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Impact of probe pressure variability on prostate localization for ultrasound-based image-guided radiotherapy

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ABSTRACT

Purpose: To evaluate the impact of transabdominal probe pressure on prostate positioning with an intramodality ultrasound (US) image-guided-radiotherapy system and to quantify pressure variability over the treatment course.

Material and methods: 8 prostate cancer patients (group A) and 17 healthy volunteers underwent 3 consecutive US images with increasing probe pressure levels, and 1 CT acquisition for the group A only. Prostate positions were compared after manual registration of the first US image contour projected on 2 others. Group A's pressure levels were quantified by measuring skin-to-skin distances between corresponding CT–US images. The same methodology was used on paired CT/CBCT–US images acquired during treatments of 18 prostate cancer patients to determine whether the different pressure levels applied to the group A were close to the clinical practices and to quantify pressure variability along the treatment course.

Results: 84% of 3D prostate displacements were above 2 mm for at least one pressure level. Probe pressures deliberately applied were similar to the ones observed clinically. The latter drastically varied between sessions.

Conclusion: Even with an intramodality system, probe pressure can impact prostate localization because of the pressure variability along the treatment course. Therefore, margins should be expanded from 0.5 to 1.2 mm to ensure treatment accuracy.

Image guided radiotherapy (IGRT) enables the correction of the patient set-up at the beginning of a treatment session [1]. According to the tumor localization and the available imaging modalities, the positioning strategy will differ from one patient to another. For prostate cancer, a soft tissue registration based on volumetric imaging modality or implanted marker is required since prostate and bone motions are not correlated [2]. The use of a three-dimensional (3D) transabdominal (TA) ultrasound (US) system could be a better alternative to X-ray based modalities because US-based imaging offers better tissue contrast [3] and is non-invasive and non-irradiating, therefore avoiding the associated risks for the patient [4]. 3 different TA-US devices were commercialized over the past 15 years: BAT® (Nomos, Pittsburgh USA) [5], SonArray® (Varian, Palo Alto USA) [6] and Clarity® (Elekta, Stockholm Sweden) [7]. With BAT® and SonArray® devices, patient positioning is performed using 2 different modalities: Computed Tomography (CT) reference contours are registered on US treatment images to measure target misalignments. In contrast, the Clarity® equipment is an intramodality system that compares US images acquired at each treatment session to a reference US image acquired during the planning CT acquisition. This last method could potentially provide a more accurate prostate alignment [8].

Several reports showed that the accuracy of US prostate localization depends on the probe pressure applied during images acquisition with observed displacements up to 10 mm [5,7,9,10]. Therefore, to ensure better accuracy of the US positioning systems, it is recommended applying as low as possible pressure to obtain sufficient contact for image quality. However different studies suggested that an intramodality device has the potential to minimize the uncertainty on prostate location due to probe pressure compared to an intermodality system if the pressure is kept constant over the treatment course [7,11,12].

In this paper, we investigated the impact of the probe pressure on prostate localization with the Clarity® TA-US system on 17 healthy volunteers and 8 patients. We also evaluated the reproducibility of the pressure along the treatment course of 18 patients by

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calculating the skin-to-skin distance between paired US/Cone-Beam Computed Tomography (CBCT) images. We finally estimated the margin to account for the uncertainty due to prostate displacement implied by the probe pressure.

Methods and materials

3D ultrasound IGRT system

The US-IGRT system (Clarity®, Elekta) was fully described elsewhere [7]. Briefly, it is based on a TA probe tracked by an infrared camera. For each acquisition, several hundred 2D-US slices are acquired during a probe sweep and merged in a 3D image. The probe is placed above the superior bladder volume for each acquisition allowing visualization of a large part of the prostate before US waves interfere with the pubic bone (Fig. 1(a)).

During the planning CT session, a reference US image is acquired with the same patient set-up as during CT acquisition. The 3D-US image is directly superimposed on the CT image through a room calibration process, allowing visualization of the US and CT in the same coordinate space. Over the treatment course, a US image is acquired at the beginning of each daily fraction and registered on the reference US image. For this study, US images were collected for investigation only and not used for patient positioning.

Measurement of prostate displacement due to probe pressure

17 healthy volunteers (group V) (age: 30.8 ± 6.2 years, Body Mass Index (BMI = Mass/Height^2): 21.4 ± 2.4 kg $*$ m^{-2}) and 8 patients (group A) (age: 68.6 ± 7.3 years, BMI: 25.8 ± 2.6 kg $*$ m^{-2}) were included in this study. Written informed consent was given by all patients included in group A. Both groups were given a strict protocol for bladder filling. Indeed a comfortable full bladder is required to have a US image of good quality. Patients and Volunteers were also asked to remain motionless during the session and were installed in supine position with an immobilization device under their knees. They all underwent 3 consecutive 3D-TA-US acquisitions (Fig. 1(b)) performed by the same therapist applying soft, moderate and strong pressure (image 1, 2 and 3 respectively). Soft pressure was defined as the minimal pressure required for obtaining sufficient image quality. The strong pressures applied did not induce any discomfort for the group. The time between image 1 and 3 never exceeded 3 min. Group A underwent an additional CT acquisition in the same position as for US acquisitions. The CT acquisition was performed before the 3 US acquisitions.

The prostate contour (vol_ref) was jointly delineated on the first image by 3 operators trained to US image analysis. Then vol_ref was duplicated on images 2 and 3 and manually registered by only taking into account the translations, in agreement by the 3 operators (vol_2 and vol_3). Prostate shifts were obtained by calculating the displacement vectors between the centers of mass of vol_2 and vol_3 with respect to vol_Ref.

Variability of probe pressure during a treatment course

Reference CT–US and daily CBCT–US acquisitions were retrospectively analyzed for 18 patients (group B) (age: 75.1 ± 6.1 years, BMI: 24.6 ± 3.8 kg $*$ m^{-2}) treated for prostate cancer. The patients were given the same protocol for bladder filling as the one given to groups A and V for both planning CT acquisition and treatment sessions. 8 properly trained therapists were involved in this study and had to apply the minimal pressure required to obtain sufficient image quality. Reference US images were acquired just after the CT acquisition and the time interval between the two images was about 3 min. Daily US images were acquired at the beginning of each treatment session and immediately followed by a CBCT acquisition in order to minimize patient motion between the 2 images. Just after US acquisition the operators ensured that the skin marks were still aligned with the lasers before performing the CBCT acquisition. The time interval between the US and CBCT images was 3 min and time for each acquisition was less than 2 min. A total of 18 CT–US and 228 CBCT–US images were collected.

In this section, the probe pressure was quantified by measuring the distance between the skin at rest, visualized on the CT or CBCT image, and the skin under probe pressure visualized on the corresponding US image, in the principal pressure direction. No registration was applied since all images were acquired in the same room coordinates system. For each 2D-US slice i that composes a 3D-US acquisition, we considered the center C_i of the acquisition cone at the surface (Fig. 2(a)), and the pressure direction D_i in the principal acquisition direction and measured the distance L_i from C_i to the CT skin surface, along D_i. The probe distance was computed as the mean of L_i distances (Fig. 2(b)). The probe distance measured with the combined CT-US image was referred as the reference pressure. The calculations were performed by using an *in-house* software based on the Insight Segmentation and Registration Toolkit.

Statistical analysis

Different statistical analyses were carried out using the R software (R Core Team, 2012) on the patient BMI, the bladder filling

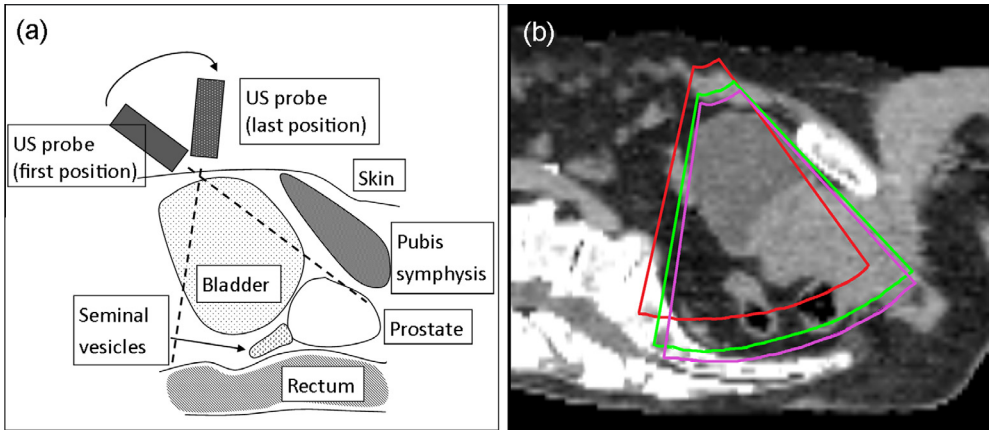

Fig. 1. (a) Schematic sagittal view of the pelvic anatomy, (b): sagittal view of a patient CT scan, with projection of the three edges of the TA-US images. In red, green and pink, the US image edges acquired with soft, moderate and strong pressures, respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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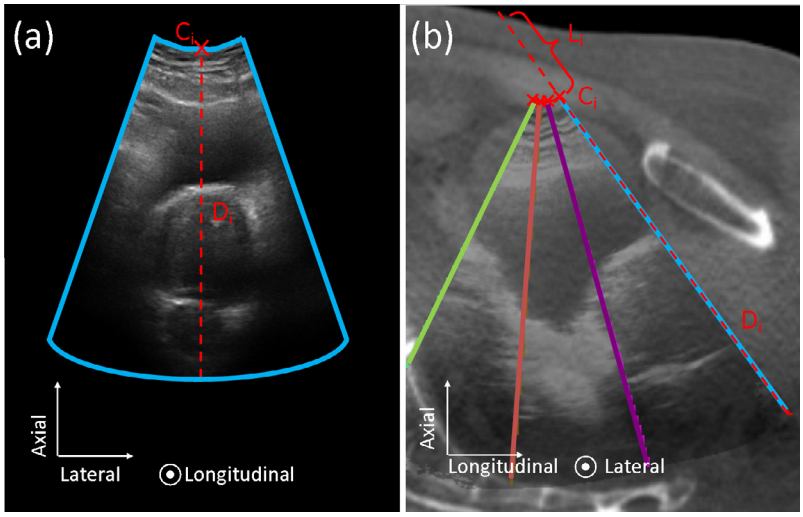

Fig. 2. (a) 2D-US image. Ci represents the probe surface center point. The dotted red line Di is the direction of the 2D-US slice. The blue line defines the border of the 2D-US slice. (b) 3D-US image registered on a corresponding CBCT image. The blue, purple, pink and green lines correspond to some 2D-US slices of the 3D-US image. Li is the distance between Ci and the skin on the CBCT according to the direction Di in dotted red line. The probe distance is the average of the Li distances calculated over all the 2D-US slices. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

and the operator effect to investigate whether these parameters influence the probe pressure variability. The correlation factor and the associated p value were calculated between the BMI and the standard deviation of the probe pressure distribution of each patient in group B. Likewise, CBCT images of 6 patients in group B (96 images) were segmented in order to calculate for each patient the correlation between the bladder filling and the associated probe pressure. Operator's names were also registered during the US acquisitions of the group B to check whether there was an influence of the therapist. An ANOVA test with two factors (therapists and patients) was performed on the pressure values to investigate this last parameter.

Finally, a statistical analysis was performed on groups A and B to determine whether the pressure levels applied during US images acquisitions for the group A were representative of the ones applied during a treatment course. For the group A, the distance between the patient skin visualized on the CT image and on the 3 different 3D-TA-US images acquired with different pressures was measured using the methodology described above. A linear mixed effects (lme) analysis of the relationship between pressure and groups was performed using the lme4 (Bates, Maechler & Bolker, 2012) package. The group was considered as fixed effect whereas the patients were considered as random factor. The p value was obtained by likelihood ratio tests of the full model with the effect in question (the group) against the model without the effect in question [13].

Minimal statistical significance was defined as $p < 0.05$.

Margins calculation

Margin calculations were performed according to the methodology described by van Herk et al. so that a minimum of 95% of the prescribed dose covers the volume for 90% of the patient population [14]. Clinical target volume (CTV) to planning target volume (PTV) margins were calculated by considering only the uncertainties related to the target position. The margin was expressed as follows:

$$\text{Margin} = 2.5 * \sqrt{\sum\nolimits^2_{\text{pressure}} + \sum\nolimits^2_{\text{intrafraction}}} + 0.7 * \sqrt{\sigma^2_{\text{pressure}} + \sigma^2_{\text{intrafraction}} + \sigma^2_{\text{IO}}}$$

The displacements of the prostate due to the different probe pressure levels found on the groups V and A were used to quantify the systematic ($\sum_{\text{pressure}}$) and random (σ_{pressure}) errors. The hypotheses were: (i) prostate displacements were only due to the probe pressure, (ii) they followed a normal probability distribution, (iii) the population was assumed to be homogeneous, (iv) the reference positions were valued within the distribution. Calculations of inter-patient standard deviation and root mean square of intra-patient standard deviations gave under these conditions $\sum_{\text{pressure}} = \sigma_{\text{pressure}}$ since the variability of the prostate displacement due to probe pressure impacts both the treatment preparation and the treatment execution.

The errors due to the inter-operator uncertainties (σ_{IO}) and the intrafraction prostate motion ($\sum_{\text{intrafraction}}$ and $\sigma_{\text{intrafraction}}$) were taken from the studies of van der Meer et al. [7] and Litzenberg et al. [15], respectively (Table 1).

Results

Prostate displacement measurement on the groups A and V

The acquisitions were reviewed in order to verify that image quality was suitable for easy prostate and bladder identifications. One volunteer was excluded due to empty bladder. Fig. 3 displays the values of the additional prostate shifts obtained with moderate

Table 1
Margin calculation results taking into account systematic and random error due to probe pressure, inter-operator uncertainties and intrafraction motion.

Uncertainties	Direction (mm)		
	AnteroPosterior	SuperoInferior	Lateral
Probe pressure	$\sigma_{\text{pressure}} = 1.3$	$\sigma_{\text{pressure}} = 1.5$	$\sigma_{\text{pressure}} = 0.5$
Inter-operator uncertainties [6]	$\sigma_{\text{IO}} = 2.2$	$\sigma_{\text{IO}} = 2.9$	$\sigma_{\text{IO}} = 2.6$
Intrafraction motion [11]	$\sum_{\text{intrafraction}} = 2.2$ $\sigma_{\text{intrafraction}} = 0.8$	$\sum_{\text{intrafraction}} = 2.6$ $\sigma_{\text{intrafraction}} = 1.2$	$\sum_{\text{intrafraction}} = 0.7$ $\sigma_{\text{intrafraction}} = 0.2$
Margins without probe pressure	7.1	8.7	3.5
Margins with probe pressure	8.3	9.9	4.0

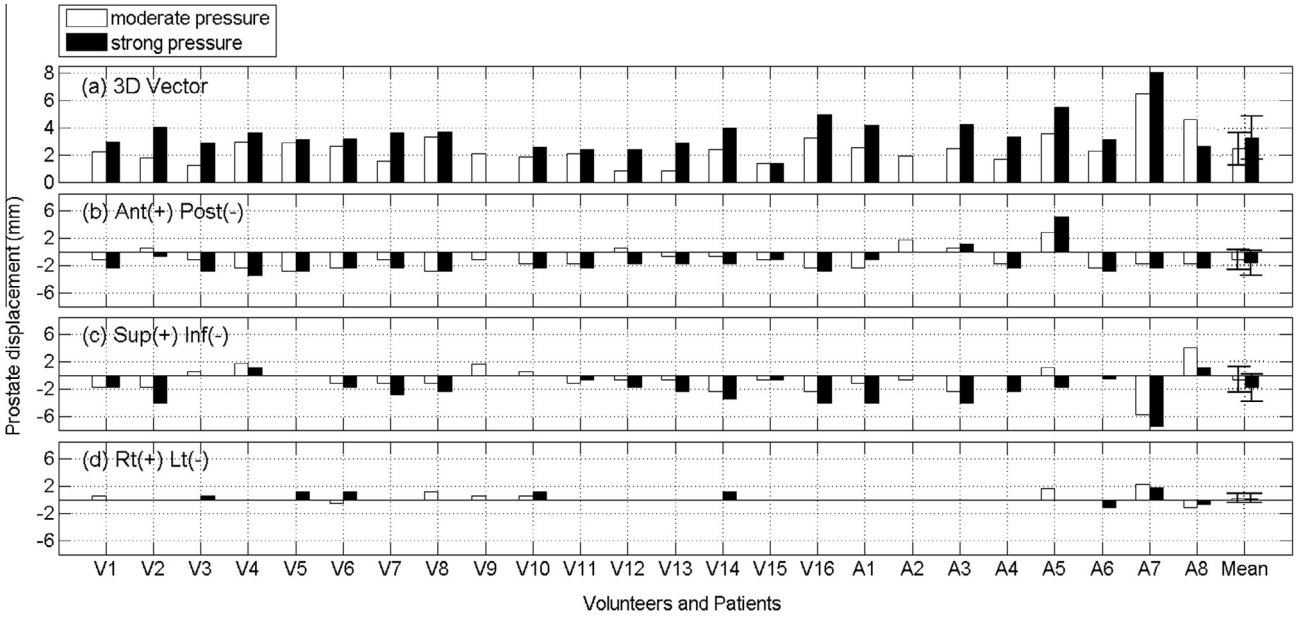

Fig. 3. Prostate volume displacements observed with moderate and strong pressure level relative to the soft pressure level for the groups A and V. (a) 3D displacement, (b) anterior (+), posterior (−) direction, (c) superior (+) inferior (−) direction, (d) right (+) left (−) direction. Mean is the average value of prostate displacements over the groups A and V.

and strong pressures compared to the soft pressure. 84% of the groups underwent a 3D prostate displacement greater than 2 mm for at least one pressure level (corresponding to the match variability measured by van der Meer et al. [7]). The average and standard deviation of 3D prostate displacements were 2.5 ± 1.2 mm and 3.3 ± 1.6 mm for the moderate and strong pressures, respectively. Except for one patient, no prostate displacement above 2 mm was observed in the lateral direction. For the supero-inferior axis, displacements greater than 2 mm were only found in the inferior direction except for one patient. The maximal observed prostate shift was 7.5 mm in the inferior direction. The prostate displacement was above 2 mm in the posterior direction for 10 persons whereas one patient had a noticeable prostate displacement in the anterior direction.

Measurement of probe distance between CT/CBCT skin and US skin on the groups A and B

The calculated probe distance and the BMI are presented in Fig. 4 for the groups A and B.

For the group B, the box-and-whisker plot shows the variability of the probe pressure over the treatment course. The intrapatient variability of the probe pressure was not significantly correlated to the BMI ($R = 0.42$, $p = 0.08$) nor to the bladder filling ($R < 0.50$, $p > 0.05$). Besides, no significant influence of the operator was observed ($p = 0.12$). Furthermore, the probe distance corresponding to the reference pressure was outside of the probe distance range measured during the treatment for 3 patients.

For the 8 patients of the group A, the probe distances were correlated to the 3 pressure levels: the higher the pressure, the larger the probe distance. Besides, according to the lme analysis, the probe distances obtained on group A were not significantly different from those measured on group B ($p = 0.74$), suggesting that even strong pressures were applied during the treatment course.

Margins calculation

Margins calculation results are given in Table 1. The use of this TA-US modality would require an increase of CTV-to-PTV margins of 1.2, 1.2 and 0.5 mm in supero-inferior, antero-posterior and lateral directions, respectively to take into account the probe pressure impact. The maximal margin was 9.9 mm in the superior–inferior direction.

Discussion

The first objective of this work was to study the impact of the probe pressure on prostate localization when using a 3D-TA-US positioning device. To our knowledge, 4 studies investigated this issue with various US devices (Supplementary data, Table 2) [5,7,9,10]. Similar to this paper, they showed that the pressure applied during US image acquisition may induce a prostate displacement whatever the acquisition process (static or sweeping). Our results are consistent with van der Meer et al. [7] who used the same imaging modality and obtained a comparable average prostate displacement. However, contrarily to them, we did not notice any appreciable impact of probe pressure on the lateral direction and we found that, at least, a soft pressure was required to obtain an image of sufficient quality to correctly visualize the prostate. This soft pressure may imply a displacement of the prostate which is difficult to quantify since it would require manual registration between US and CT images. Nonetheless a manual registration would involve additional uncertainties since prostate is smaller on US than on CT images [3] and in most cases not entirely visible because of the pubic bone. Besides, it has been demonstrated that discrepancies between absolute measurement of prostate localization on CT and US images due to speed of sound aberration also impact manual registration [16].

The maximal prostate shift (7.5 mm) reported here was noticeably less important than in the study of Artignan et al. [9]. These discrepancies may be explained by the probe location on the abdomen, directly above the prostate versus the superior bladder volume, and by the different orders of magnitude of the pressures applied in the mentioned studies. Indeed different artifices were used to quantify the pressure but none of the studies measured absolute pressure values. Static acquisitions enable accurate quantification of the distance between the different probe positions whereas recent 3D-TA-US systems requires a manual sweep of

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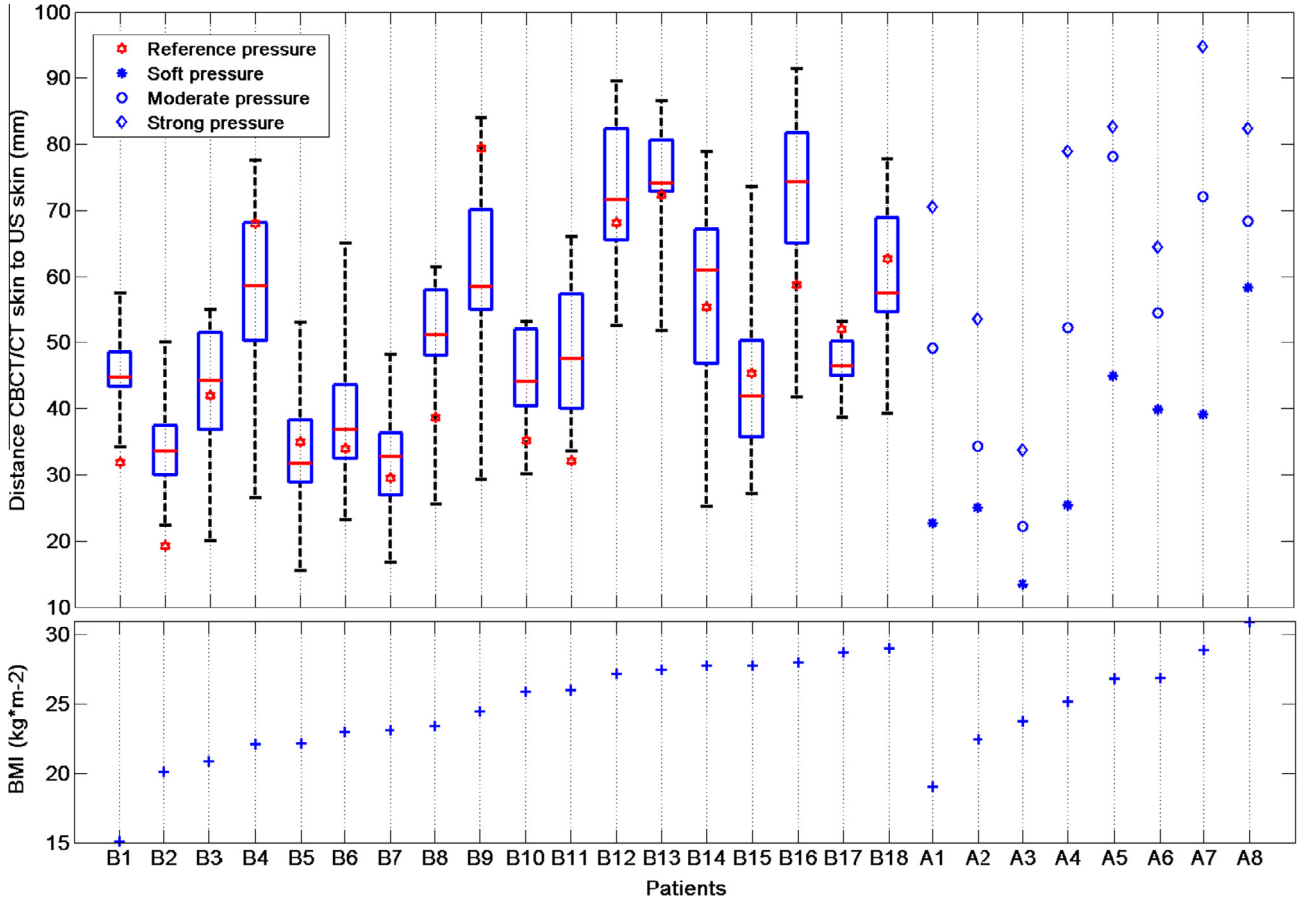

Fig. 4. Probe distance and BMI for the cohorts A and B. Box-and-whisker plots represent the median probe distance (red line) observed during the treatments of the group B, the 25th and 75th percentiles (edges of the box), and total range (extent of whiskers). The reference probe distance is plotted in red. For the eight patients of the cohort A, the probe distances corresponding to the three pressure levels are represented. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

the probe which makes it difficult to evaluate and reproduce pressure from one session to the other. Therefore the second objective of this study was to propose an original method to quantify the pressure using an automated process based on CT/CBCT images paired with US images. Thanks to this method, the gradual pressures applied for the group A were related to the ones routinely exercised during a treatment course (group B).

In clinical practice, different studies suggested that an US intramodality device has the potential to minimize the uncertainty on prostate location due to probe pressure [7,11,12]. Indeed, the prostate is likely to be shifted relative to the planning CT, due to probe pressure and the same shift value will be reported on all the US images if the pressure is kept constant between reference and daily acquisitions. Under this condition the inter-fraction shifts reported from intramodality US registration can be taken as the prostate shift assuming that other sources of errors than probe pressure are negligible. However, we showed that the pressure is difficult to reproduce from one session to another, even with trained therapists. This variability could be explained by both operator-dependent and patient-dependent factors.

With regard to the results obtained in this study, we assumed that this US image based positioning modality can be used as a reference system only if margins which take into account these uncertainties are used. Systematic and random uncertainties due to intrafraction motions were taken from Litzenberg et al. [15] who monitored the prostate movements with the Calypso® system during 8 min, which corresponds to the average duration of our treatment fractions. The uncertainty of the manual US registration procedure was considered as the inter-operator variability of this operation and derived from van der Meer et al. study [7]. Under these conditions, the impact of the probe pressure variability on prostate positioning would increase the margins by 1.2, 1.2 and 0.5 mm in the antero–posterior, supero-inferior and lateral directions, respectively.

Conclusion

We demonstrated in this study that US probe pressure impacts prostate localization even with an intramodality repositioning device. The applied pressure is difficult to reproduce from one session to the other due to the manual sweeping acquisition technique. Therefore, this system can be used routinely provided that probe pressure impact is included in the treatment uncertainties used to calculate margins, balanced against the potential margin reduction achieved through image guidance.

Conflicts of interest

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2014.02.008.

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