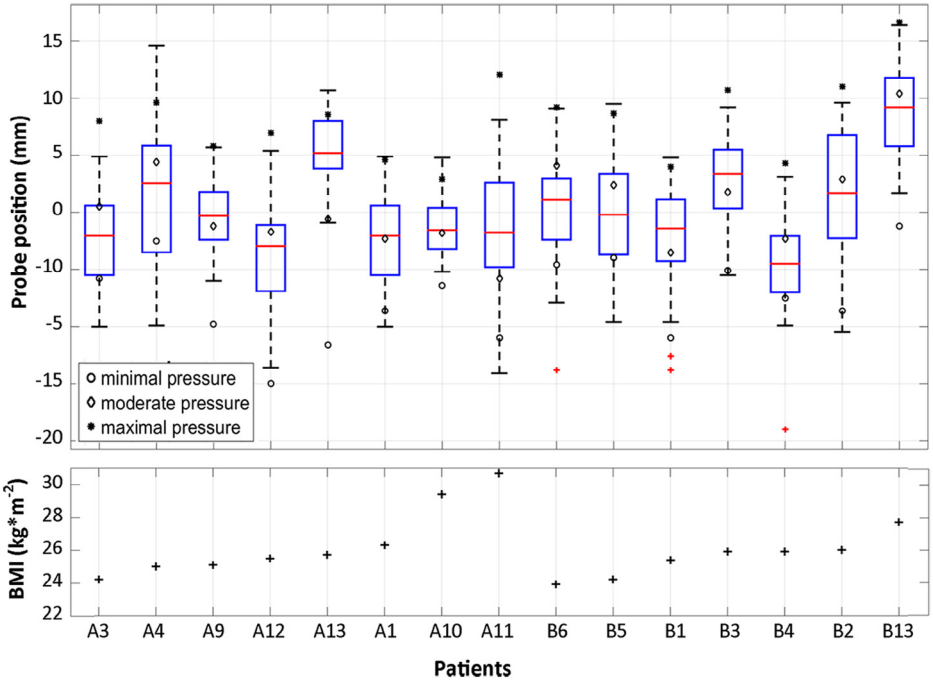

Figure 5. Probe distances distributions and BMI for cohorts A and B. Box-and-whisker plots represent the median probe distance (red line) observed during the treatment courses, the 25th (q_1) and 75th (q_3) percentiles (edges of the box), and total range (extent of whiskers). Outliers are defined as values outside the range defined by $q_1 \pm 2.7^{*}\sigma$ (q_3–q_1) with σ the standard deviation of the considered distribution, and are represented by a red cross. The probe distances corresponding to the three pressure levels (soft, moderate and strong) are represented and superimposed on the distributions of each patient.

large discrepancies between registration results obtained with TA-US intramodality devices and other IGRT modalities, with shift agreements at ± 5 mm between 73% and 77% [5] and LOA values close to 10 mm [5,6] in all directions. Using the same intramodality US-IGRT device as in the present study and TA acquisitions, similar discrepancies were obtained in our hospital when comparing TA-US/TA-US versus CT/CBCT registrations [15]. By contrast, a better shift agreement was observed when comparing TP-US modality to soft-tissue based CBCT registration, with values above 90% in all directions, except for the AP (76.6%) direction for prostate and the SI (85%) direction for post-prostatectomy.

Different parameters can explain the differences observed between TA-US and TP-US results. First, the quality of TA-US images is a limiting factor since it requires an adequate acoustic window, i.e. a full bladder [16]. From our clinical experience, 100% of the TP-US images against only 80% of the TA-US images were of sufficient quality to be analyzed. Secondly, inter-operator uncertainties are minimized with the TP-US since the probe is fixed to a base plate and the sweeping is automated. However, it is shown in this study that the probe pressure can still vary from one session to the other as observed with the TA-US system [9]. Nonetheless, the consequences are different since the pressure is kept constant during the whole treatment session with the TP probe, which guarantees that the prostate is in the same place during image acquisition and treatment. With the TA-US probe, the reference pressure applied during the simulation session must be reproduced to guarantee the accuracy of pre-treatment positioning, since the probe is not kept in place during the irradiation session.

It was shown in this study that strong pressures may be applied but are rarely replicated during the treatment. The consequences may be different between prostate and post-prostatectomy localizations. A strong pressure results in a rigid translation of the prostate whereas it leads to a deformation of the prostatic bed for post-prostatectomy patients. Besides, prostatic beds are naturally subject to deformations [17], which explains the emergence of new adaptive strategies for treating this localization [18]. Hence, for post-prostatectomy cases, a simple treatment couch translation cannot correct shifts that may be induced either by pressure or anatomical changes.

Despite a much better agreement found with TP-US compared to TA-US versus other reference imaging modalities, significant systematic differences were still observed between CBCT and TP-US measurements on some patient data. The calibration process was not involved, since systematic differences were patient dependent. One explanation could be that CT and US_{ref} images are not acquired exactly at the same time, which permits intrafraction motion between the 2 acquisitions and can generate systematic differences during the superimposition process of the US_{ref} and CT images. Since monitoring the RPV in the CT-room with the TP-US device is not possible, a solution to measure this displacement could be to manually register the TP-US image on the CT image. However this would involve additional uncertainties inherent to inter-modality registration [8]. Likewise, patients can move between TP-US and CBCT acquisitions. It was shown in this study that it mainly impacted the AP direction for prostate patients. Similar movements between TP-US and CT acquisitions may partly explain the observed systematic shifts for prostate patients.

The image quality of CBCT acquisitions could also affect the accuracy of soft-tissue CT/CBCT registration. In particular, for post-prostatectomy patients, accurate localization of the vesico-ureteric anastomosis is known to be difficult on CBCT images [19]. Conversely, on US images, the RPV is only defined in the inferior direction, and arbitrarily truncated in the superior direction. Therefore, the registration of US images only relies on one boundary instead of 2 for other directions and both hypotheses may explain the larger uncertainty observed in the SI direction.

For prostate patients, many comparisons between reference IGRT modalities for pre-treatment localization can be found in the literature. Barney et al. reported a poor correlation in SI and AP directions between registration based on markers with kV images

and soft-tissue based CBCT registration (shift agreement at 5 mm below 73% for AP and SI directions), while a good correlation was found in the LR direction (97.2%) [20]. Similarly Moseley et al. compared soft-tissue registration using CBCT to markers with MV portal imaging registration and found percent shift agreements at 5 mm below 65% in SI and AP directions, while in the LR direction it was above 90% [21]. Hence, with shift agreements above 95% for SI and LR directions, and above 75% for the AP direction, the correlation between CBCT and TP-US modalities was found larger than correlations between CBCT and marker based 2D-kV or 2D-MV systems. Note that even if a marker-based IGRT modality could be considered as the reference method for prostate pretreatment localization, it can also be subject to inaccuracies due to marker migration or deformation of surrounding tissues.

Conclusion

TP-US based repositioning of prostate and post-prostatectomy localizations is a fast and reliable method to ensure accurate delivery of treatment plans, with the advantage of being non-invasive and non-ionizing. The development of an algorithm for automatic registration of the TP-US images should still be considered to simplify the therapist training [22] even if the inter-operator variability of the registration processes of the two modalities was found similar for both localizations in this study. Further investigations are in progress for evaluating the performances of intrafraction monitoring with this device.

Conflict of interest

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