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**Determination of intrafraction prostate motion during external beam radiotherapy
with a transperineal 4D ultrasound real-time tracking system**

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Short title: Intrafraction prostate motion tracking using 4D ultrasound

Key words: VMAT, intrafraction prostate motion, IGRT, 4D ultrasound tracking

Conflict of interest

D. S. K. Sihono, S. Heitmann, S. von Swietochowski, M. Grimm: no competing interests

M. Ehmann: teaching honoraria, travel expenses from Elekta

J. Boda-Heggemann: research grant, teaching honoraria, travel expenses from Elekta

F. Lohr: research grants from Elekta and IBA, teaching honoraria from Elekta and IBA, board honoria from C-Rad and works for the IBA advisory board.

F Wenz: research grants from Elekta and IBA, teaching honoraria from Elekta, works as consultant and for the advisory board of Elekta.

H. Wertz: research grant and teaching honoraria from Elekta and IBA.

Determination of intrafraction prostate motion during external beam radiotherapy with a transperineal 4D ultrasound real-time tracking system

Abstract:

Purpose/Objective: To determine intrafraction prostate motion during Volumetric Modulated Arc Therapy (VMAT) using transperineal ultrasound (US) real-time tracking.

Material and Methods: 770 US monitoring sessions in 38 prostate cancer patients' VMAT treatment series were retrospectively evaluated. Intrafraction motion assessment of the prostate was based on continuous position monitoring with a 4D US system along the three directions; left(+)-right (LR), anterior(+)-posterior (AP), and inferior(+)-superior (SI). The overall mean values and standard deviations (SD) along with random and systematic errors were calculated.

Results: The mean duration of each monitoring session was 254s. The mean (μ), the systematic error (Σ) and the random error (σ) of intrafraction prostate displacement were $\mu=(0.01, -0.08, 0.15)\text{mm}$, $\Sigma=(0.30, 0.34, 0.23)\text{mm}$ and $\sigma=(0.59, 0.73, 0.64)\text{mm}$ in LR, AP and SI direction, respectively. The percentage of treatments for which prostate displacement $\leq 2\text{mm}$ was 97.01%, 92.24%, and 95.77% in the LR, AP, and SI directions, respectively. At 60s, a vector length of prostate displacement $>2\text{mm}$ was present in 0.67% of the data. The percentage increased to 2.42%, 6.14%, and 9.35% at 120s, 180s and 240s, respectively.

Conclusion: The magnitudes of intrafraction prostate motion along the SI and AP directions were comparable. On average the smallest motion was in the LR direction and the largest in AP direction. Most of the prostate displacements were within a few millimeters. However, with increasing treatment time (e.g. during hypofractionation), larger 3D prostate displacements up to 18.30mm could be observed. Shortening treatment time can reduce the impact of intrafraction motion and potentially allows smaller safety margins.

Keywords: VMAT, intrafraction prostate motion, IGRT, 4D ultrasound tracking

1. Introduction

Interfraction and intrafraction organ motion during external beam radiotherapy can cause geometric and dosimetric inaccuracies. Image guidance has the potential to reduce those uncertainties and caused a major change in radiotherapy. Particular for extracranial treatment regions such as lung, abdomen or pelvis, organ motion plays a major role and has to be considered carefully. For an accurate radiotherapy treatment of the prostate it is very important to know exactly the motion of the target and surrounding organs. In many studies the movement of organs such as the prostate during treatment is described, using magnetic resonance imaging (MRI) [1,2], real-time tracking with implanted electromagnetic transponders [3,4], kilovoltage (kV) and megavoltage (MV) imaging of implanted fiducials [5-8] or ultrasound [9,10].

Interfraction motions or setup errors can be reduced by improving the patient setup accuracy using the most advanced localization techniques. To increase dosimetric accuracy and reduce the intrafraction motion and its effects, real-time motion monitoring and tracking is required during the treatment. Understanding the characteristics of prostate intrafraction motion is still important in order to reduce its negative effects.

4D ultrasound (US) provides a method for soft tissue detection without any additional ionizing radiation and dose exposure to the patient. Transabdominal ultrasound (TAUS) has been commonly used for pre-treatment interfraction corrections. Using this system, bladder filling plays an important role for image quality and positioning accuracy. In general the bladder of the patient should have a constant filling (more than half full) during the whole treatment course. This can be a challenge for patients with pre-existing or therapy associated genitourinary problems. Transperineal ultrasound (TPUS) has the advantage to overcome this limitation. Initial studies have reported the prostate imaging performance with good image

quality of TPUS [11-13]. Current technology allows intrafraction real-time monitoring of prostate motion using TPUS.

The intrafraction prostate motion could be considerable for some patients and it could be irregular and unpredictable [14]. Accurate characterization of prostate motion may help to determine the optimal margins to optimize the tumor control probability (TCP) and, at the same time, to reduce the normal tissue complication probability (NTCP). However, because of the irregular and unpredictable motion of the prostate over time, fixed safety margins may be not sufficient to optimally compensate for this motion. Online tracking and intrafraction motion compensation strategies might be more advisable but have in general not found their way into clinical routine yet.

In addition, there is a strong push towards hypofractionated radiotherapy as a new standard of care for external-beam radiotherapy of localized prostate cancer [15-17]. This could potentially lead to longer treatment times, lower fraction numbers, higher dose per fraction and thus an increased risk of irradiating a substantial amount of dose off-target during each treatment session. Thus real time monitoring for prostate treatments becomes very important for hypofractionated treatment strategies particularly if no high dose rate flattening filter free techniques are used to compensate the longer treatment times. It will allow suitable reactions such as treatment beam interruption or online adaptation if the position deviation of the prostate is larger than a certain pre-defined threshold.

In this study intrafraction prostate motion during external beam radiotherapy was assessed using transperineal 4D US real-time monitoring.

2. Material and Methods

A total of 770 US monitoring sessions in 38 primary prostate cancer patient series were retrospectively evaluated. The retrospective evaluation was approved by the IRB/ethics committee. All 38 patients received normo-fractionated external beam radiotherapy at our department with a cumulative dose of 75Gy. The average age of patients was 74.5 ± 4.5 years (median 75.1 years, range 64.0–87.8 years).

All patients underwent a reference US scan with the Clarity 4D ultrasound system (Elekta AB, Stockholm, Sweden) on the CT couch after defining the isocenter in the planning CT. The reference US scan was stored in the Clarity server. The planning CT dataset was sent to the treatment planning system (Monaco 5.0, Elekta AB). The targets and organs at risk were contoured and a treatment plan was created. Afterwards, the CT images, structure set and treatment plan were sent to a record-and-verify system (Mosaiq, Version 2.5, Elekta AB) and the Clarity workstation for creating ultrasound IGRT position references by registering the US scan to the treatment isocenter. Patients were treated with Elekta Versa HD linear accelerators (Elekta AB) equipped with 0.5cm leave width of multileaf collimator using an energy of 10MV with 2 arcs VMAT treatment plans and delivery times of 2–4min. For reproducibility of bladder and rectum filling, all patients had to follow the departments SOPs for prostate cancer patients: Every patient had to empty his rectum before every fraction. Regarding bladder filling patients had to empty the bladder on arrival and drink half a liter of water half an hour before the treatment. This could be done also at home, if the patient's home was within a certain distance to the department.

While interfraction patient positioning and filling of the rectum and prostate was evaluated and controlled daily by kV cone-beam CT (CBCT), intrafraction motion of the prostate was tracked during 770 fractions by 4D perineal US. The Clarity US system was used in combination with an auto-scanning perineal US probe which provided in average one image

per 0.5s [18]. To minimize inter-user variability every user of the system had to have a special training where a special focus was laid on that issue. The combination of skin markers, special positioning cushions as well as new technical features like ‘live guidance’ and the evaluation of the perineal probe in relation to the patient in the cone-beam CT should have reduced the inter-user variability to a level, as low as possible.

2.1. Motion analysis

Each of the treatment sessions was analyzed to determine the time in which the prostate was displaced by a certain distance. The time span the prostate was shifted >2, >4, >6, >8, and >10mm was scored for each direction and also for vector length. A total of 770 tracking sessions were available for analysis. The tracking data consisted of the deviation of the geometric center of the prostate from their prescribed position as a function of time. Positive values indicated movement toward the anterior, inferior, and the patient’s left direction. The displacement in each direction was used to calculate the vector length (vlength).

2.2. Patient population-based margin calculation

Based on the van Herk formula [19], the CTV-PTV margin needed to cover the CTV with 95% of the dose for 90% of patients is given by:

$$M = 2.5 \Sigma + 0.7\sigma \quad (1)$$

where Σ is the standard deviation of the systematic error and σ is the standard deviation of the random error.

3. Results

All US monitoring sessions were judged by trained radiation oncologists to be of acceptable quality (96% of all tracking session available for the studied patients). The mean duration of each monitoring session was 254s.

3.1. Motion analysis

A wide range of prostate displacements was observed among the 770 fractions. Figure 1 shows the histogram of prostate motion from all fractions in all directions including the vector length. As it can be seen in Figure 1 the prostate position was rather stable in LR direction. In SI and AP direction, the prostate displacements were comparable. Most of prostate displacements were within 2 mm, which is 97.01%, 92.24%, and 95.77% in LR, AP, and SI direction, respectively.

The data from all 770 fractions (the observed mean, median, and range of time spent percentage) for prostate displacements (vector length and three directions) >2 , >4 , >6 , >8 , and >10 mm are presented in Table 1. The largest percentage values for prostate displacements (vlength) of >2 , >4 , >6 , >8 , and >10 mm that occurred in one treatment fraction of a patient were 99.37%, 73.48%, 61.37%, 31.11%, and 21.92% of the observation time. Analyzing all fractions for this patient, the corresponding values were 27.24%, 9.48%, 3.57%, 1.45%, and 1.02% as we can see in Table 2. All individual patient data are presented in Table 2 for the vector length displacement as well as prostate volume, US session amount and average US tracking time.

The magnitude and duration of the prostate displacements varied widely among the 38 patients. The average, median, and range of values observed for the population of 38 patients for each of the three directions, as well as the vector length, are presented in Table 3. The boxplots of the prostate displacements (vector length) for each patients are shown in Figure 2.

The horizontal band indicates the median, the lower and the upper edges of the box explain the first (25th) and third (75th) quartiles. The lower and the upper extremes of the whiskers, display the 5% and 95% quantiles values. Single data point outliers are the maximum prostate displacements.

The relation of prostate displacement with time is listed in Figure 3. The percentage of prostate displacement frequency increased with longer observation time. At 60s, a vector length of prostate displacement > 2 mm could be observed in 0.67% of the data. The percentage values increased to 2.42%, 6.14%, and 9.35% at 120s, 180s and 240s, respectively.

3.2. Patient population-based margin calculation

The mean (μ), the systematic error (Σ) and the random error (σ) of intrafraction motion of prostate were $\mu = (0.01, -0.08, 0.05)$ mm, $\Sigma = (0.30, 0.34, 0.23)$ mm and $\sigma = (0.59, 0.73, 0.64)$ mm in LR, AP and SI direction respectively. Using the van Herk formula, a margin was calculated to account for intrafraction motion. Margins of 1.25 mm, 1.33 mm, and 1.10 mm were calculated in the LR, AP, and SI directions, respectively.

4. Discussion

Interfraction motion or setup errors can be reduced by improving the patient setup accuracy using advanced localization techniques such as CBCT. To reduce intrafraction motion and its effects, real-time motion monitoring and tracking is required during treatment which can be achieved for example by using transperineal ultrasound.

The accuracy of the prostate tracking algorithm has been validated by Lachaine et al. [18] using an ultrasound phantom on a motion platform with certain motion patterns. Lachaine et al. discovered that the mean and standard deviation of the differences between the measured and the given reference values were 0.2 ± 0.4 mm, -0.2 ± 0.2 mm, and -0.0 ± 0.2 mm, in the

1 LR, AP, and SI directions, respectively. Another comparison study between the TPUS
2 autoscan system and the Calypso system (Varian Medical Systems, Palo Alto, CA, USA) was
3 performed by Abramowitz et al. [20]. The Calypso system utilizes transponders implanted
4 into the prostate for positional tracking. Abramowitz et al. designed a motorized phantom
5 combined with a prostate-equivalent structure. They found good agreement between the two
6 systems in tracking the embedded prostate-like sphere [21].

7 The use of Clarity for interfraction motion has been reported by Li et al. [22]. They
8 concluded that the system was feasible and achieved higher accuracy on longitudinal and
9 vertical axes compared to bone-match. Intrafraction prostate motion has been estimated using
10 various monitoring methods, including magnetic resonance imaging (MRI) [1,2], real-time
11 tracking with implanted electromagnetic transponders [3,4], kilovoltage (kV) and
12 megavoltage (MV) imaging of implanted fiducials [5-7] and ultrasound [9]. The intrafraction
13 prostate movements observed in this study were generally small ($< 2\text{mm}$) but larger shifts
14 with more than 5mm were also seen in some patients. The prostate displacements were
15 occasional fast shifts (e.g., due to muscle contraction, within seconds), short-term shifts (e.g.,
16 due to gas passage, within several to tens of seconds), continuous displacement (e.g., due to
17 rectal/bladder filling), and the combination of various movements. The smallest
18 displacements occurred in the lateral direction. The anterior and superior shifts were often
19 occasional or short-term due to gas passage and sometimes correlated with each other. Those
20 results were consistent with other reports [14,23,24]. The mean values of the prostate motion
21 in the anterior–posterior direction indicate that the prostate drifts more into the posterior
22 direction while in superior–inferior direction the prostate drifts mainly into the inferior
23 direction. This phenomenon has also been reported by other researchers [4,14,25].

24 The systematic error (Σ) and the random error (σ) of intrafraction motion found in this dataset
25 were small. Margins of ~ 1.1 to 1.3mm to consider solely for intrafraction motion were

1 calculated. The systematic errors reported by Litzenberg et al. [26] included also setup errors
2 and were larger, with $\Sigma = 0.67$ mm in the LR direction, 2.15 mm in the AP direction and 2.62
3 mm in the SI direction. Adamson et al. [27] reported that for protocols with CBCT guidance
4 in hypofractionated radiotherapy, RL, AP, and SI margins of 2, 4, and 3 mm are sufficient to
5 account for translational errors.

6 However, because the prostate motion is random, sporadic and very individual, the prediction
7 of the prostate motion is difficult [28]. Even for one patient, the prostate motion can differ
8 from one fraction to another. Because of the very asymmetric distribution of prostate motion
9 probability and the amount of motion over time, fixed general safety margins to compensate
10 for intrafraction motion are not completely suitable to account for accurate motion
11 compensation. Even individual patient-specific margins might not be sufficient. At the
12 beginning the motion can be over-compensated while at the end of the fraction the margin
13 could be not sufficient anymore.

14 Langen et al. [4] reported that long treatment times result in an increasing frequency of large
15 displacements, which could also be observed in our study. This could be particularly highly
16 relevant when hypofractionation concepts lead to longer treatment times for the patient. The
17 feasibility of hypofractionated radiotherapy as a new potential standard of care for external-
18 beam radiotherapy of localized prostate cancer has already been shown in some studies [15-
19 17]. Longer treatment times will increase the risk of placing a substantial amount of high
20 dose outside the target. More than 5 mm motion has been observed during regular IMRT
21 treatment for some patients [25,14,4]. Larger margins could be used to compensate this
22 effect. But larger margins will also result in an increased NTCP and should be avoided if
23 possible. Shortening the treatment time (e.g. due to high dose rate flattening filter free
24 techniques) should therefore be an important objective and in addition, adaptive motion
25 management will be beneficial. A 4D ultrasound system offers a non-invasive method for

online prostate motion monitoring without delivering additional ionizing radiation dose to the patient. If the prostate displacement is larger than a certain threshold (e.g. oriented on the specific safety margin) this error can be detected and the treatment beam could be interrupted or even adapted to avoid larger dose deviations in the targets and organs at risk and larger safety margins.

One of US system's disadvantages is user dependence. This disadvantage can be minimized by additional user trainings and new features in the US system such as positioning guidance of the probe.

5. Conclusion

The 4D ultrasound system offers a non-invasive method for online organ motion tracking without additional ionizing radiation dose to the patient. Magnitudes of intrafraction prostate motion along the SI and AP directions were comparable. On average the smallest motion was in the LR direction and the largest in AP direction. Most of the prostate displacements were within a few millimeters. However, with increased treatment time, larger vector length prostate displacements up to 18.30 mm could be observed. This could be highly relevant when hypofractionation concepts lead to longer treatment times for the patient. Particularly in those situations US online tracking and monitoring can help to maximize treatment precision, minimize dose to organs at risk and prevent severe dosimetric errors inside the patient. Shortening the treatment time can reduce the probability for intrafraction motion in addition.

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Figure Legends

Figure 1. Histogram of prostate displacements in SI, LR, AP direction and vlength from all 770 fractions

Figure 2. Boxplots of the prostate displacements (vector length) for each patient. The horizontal band within the box indicates the median, the lower and the upper edges of the box explain the first (25th) and third (75th) quartiles. The lower and the upper extremes of the whiskers, display the 5% and 95% values. Single data point outliers are the maximum prostate displacements.

Figure 3. The histogram of prostate displacement (vector length) related to time from all 770 fractions.

Table Legends

Table 1. Percentage of time the prostate was displaced by >2, >4, >6, >8, and >10 mm from all 770 fractions

Table 2. Prostate volume, US session amount, average US tracking time and the percentage of time the prostate was displaced by >2, >4, >6, >8, and >10 mm for each patient

Table 3. Percentage of time the prostate was displaced by >2, >4, >6, >8, and >10 mm calculated for each patient

Table 1. Percentage of time the prostate was displaced by >2, >4, >6, >8, and >10 mm from all 770 fractions

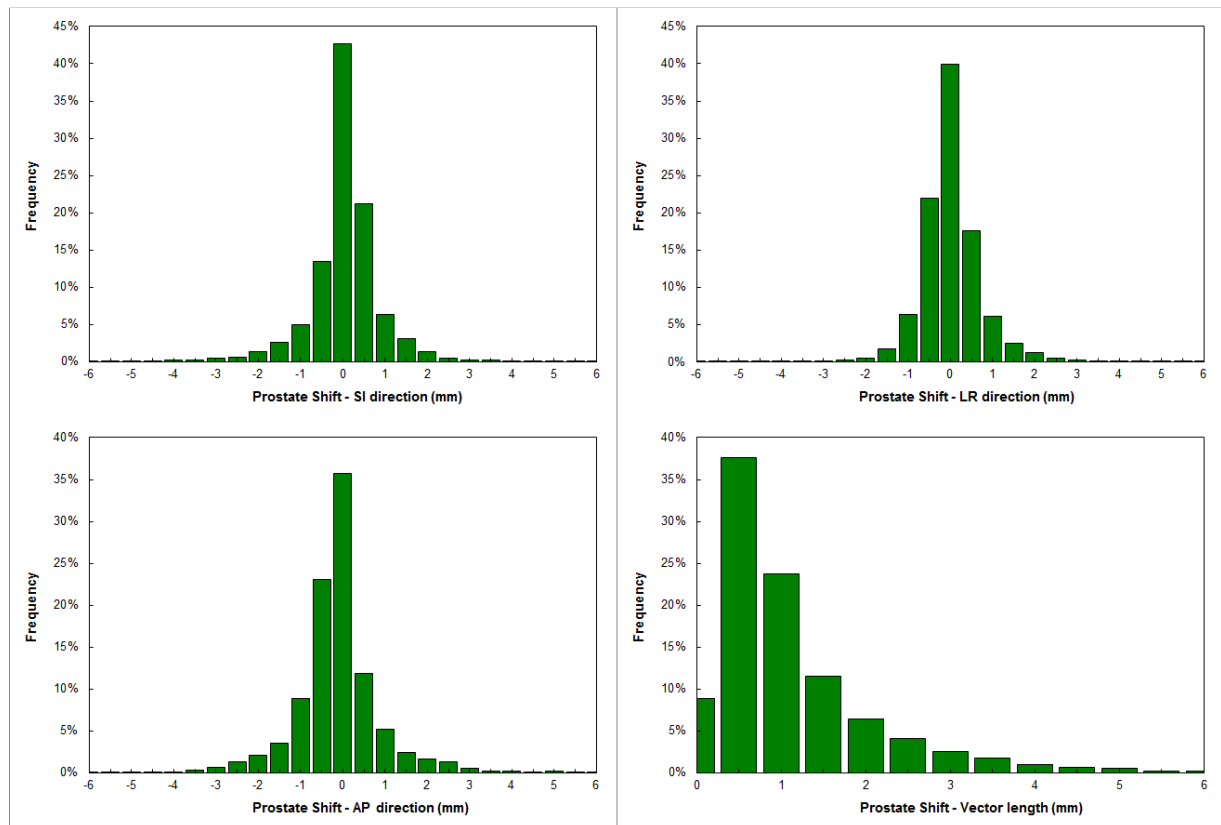
		> 2 mm (%)	> 4 mm (%)	> 6 mm (%)	> 8 mm (%)	> 10 mm (%)
vLength	Mean	12.49	2.29	0.56	0.24	0.11
	SD	22.39	9.64	5.01	3.10	1.78
	Median	0.00	0.00	0.00	0.00	0.00
	Min	0.00	0.00	0.00	0.00	0.00
	Max	99.37	86.99	71.55	62.83	41.40
SI	Mean	3.36	0.44	0.09	0.05	0.03
	SD	11.60	4.38	1.68	1.48	0.75
	Median	0.00	0.00	0.00	0.00	0.00
	Min	0.00	0.00	0.00	0.00	0.00
	Max	94.29	74.78	44.05	41.13	20.88
LR	Mean	2.20	0.44	0.17	0.04	0.00
	SD	9.68	4.76	2.87	1.12	0.00
	Median	0.00	0.00	0.00	0.00	0.00
	Min	0.00	0.00	0.00	0.00	0.00
	Max	93.57	85.70	71.41	30.95	0.00
AP	Mean	5.98	0.78	0.11	0.06	0.05
	SD	15.39	5.27	1.78	1.48	1.47
	Median	0.00	0.00	0.00	0.00	0.00
	Min	0.00	0.00	0.00	0.00	0.00
	Max	95.36	64.89	41.72	40.77	40.72

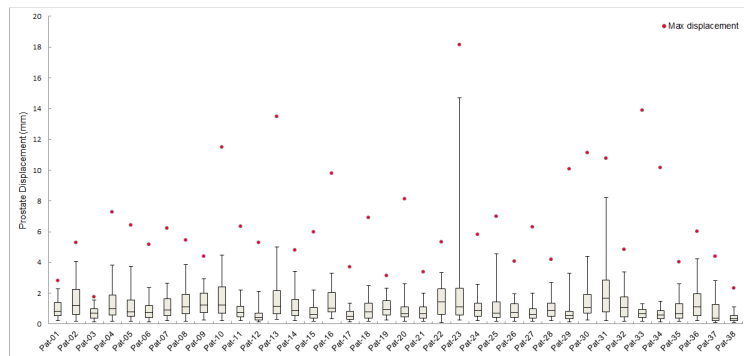
Table 2. Prostate volume, US session amount, average US tracking time and the percentage of time the prostate was displaced by >2, >4, >6, >8, and >10 mm for each patient

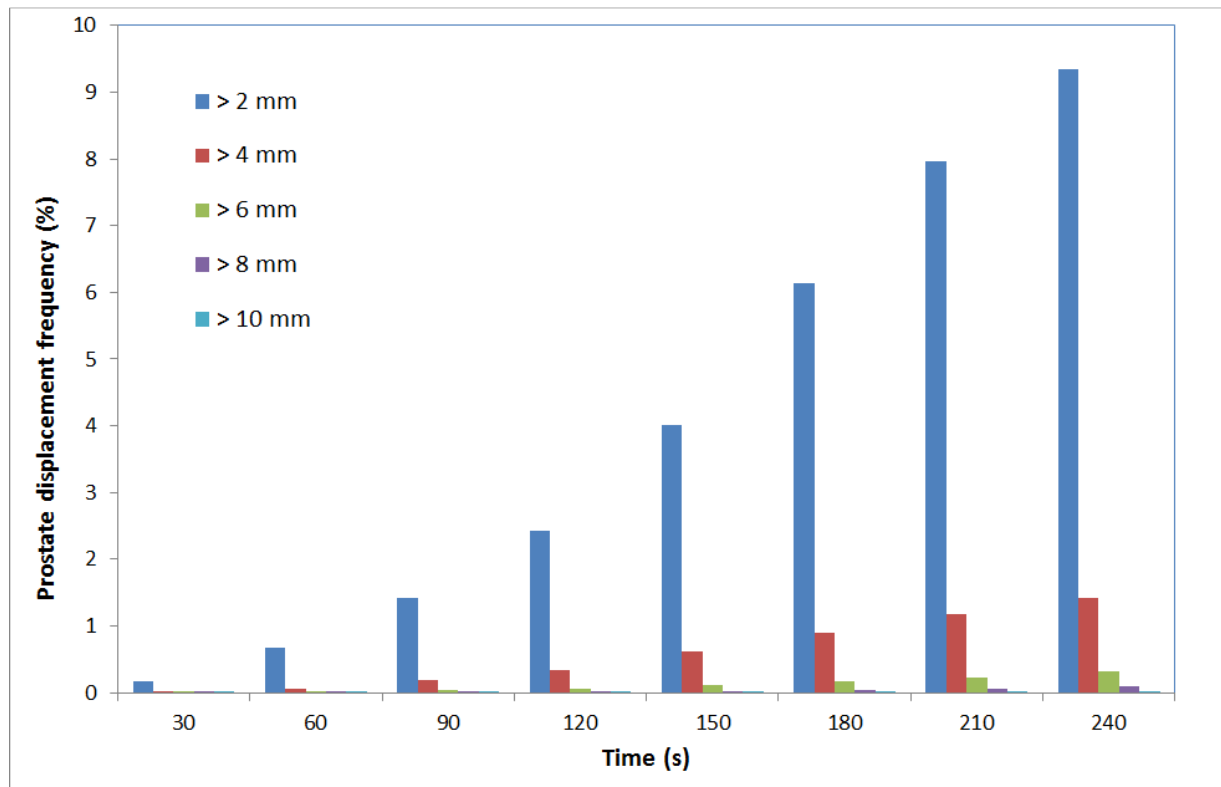
Pat No.	Prostate Volume (cc)	US Session	Average US Tracking Time (s)	Prostate Displacement				
				> 2 mm (%)	> 4 mm (%)	> 6 mm (%)	> 8 mm (%)	> 10 mm (%)
1	62.25	5	321	9.47	0.00	0.00	0.00	0.00
2	74.24	9	324	28.76	5.44	0.00	0.00	0.00
3	34.07	4	229	0.00	0.00	0.00	0.00	0.00
4	51.53	26	260	23.35	3.91	1.28	0.00	0.00
5	49.01	18	264	17.19	3.88	0.22	0.00	0.00
6	35.7	22	282	8.14	0.85	0.00	0.00	0.00
7	20.29	21	281	16.22	0.82	0.07	0.00	0.00
8	57.9	22	297	23.73	4.32	0.00	0.00	0.00
9	30.55	26	309	25.55	0.33	0.00	0.00	0.00
10	45.75	20	279	33.64	6.78	0.86	0.66	0.29
11	57.62	18	260	5.82	0.35	0.06	0.00	0.00
12	65.87	17	245	5.55	1.39	0.00	0.00	0.00
13	70.58	19	267	27.24	9.48	3.57	1.45	1.02
14	52.13	22	239	19.27	1.87	0.00	0.00	0.00
15	29.23	23	232	7.49	0.16	0.00	0.00	0.00
16	33.44	7	220	25.63	2.22	1.03	0.67	0.00
17	22.58	27	237	0.48	0.00	0.00	0.00	0.00
18	70.49	19	210	8.75	1.81	0.21	0.00	0.00
19	117.72	6	253	7.10	0.00	0.00	0.00	0.00
20	42.34	33	247	8.86	2.12	1.21	0.10	0.00
21	40.49	24	221	5.08	0.00	0.00	0.00	0.00
22	83.28	9	248	35.46	2.17	0.00	0.00	0.00
23	32.67	26	275	29.48	16.61	10.79	6.25	5.88
24	53.34	23	240	10.88	2.84	0.00	0.00	0.00
25	38.04	28	239	20.18	5.64	2.30	0.00	0.00
26	82.99	30	259	4.63	0.16	0.00	0.00	0.00
27	51.18	30	212	4.96	1.20	0.04	0.00	0.00
28	65.05	33	226	10.21	0.16	0.00	0.00	0.00
29	19.32	29	232	8.78	3.31	1.70	0.96	0.03
30	42.34	18	252	24.14	7.15	0.05	0.05	0.05
31	135.44	27	271	43.45	11.41	6.69	5.60	1.15
32	22.88	10	273	17.99	1.91	0.00	0.00	0.00
33	52.83	27	243	0.49	0.08	0.04	0.01	0.01
34	57.27	26	245	1.49	0.04	0.01	0.01	0.01
35	69.9	7	236	13.39	0.02	0.00	0.00	0.00
36	58.48	27	248	24.37	6.29	0.01	0.00	0.00
37	37.25	9	271	8.40	1.16	0.00	0.00	0.00
38	48.7	23	222	0.29	0.00	0.00	0.00	0.00

Table 3. Percentage of time the prostate was displaced by >2, >4, >6, >8, and >10 mm calculated for each patient

		> 2 mm (%)	> 4 mm (%)	> 6 mm (%)	> 8 mm (%)	> 10 mm (%)
vLength	Mean	14.89	2.79	0.79	0.41	0.22
	SD	11.21	3.67	2.10	1.35	0.97
	Median	10.55	1.60	0.00	0.00	0.00
	Min	0.00	0.00	0.00	0.00	0.00
	Max	43.45	16.61	10.79	6.25	5.88
AP	Mean	7.14	0.98	0.23	0.16	0.15
	SD	6.69	2.02	0.98	0.94	0.94
	Median	4.56	0.04	0.00	0.00	0.00
	Min	0.00	0.00	0.00	0.00	0.00
	Max	26.12	9.77	5.92	5.79	5.78
LR	Mean	3.15	0.51	0.22	0.07	0.00
	SD	4.10	1.39	0.95	0.38	0.00
	Median	1.51	0.00	0.00	0.00	0.00
	Min	0.00	0.00	0.00	0.00	0.00
	Max	14.42	7.75	5.66	2.34	0.00
SI	Mean	3.68	0.65	0.21	0.16	0.08
	SD	4.46	2.23	1.02	0.95	0.48
	Median	2.85	0.00	0.00	0.00	0.00
	Min	0.00	0.00	0.00	0.00	0.00
	Max	14.91	13.00	6.25	5.84	2.96







Summary

Prostate movement and displacement during radiotherapy is depending on treatment time. New hypofractionated radiotherapy regimens for localised prostate cancer require longer treatment times with consequently an increased risk of placing a substantial amount of dose outside the target. Thus real time monitoring in prostate treatment becomes more important. We analysed the prostate motion during external beam radiotherapy with transperineal 4D ultrasound real-time monitoring.