

Prostate cancer treated with image-guided helical TomoTherapy[®] and image-guided LINAC-IMRT

Correlation between high-dose bladder volume, margin reduction, and genitourinary toxicity

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Abstract

Background We compared different image-guidance (IG) strategies for prostate cancer with high-precision IG intensity-modulated radiation therapy (IMRT) using TomoTherapy[®] (Accuray Inc., Madison, WI, USA) and linear accelerator (LINAC)-IMRT and their impact on planning target volume (PTV) margin reduction. Follow-up data showed reduced bladder toxicity in TomoTherapy patients compared to LINAC-IMRT. The purpose of this study was to quantify whether the treatment delivery technique and decreased margins affect reductions in bladder toxicity.

Patients and methods Setup corrections from 30 patients treated with helical TomoTherapy and 30 treated with a LINAC were analyzed. These data were used to simulate three

IG protocols based on setup error correction and a limited number of imaging sessions. For all patients, gastrointestinal (GI) and genitourinary (GU) toxicity was documented and correlated with the treatment delivery technique.

Results For fiducial marker (FM)-based RT, a margin reduction of up to 3.1, 3.0, and 4.8 mm in the left–right (LR), superior–inferior (SI), and anterior–posterior (AP) directions, respectively, could be achieved with calculation of a setup correction from the first three fractions and IG every second day. Although the bladder volume was treated with mean doses of 35 Gy in the TomoTherapy group vs. 22 Gy in the LINAC group, we observed less GU toxicity after TomoTherapy.

Conclusion Intraprostate FMs allow for small safety margins, help decrease imaging frequency after setup correction, and minimize the dose to bladder and rectum, resulting in lower GU toxicity. In addition, IMRT delivered with TomoTherapy helps to avoid hotspots in the bladder neck, a critical anatomic structure associated with post-RT urinary toxicity.

Keywords Tomotherapy · Fiducial markers · Adverse effects · Organs at risk · Margins

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Behandlung des Prostatakarzinoms mit bildgeführter helikaler Tomotherapie und bildgeführter LINAC-IMRT

Korrelation zwischen Harnblasenhochdosisvolumen, Reduktion des Sicherheitsabstands und urogenitaler Toxizität

Zusammenfassung

Hintergrund Wir haben im Rahmen der Prostatakarzinombehandlung verschiedene bildgeführte (IG) Strategien der hochpräzisen intensitätsmodulierten Radiotherapie (IMRT) unter Einsatz der Tomotherapie (TomoTherapy®, Accuray Inc., Madison, Wisconsin, USA) und der Linearbeschleuniger(LINAC)-IMRT sowie deren Einfluss auf die Margingröße verglichen. Wie Nachsorgeuntersuchungen zeigten, war die Harnblasentoxizität bei Patienten mit Tomotherapie im Vergleich zur LINAC-IMRT geringer. In der vorliegenden Studie sollte quantifiziert werden, ob das Bestrahlungsverfahren und reduzierte Sicherheitssäume Einfluss auf die Verringerung der Blasentoxizität haben.

Patienten und Methoden Es erfolgte eine Analyse der Lagerungskorrekturen von 30 Patienten mit helikaler Tomotherapie und weiteren 30 Patienten, die mit einem LINAC behandelt wurden. Mithilfe dieser Daten wurden drei IG-Protokolle simuliert, basierend auf den Korrekturen von Lagerungsfehlern und auf einer limitierten Zahl bildgeführter Bestrahlungen. Bei allen Patienten wurde die gastrointestinale (GI) und urogenitale (GU) Toxizität dokumentiert und mit dem Bestrahlungsverfahren in Beziehung gesetzt.

Ergebnisse Bei Anwendung einer Radiotherapie mit Goldmarkern konnte durch Berechnung einer Lagerungskorrektur aus den ersten 3 Fraktionen und einer IG-Untersuchung an jedem zweiten Tag eine Marginreduktion von bis zu 3,1, 3,0 und 4,8 mm in Links-rechts-, superior-inferiorer bzw. anterior-posteriorer Richtung, bei gleichzeitiger Reduzierung der IG-Dosis erreicht werden. Obwohl das Blasenvolumen in der Tomotherapiegruppe mit mittleren Dosen von 35 Gy behandelt wurde, während die LINAC-Gruppe 22 Gy erhielt, war eine geringere urogenitale Toxizität nach Tomotherapie zu verzeichnen.

Schlussfolgerung Goldmarkerbasierte IGRT der Prostata ermöglicht kleinere Sicherheitssäume. Sie helfen, die Häufigkeit bildgeführter Bestrahlungen mithilfe geeigneter IG-Protokolle zu verringern und die Strahlendosis in Blase und Rektum zu minimieren. Dadurch sinkt die urogenitale Toxizität. Darüber hinaus lassen sich mit IMRT unter Einsatz der Tomotherapie „Hotspots“ am Blasen Hals vermeiden, einer kritischen anatomischen Struktur, die im Zusammenhang mit der Hamwegstoxizität nach Radiotherapie steht.

Schlüsselwörter Prostatakarzinom · Harnblasentoxizität · Goldmarker-basierte IGRT · Helikale Tomotherapie · Margins

Radiotherapy (RT) is an important modality in the primary or postoperative treatment of prostate cancer. External beam radiation therapy (EBRT) has progressed over the past 25 years from a conventional four-field box technique, via three-dimensional conformal RT, to intensity-modulated RT (IMRT), with image-guided RT (IGRT) representing the most precise option [1–4]. Accurate targeting of the prostate is a vital component of prostate cancer RT, to ensure delivery of the maximal radiation dose to the target volume. In addition, the prescribed radiation dose is often limited by the tolerance of adjacent critical organs, in particular the bladder and rectum. Significant interfraction prostate motion within the pelvis is well established [5, 6] and can lead to geographic missing of the target. To compensate for these setup errors, margins are required for specific radiation techniques. Unfortunately, larger safety margins result in an increased volume of bladder and rectum receiving doses of 70 Gy or above. The limiting factor for dose escalation in radical RT is the increased rate of acute and late treatment-related toxicity. The use of IG platforms for in-room detection and correction of setup errors offers a good opportunity to reduce margins [7]. Helical TomoTherapy (HT) and a linear accelerator (LINAC) on-board detector are platforms that incorporate volumetric megavoltage (MV) computed tomography (CT) imaging to visualize and correct any setup discrepancies, with a kilovoltage (kV) CT simulation performed prior to treatment.

One possibility for matching the kVCT and the MVCT is to use bony anatomy; however, the prostate is not attached directly to bone [8]. Because of the poor MV image quality, it is usually difficult to localize the prostate gland. A common method to decrease geographic mistargeting of the prostate is to implant fiducial markers (FMs), which can be visualized on an MV beam and serve as a surrogate for prostate position [9, 10]. The stability of these fiducials has been reported [11, 12].

We treated prostate cancer patients with high-precision IG-IMRT using TomoTherapy® (Accuray Inc., Madison, WI, USA) and LINAC. The follow-up data showed reduced bladder toxicity in TomoTherapy patients compared to those treated with LINAC-IMRT. The purpose of this study was to correlate the reduced urinary toxicity with the treatment delivery technique. We evaluated the average setup correction for three IG methods and the resulting margin reduction on both treatment techniques. We then compared the treatment planning and delivery factors with bladder and rectal toxicity.

Materials and methods

Patient data and study design

The current study was approved by the local ethics committee and all patients gave their written informed consent.

From October 2012 to March 2014, 60 consecutively treated patients with histologically proven adenocarcinoma of the prostate were treated using IMRT. Two different treatment protocols were analyzed retrospectively: in trial A 30 patients were treated with LINAC Oncor® (Siemens, Erlangen, Germany); in trial B, 30 patients were treated using the TomoTherapy® unit. Patients' demographic and treatment characteristics are given in Table 1.

Preparation and treatment planning

For patients in trials A and B, three FMs were implanted under transrectal ultrasound guidance. After 1 week of adaptation, a treatment planning kVCT was performed with patients in the supine position, using a large bore Light-Speed® scanner (General Electric, Chicago, IL, USA) and a slice thickness of 1.25 mm. All patients were asked to have a filled bladder and drink 500 ml of oral contrast medium half an hour before scanning. To ensure emptying of the rectum, laxatives were given the evening before, and an enema (Mikroklist®) was administered prior to CT simulation the next morning.

The clinical target volume (CTV; including the seminal vesicles in high-risk patients), bladder, rectum from the anal verge to the beginning of the sigmoid colon, and femur heads were contoured manually using the Oncentra Masterplan® treatment planning system. Using the in-built algorithm, the planning target volume (PTV) was generated by expansion of the CTV with an isotropic 8-mm margin, except for a 5-mm margin posteriorly. Dose constraints and acceptance criteria for the bladder, rectum, and femoral heads were the same for the HT and LINAC groups.

All patients were treated with IMRT given at 2.0 Gy per fraction specified to the encompassing PTV isodose (ICRU 62) to a total dose 74–78 Gy (radical RT).

Target localization and treatment delivery

In all patients, daily positioning was performed using the skin markers, while CT was performed according to the room laser coordination system (LAP, Lüneburg, Germany). IG was performed in all patients immediately before irradiation in the treatment position.

IG for the LINAC group (trial A) was achieved with MV cone beam (CB) CT and a resolution of 512 pixels. A radiation dose of about 7–8 cGy for one MVCB-CT MVi-sion® was determined. The total delivered IG dose for the

Table 1 Patient, treatment, and follow-up characteristics, and incidence of genitourinary toxicities in %

		Trial A (LINAC + FM)	Trial B (HT + FM)
Number of patients		30	30
Age (years)	Min.	56	63
	Max.	83	83
	Mean	72.97	74.33
Gleason score	5	3	0
	6	11	14
	7	11	13
	8	4	1
	9	1	1
	10	0	1
	Unknown	0	0
Pre-treatment PSA (ng/ml)	Min.	0.013	0.07
	Max.	30.4	83.2
	Mean	7.90	10.96
	Unknown	2	0
Radiotherapy dose (Gy)	Min.	72	72
	Max.	76	76
	Mean	74.27	74.47
Median follow-up (months)		22.03	14.41
Genitourinary toxicities (%)	Grade 0	54	69
	Grade ≥ 1	46	31
	Grade ≥ 2	33	14
	Grade ≥ 3	10	0
	Grade ≥ 4	0	0
	<i>p</i> -value	0.125	
Chi-square test Pearson (asymptotic significance)	0.078		
Mean dose in PTV (Gy)		74.27	74.47
Mean bladder dose (Gy)		22	35
Max. dose (bladder minus PTV; Gy)		77.72	74.67
Mean V_{70} (bladder minus PTV; cm ³)		8.75	6.71

PSA prostate-specific antigen, HT helical TomoTherapy, FM fiducial marker, V_{70} volume receiving at least 70% of the prescribed dose

treatment was about 250 cGy [13]. Registration with the planning kVCT was first performed automatically using bony anatomy-matching function of the Siemens Software Syngo®. After this initial registration, a manual correction based on FMs was performed by a radiation therapist. The shift between these two registration algorithms was the setup error caused by interfraction prostate motion.

For each patient in trial B, daily MV fan beam (FB) CT scans with a 2-mm interslice distance were acquired prior to the daily treatment. The actual alignments were always performed on the basis of the location of the implanted fiducials and occurred manually after automatic bony anatomy/tissue fusion. A radiation dose of about 1.5 cGy for one MVFB-CT was used [14]. The delivered IG dose for the entire treatment was about 60 cGy.

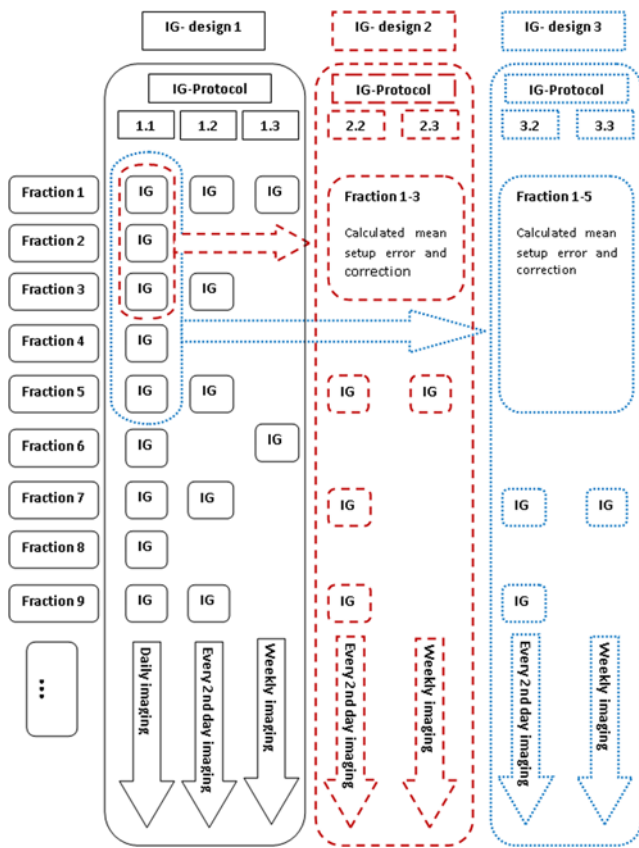


Fig. 1 Image guidance protocols: *IG* image guidance, *1.1* daily imaging, *1.2* initial fraction and imaging every 2nd day, *1.3* initial fraction and weekly imaging; *2.2* correction of mean setup error from the first three fractions and imaging every 2nd day, *2.3* correction of mean setup error from the first three fractions and weekly imaging; *3.2* correction of mean setup error from the first five fractions and every 2nd day imaging, *3.3* correction of mean setup error from the first five fractions and weekly imaging. Colors refer to Table 3

A total of 2220 IG treatment sessions were available for analysis, with an average of 37–39 alignments per patient. The deviation of the setup, based on imaging, was calculated in the left–right (LR), superior–inferior (SI), and anterior–posterior (AP) dimensions.

Error analysis and statistics

The day-to-day variation in the position of the prostate relative to the skin markings is the interfraction motion and internal movement of the prostate over the course of a single treatment is the intrafraction motion. For all patients, the mean and standard deviation of the daily performed setup corrections defined the systematic and random errors. From these data, the population average of systematic errors (Σ) and random errors (σ) was calculated [15]. For each patient, setup corrections from the daily IG history were used to simulate different IG protocols (Fig. 1). IG design 1 involved using the first fraction to correct the systematic error com-

bined with different frequencies of repetition of the IG for correcting the random error during the treatment. IG designs 2 and 3 involved using, respectively, the first three and first five fractions for correcting the systematic error. The van Herk's margin formula ($2.5\Sigma + 0.7\sigma$) was used to determine the PTV margin that would ensure a minimum of 95% dose coverage for 90% of patients [16]. According to this formula, the systematic error made a greater contribution to calculation of the treatment margin than did the random component. Therefore, it was very important to accurately estimate this error by using new IG protocols.

In the new IG protocols, we calculated a systematic setup error correction as the average displacement over 1, 3, or 5 consecutive days. For the random errors, the influence of imaging frequency (daily, every second day, and weekly imaging) was determined. A decrease in imaging frequency with new IG protocols will lead to an increase in IG protocol-specific population systematic and random errors.

Statistical analysis of toxicity for LINAC and HT fiducial-based IGRT was performed with SPSS software (version 22.0; IBM SPSS Statistics for Windows, IBM Corp., Armonk, NY, USA). The Chi-square test or Fisher's exact test was used with a significance level set at $\alpha = 0.05$.

Follow-up

All patients were continuously followed before and after RT. Patients were scheduled for follow-up visits at 6 weeks and then 1 year after the end of treatment, and once a year thereafter until 5 years of follow-up were completed. Evaluation of gastrointestinal (GI) and genitourinary (GU) symptoms was performed according to Radiation Therapy Oncology Group (RTOG) guidelines. Documentation of adverse effects included changes in Karnofsky performance status, urinary retention, development of urethral stricture, hematuria, nocturia, urinary frequency, dysuria, and fecal incontinence. A strict definition of the grading system was used for grades 1–4: grade 1 was defined as minimal side effects not influencing activities of daily living and grade 4 as life threatening, in which urgent treatment or interventions were needed.

Results

Interfraction prostate displacement resulting from bony anatomy fusion

For all patients (trials A and B), a total of 2220 fractions were analyzed. The mean interfraction systematic and random setup uncertainties for daily bone and FM-IGRT are shown in Table 2.

We observed an overall mean magnitude of interfractional shifts for FMs in comparison to bony anatomy of 2 mm posterior and about 2 mm in the inferior direction; however, there was no shift in the lateral direction (Fig. 2a, b, c). Thus, an additional nonuniform larger margin in the posterior and inferior directions based on IG bone fusion would be needed to cover the CTV because the organ motion is not included. However, an enlarged posterior margin could be associated with increased GI and GU toxicity. The magnitude of the shifts was independent of imaging technique (MVCB and MVFB), although the spreading in the SI direction was smaller for the FB because of the split imaging procedure (Fig. 2a).

IGRT protocol determination of margins

Daily imaging results in high patient exposure and could account for one more additional fraction (an open field; including organs at risk, OAR) for the complete treatment dose, depending on the IG technique used. The goal during IG should be minimization of exposure without altering or even with improvement in patient benefit.

Analysis of the data in Table 3 showed that all scenarios were effective in reducing the mean systematic error compared to no IGRT. The systematic error decreased with more frequent imaging. In contrast, the random errors were not

much affected with increased imaging frequency. Under the assumption that interfraction motion is “zero” with daily fiducial-based alignment, a theoretical margin size of zero can be inferred. However, this does not include all uncorrectable uncertainties (intrafraction motion [17–20], flat panel, CT resolution, and treatment planning calculation grid size). Therefore we created an “IG baseline” including the aforementioned uncertainties.

These uncertainties required a minimum margin of 3 mm in the LR and 5 mm in the SI and AP directions. In Fig. 3, an overcorrection for a daily FM-based IGRT is shown, because the margin size is under the IG baseline. This IG baseline could be achieved with a mean setup error correction over the first three fractions and imaging every second day (Fig. 1; IG design 2.2). In addition, with this design, the imaging exposure could be reduced to half compared to daily imaging.

Finally, if only bony anatomy was used for alignment, the required margins would be 8 (LR), 9 (SI), and 12 mm (AP).

Toxicity

Although IGRT with FMs was performed in trials A and B (Table 1), we observed more symptoms of GU toxicity grades 1–3 in the LINAC-IMRT group compared to patients treated with TomoTherapy-based IMRT. No grade 3 GU toxicity occurred in the fiducial-based TomoTherapy group and, overall, no fecal (GI) or grade 4 GU toxicity was observed in any group. In spite of the bladder having been treated with higher mean doses of 35 Gy in the TomoTherapy group vs. 22 Gy in the LINAC group, there was less GU toxicity observed after TomoTherapy.

Table 2 Systematic Σ and random σ setup error between automatic bone matching and manual fiducial marker-based alignment

	Daily bone IGRT		Daily FM IGRT	
	Σ	σ	Σ	σ
LR (mm)	1.72	1.99	1.76	2.23
SI (mm)	1.30	1.46	2.09	2.26
AP (mm)	2.38	2.33	2.51	3.20

IGRT image-guided radiotherapy, FM fiducial marker, LR left–right, SI superior–inferior, AP anterior–posterior

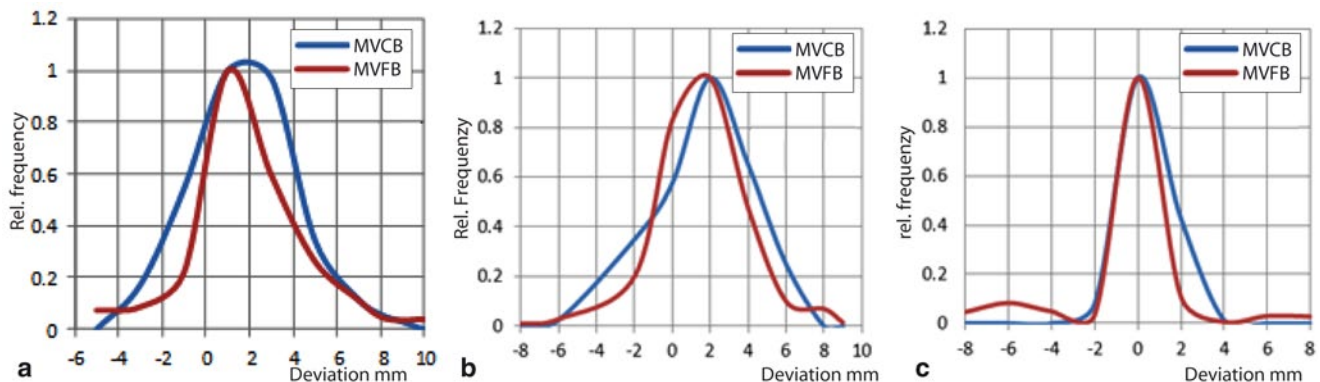


Fig. 2 a–c Mean deviations of fiducial marker (FM) position from bony anatomy position in three dimensions. a superior–inferior, b anterior–posterior, c left–right. MVCB megavoltage cone beam, MVFB megavoltage fan beam

Table 3 Systematic (Σ) and random (σ) errors and population-based margins calculated for the no image guidance (IG) scenario and for each combination of IG protocol. See also Fig. 1

Fiducial marker based IGRT									
	IG design 1			IG design 2			IG design 3		
	No IGRT			No IGRT			No IGRT		
	Σ	σ	Margin	Σ	σ	Margin	Σ	σ	Margin
LR (mm)	2.56	2.28	8.00	1.76	2.23	5.97	1.62	2.16	5.56
SI (mm)	2.87	2.38	8.85	2.09	2.26	6.79	1.42	2.17	5.06
AP (mm)	3.99	3.31	12.30	2.51	3.20	8.50	2.53	3.15	8.54
	IG Protocol 1.3 (weekly)			IG Protocol 2.3 (weekly)			IG Protocol 3.3 (weekly)		
LR (mm)	2.05	2.27	6.73	1.37	2.09	4.90	1.35	2.01	4.79
SI (mm)	2.29	2.35	7.36	1.68	2.15	5.70	1.18	2.07	4.40
AP (mm)	3.22	3.31	10.37	2.04	3.07	7.25	2.10	2.95	7.31
	IG-Protocol 1.2 (every 2nd day)			IG-Protocol 2.2 (every 2nd day)			IG-Protocol 3.2 (every 2nd day)		
LR (mm)	1.24	1.93	4.45	0.84	1.72	3.30	0.80	1.67	3.17
SI (mm)	1.43	2.12	5.07	1.08	1.87	3.99	0.74	1.68	3.04
AP (mm)	1.97	2.89	6.94	1.23	2.51	4.84	1.26	2.49	4.88
	IG-Protocol 1.1 (every day)			(Every day)			(Every day)		
LR (mm)	Theoretical error and margin size by daily IGRT is zero, but it is not possible in practice because of uncertainties such as IG								
SI (mm)	resolution, intrafractional prostate movement, and fiducial marker shifts								
AP (mm)									

IG image guidance, IGRT image-guided radiotherapy, LR left–right, SI superior–inferior, AP anterior–posterior

Discussion

Margin reduction

The directional analysis for daily fiducial IGRT compared to bone fusion showed a greater setup uncertainty in the AP and SI directions than in the LR direction. The high SI systematic error is a plausible consequence of lower bladder filling during the treatment course compared to the bladder filling at simulation [21–24]. These deviations could not be observed in bone IGRT, which involved a low systematic error in the SI direction (Fig. 4a). These findings are in agreement with those of previous studies [25–29] and can be explained as follows: positioning in the AP dimension is variable because of variable and nonreproducible daily filling of the rectum; therefore, the random error is higher in FM-based IGRT. The systematic error of over 2 mm in the AP direction could be associated with greater patient relaxation during treatment than at the time of CT simulation (Fig. 4b). The IG design 2.2 with PTV margins of 3 mm (LR) and 5 mm (SI, AP) resulted in reduced bladder neck dose.

Toxicity

For prostate cancer RT, we found that TomoTherapy provided excellent target coverage with higher dose uniformity despite a large penumbra. The mean maximum dose (hotspot) for a created structure “bladder minus PTV” was 3 Gy higher with LINAC-IMRT technique compared to TomoTherapy-IMRT (77 vs 74 Gy) using the same con-

straints. The volume of the structure exposed to 70 Gy or more (V_{70}) was 2 cm³ larger in the LINAC group. In addition to this dose, a MVCB imaging dose (about 2 Gy) had to be added. The bladder neck was located within this more highly irradiated volume, which may explain the increased bladder toxicity observed after LINAC-based IMRT.

There is evidence to suggest that the mean bladder dose has only a small influence on bladder toxicity. However, the most critical anatomic structure associated with post-RT urinary toxicity is not well established. Retrospective reports have drawn associations between various factors such as urethral dose, prostate volume, or use of neoadjuvant androgen deprivation therapy and increased risk of significant acute urinary toxicity [30, 31]. Several small retrospective reports have addressed the correlation of urinary toxicity with the dose to the lower urinary tract segments [32] and described an association between the dose to the urethral base/bladder neck and urinary toxicity [33]. A recent Dutch trial demonstrated that a volume >2 cm³ receiving a high dose (80 Gy) and a >47-Gy dose administered to the trigone are associated with a significantly increased risk of late urinary obstruction [34]. Heemsbergen et al. demonstrated that hotspots were correlated with the incidence of bladder neck obstructions. This might be due to the fact that bladder hotspots are usually found in the area of the bladder neck close to the CTV. Furthermore, hotspots were mainly associated with urinary retention within 2 years. In addition, the dose just cranial to the prostate is probably predictive for bladder neck obstruction, because the bladder neck moves in and out of this area during treatment.

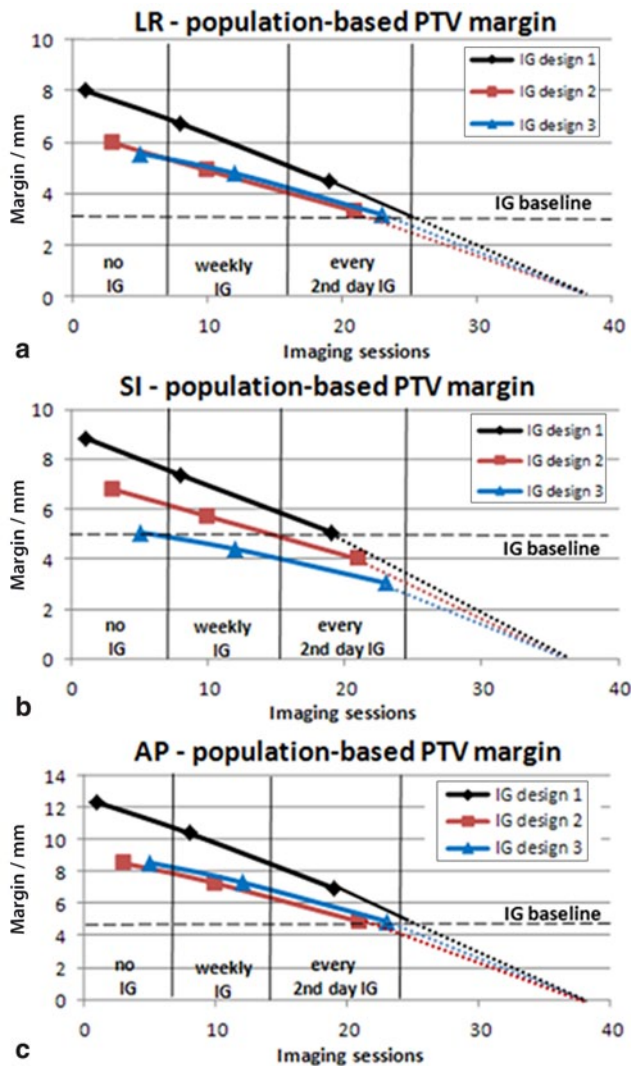


Fig. 3 a–c Margin reduction according to the imaging frequency and margins that would be needed in each dimension to accommodate the residual errors. *AP* anterior–posterior, *SI* superior–inferior, *LR* left–right, *IG* image guidance, *PTV* planning target volume

Many studies have demonstrated an improvement in the frequency and grades of GI and GU toxicity with advances in dose conformity and tumor targeting [35, 36]. TomoTherapy makes it possible to minimize the bladder volume irradiated with high doses by producing steeper high-dose gradients than LINAC-based step-and-shoot IMRT. Our findings are likely nonsignificant due to the limited number of patients. The asymptotic significance according to Pearson's chi-square test ($p=0.078$) suggests a trend toward a difference in GU toxicity between these two IMRT techniques.

Conclusion

High-precision IGRT of prostate cancer should be based on implantation of intraprostatic FMs. These are helpful for

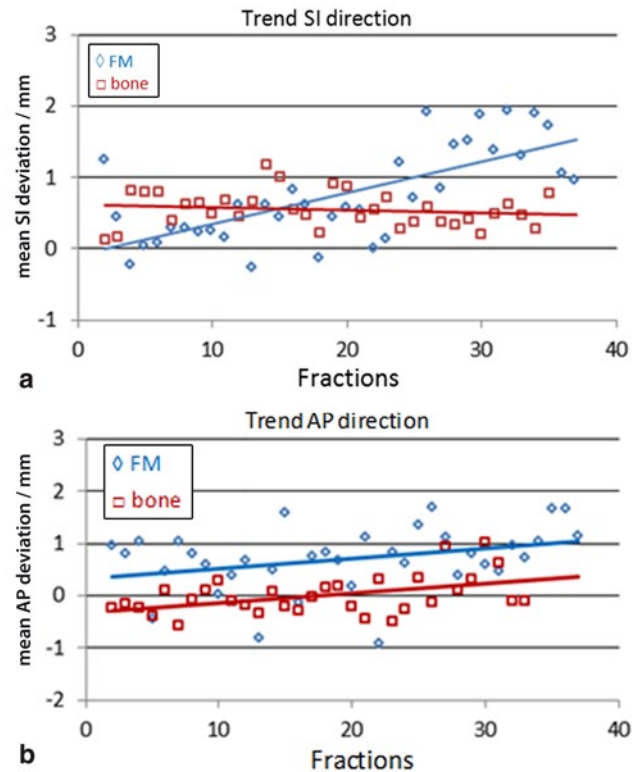


Fig. 4 a Mean superior–inferior (*SI*) deviation from bone and fiducial marker (*FM*) fusion over whole treatment time. b Mean anterior–posterior (*AP*) deviation from bone and FM fusion over whole treatment time

detecting interfractional variability in prostate position and avoiding movement of the bladder neck toward a higher isodose level. In addition, although IG frequency is decreased, narrow margins can be preserved. The combination of small margins, less-frequent imaging, and still-precise RT technologies allowing for high tumor control rates and low late toxicity paves the way for hypofractionated protocols in the future. Besides reducing the dose to the entire bladder, omitting hotspots in the bladder neck will probably lower the risk of bladder toxicity and should therefore be an important aspect in treatment plan optimization. More studies are needed to validate this strategy.

Acknowledgments SD conceived the study; acquired, analyzed, and interpreted the data; reviewed the literature; and wrote the manuscript. MS was responsible for study design; involved in collection, interpretation, and statistical analysis of data; and assisted with drafting the manuscript. TGW was responsible for coordinating the study and treatment planning; he edited the manuscript and performed a critical revision of scientific content. HS critically reviewed the manuscript. SF helped revising the draft. All authors read and approved the final manuscript.

Compliance with ethical guidelines

Conflict of interest S. Drozd, M. Schwedas, H. Salz, S. Foller and T.G. Wendt state that there are no conflicts of interest.

All studies on humans described in the present manuscript were carried out with the approval of the responsible ethics committee and in accordance with national law and the Helsinki Declaration of 1975 (in its current, revised form). Informed consent was obtained from all patients included in studies.

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