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Research Article

Evaluation of Inter- and Intra-Fractional Motion of Prostate During Radiation Therapy

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Abstract

Background: Monitoring the motion of the patient and the patient's internal organs during radiation treatment is of paramount importance for the evaluation of the treatment setup margins and the treatment accuracy. In radical treatment of prostate cancer patients, the inter-fractional and intra-fractional prostate motion was evaluated, and the appropriate setup margins were determined.

Patients and Methods: Nine radically treated patients with prostate carcinoma were included in the study. They were all treated using Volumetric Modulated Arc Therapy (VMAT) coupled with image guidance (IGRT). All the patients had three fiducial markers implanted into the prostate prior to the treatment, which were used for prostate localization on the Electronic Portal Imaging Device (EPID). Verification and correction of treatment position by analysis of orthogonal portal images was performed on a weekly basis. All translational movements were evaluated in Anterior-Posterior (AP), Medio-Lateral (ML) and Superior-Inferior (SI) directions of patient and implanted fiducal markers. Based on daily imaging before and after treatment, systematic (Σ) and random (σ) errors of patient's position were calculated, and the appropriate safety margins were calculated using the van Herk formula.

Results: Based on bony landmark alignment, inter-fractional displacements were more pronounced in the AP and ML directions, while based on fiducial markers alignment, the displacements in the AP and SI directions prevailed. Overall, larger inter-fraction displacements were found when aligning to fiducial markers. Based on fiducial marker alignment, the average inter-fraction displacements and the standard deviations were -0.11 ± 1.79 mm, -1.07 ± 1.65 mm, and -0.65 ± 1.56 mm in AP, SI and ML directions, while when aligning to bony landmarks, the average inter-fraction displacements and the standard deviations were -0.91 ± 1.33 mm, -0.01 ± 1.39 mm and -0.32 ± 1.46 mm in AP, SI and ML directions. The size of the safety margin according to van Herk's formula on implanted fiducal markers are 3.13 mm, 3.44 mm and 3.23 mm in AP, SI and ML directions.

The results of the study show that a 3 mm safety margin from the Clinical Target Volume (CTV) to the Planning Target Volume (PTV) assures that in 90% of all treatment fractions, CTV receives 95% or more of the prescribed cumulative dose.

Keywords: Intra-Fraction and Inter-Fraction Motion; Prostate Cancer; Radiotherapy; Safety Margins

Introduction

In Slovenia prostate cancer represents most common cancer in men with 19% new cancer cases every year. In the period from 2010-2014, the average incidence in Slovenia was approximately 1480 new patients per year [1]. As it is the case throughout the world, the incidence of prostate cancer in Slovenia is increasing, which can be attributed to aging of the population and particularly to programs for early diagnosis with the determination of Prostate Specific Antigen (PSA) [2]. Nowadays, more demanding and more precise irradiation techniques allow for greater precision of irradiation and thus the use of higher total doses per target volume

with lower radiation burden on adjacent healthy tissues [3]. In the case of radical irradiation of prostate cancer, high total irradiation doses are used, which can exceed the tolerances of adjacent healthy tissues, especially the rectum and urethra. For this reason, it is very important to accurately adjust the irradiation fields to the target volume, and this can ensure optimal protection of organs at risk [4-6]. During verification process which can provide more precise irradiation of the target volumes the process of Image-Guided Radiotherapy (IGRT) is used. It includes daily monitoring and tracking of the patient's or tumor's settings and allows appropriate adjustment based on deviations from the planned irradiation treatment plan [7,8]. With the use of IGRT we compare Electronic Portal Images (EPI) of patients on treatment machine with reference images (digitally reconstructed radiograph-DRR) recorded in the planning process and preparation for irradiation on the simulator (Figure 1).

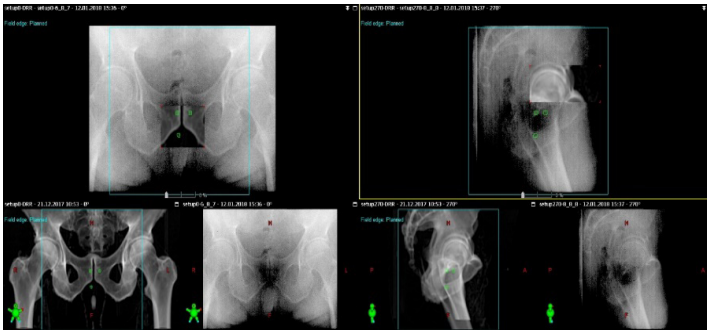

Figure 1: Registration matching process between EPI and DRR image in PortalVision program.

The development of Three-Dimensional Conformal Radiotherapy (3D-CRT) and Intensity-Modulated Radiotherapy (IMRT) has enabled delivery of escalated doses to the tumor target with sparing of the Organs at Risk (OAR).

With accurately positioning the patient, the proper settings of image control and implementation of appropriate movements, we can ensure proper and best matching of the planning target volume during irradiation. The systematic implementation of IGRT reduces the geometric abnormalities that occur in the patient's changes in setting between each fraction and the anatomical changes due to normal organ movements or as the consequence of the treatment itself. An error may occur between the individual irradiation fractions as inter-fractional displacement or at the time of single fraction as intra-fractional shift [9,10].

Inter-fractional shifts represent movements between the individual fractions of irradiation and reflect the daily deviations between the position of the isocentre on the medical linear accelerator and the defined isocentre of the irradiation plan. Inter-fractional shift is the difference between the position of patient or the tumor derived from EPID during the irradiation fraction and the corresponding alignment relative to the reference DRR image representing the irradiation plan [11]. The most common causes for inter-fractional shifts are changes in the geometric settings of the patient on the irradiation table, changed target volumes (increase or decrease in the body weight of the patient, increase or decrease in the mass of tumor), and deviations in the daily settings of fixation aids for patient installation [12]. With the on-line IGRT process, we can reduce the values of inter-factional movements (systematic and random errors) to a minimum level [13].

Movements that occur within a single irradiation fraction are called intra-fractional movements. They represent the displacement of bone structures or organs according to the position of the isocentre with a previously known position prior to irradiation in a single treatment fraction. They are divided into external set-up variations and internal organ motion [12]. The extent of movement of a patient or organs within one fraction can significantly affect the design of the safety margins in irradiation. In the case of major intra-fractional movements, larger safety margins should be used, which in turn results in a higher OAR volumes and their higher dosage load, which can lead to more frequent undesirable side effects of irradiation [14]. The causes affecting the intra-fractional movements are divided into the movements of the patient due to the uncomfortable forced position during the irradiation process and the movements of the organs in the patient, such as movement of the diaphragm during respiration [15], or in the case of prostate cancer patients' irradiation differences in daily filling of bladder and rectum [16,17].

Patients and Methods

Nine prostate cancer patients with implanted fiducial markers treated with radical intent between October 2014 and August 2015 were enrolled in this study. Patients setup was carried out on a Computer Tomography (CT) simulator. Patients were ordered to first empty urinary bladder and then drink 0.5 to 1 litre of water 30 minutes to 1 hour prior to the setup session. Patients were informed that this procedure needs to be repeated before every treatment fraction in order to assure similar urinary bladder volume compared to the one during the setup session.

CIVCO Combifix™ immobilizing devices (Civco Medical Solutions, Kalona, IA, USA) - Kneefix and Feetfix - were used at setup for immobilizing patients in supine position. The reference isocenter was chosen to match one of the fiducial markers previously implanted into the prostate, and the position of the anterior and lateral laser cross-hairs were tattooed for a reproducible patient setup during treatment. All the patients were treated on a linear accelerator Varian Unique Performance Edition (Varian Medical Systems, Palo Alto, CA, USA) using Volumetric Modulated Arc Therapy (VMAT) coupled with on-line image guidance, allowing for patient imaging and repositioning prior to every treatment fraction.

At every treatment fraction, patient was set up in an anatomically identical position during patient setup and positioned into the reference isocenter using in-room lasers. Before every treatment, two orthogonal portal images (AP and lateral) were taken using EPID, and after 2D/2D alignment of portal images with the DRR's patient's position was refined. The translational shifts needed to align the portal images with DRR's images, were recorded as inter-fractional positional errors. The patient was then irradiated and after treatment, two additional orthogonal portal images were taken after every second treatment fraction. The translational shifts needed to align the pair of portal images taken prior to the treatment with those taken after the treatment were recorded as intra-fractional positional errors.

Altogether, 3336 translational shifts on 684 portal images were analyzed. PortalVision™ aS1000 imager (Varian Medical System, Palo Alto, USA) was used for obtaining electronic portal images (1024×768 pixels). In the accompanying PortalVision application, all the translational shifts in the AP, SI and ML directions were calculated. Negative values refer to shifts in the posterior, inferior and left directions, while positive to the shifts in the anterior, superior and right directions.

Prior to the start of the treatment, each patient signed an informed consent form notifying that he has agreed with the purpose of the study and its protocol. The study was approved by the Republic of Slovenia National Medical Ethics Committee at the Ministry of Health (no. 80-07-14, dated September 19, 2014).

Statistical Analysis

The optimal values of safety margins were calculated using the van Herk formula. To assure that in 90% of all cases, the Clinical Target Volume (CTV) receives 95% or more of the prescribed cumulative dose, van Herk formula sets the safety margin width to $2.5\,\Sigma + 0.7\,\sigma$, i.e., 2.5 times the standard deviation of the systematic error plus 0.7 times the value of the random error [18,19]. Pearson correlation coefficient (r_{xy}) was used to determine the strength of the linear dependence between inter- and intra-fraction translational shifts in each direction, or between translational shifts obtained by using either bony landmarks or fiducial markers for image registration. Microsoft Office Excel 2010 (Microsoft, Redmond, USA) and GNU R (R Core Team, Vienna, Austria) was used for statistical processing and graphing. Values of $p < 0.05$ were considered as statistically significant.

Results

Evaluation of Inter-Fractional Shifts

Table 1 shows inter-fractional shifts in the AP, SI and ML directions when registering either bony anatomy or fiducial markers, averaged over the group of 9 patients. M_p denotes the group systematic error or the overall mean, Σ_p denotes standard deviation of group systematic error, σ_p denotes the random error.

	Interfractional shifts					
	Bony anatomy			Fiducial markers		
Direction [mm]	**AP**	**SI**	**ML**	**AP**	**SI**	**ML**
Average shift (Mp)	-1.06	0.18	1.62	-2.58	4.12	1.57
Average standard deviation (SDp)	2.4	1.52	1.96	3.05	1.98	2.07
Systematic error (Σp)	3.09	2.23	1.72	3.29	5.11	2.69
Random error (σp)	2.46	1.55	2.45	3.12	2.03	2.54
AP - Anterior-Posterior direction, SI - Superior-Inferior direction, ML - Medial-Lateral direction, M - average population shifts, SD - average standard deviation, Σp - population systematic error, σp - population random error.						

Table 1: Interfractional position shifts.

When registering fiducial markers, 68.95% of all inter-fractional shifts in the AP direction were in the posterior direction, 23.74% were in the anterior direction, and in 7.31% of all cases, no shift was necessary. In the SI direction, 72.15% of all shifts were in the superior direction, 20.09% were in the inferior direction, and in 7.76% of all cases, no shift was necessary. In the ML direction, 60.27% of all shifts were towards patient's right, 24.20% were towards patient's left, and in 15.53% of all cases, no shift was necessary.

Evaluation of Intra-Fractional Shifts

Table 2 shows intra-fractional shifts in the AP, SI and ML directions when registering either bony anatomy or fiducial markers, averaged over the group of 9 patients. M_p denotes the group systematic error or the overall mean, Σ_p denotes standard deviation of group systematic error, σ_p denotes the random error.

	Intrafractional shifts					
	Bony anatomy				**Fiducial markers**	
Direction [mm]	**AP**	**SI**	**ML**	**AP**	**SI**	**ML**
Average shift (Mp)	-0.91	-0.01	-0.32	-0.11	-1.07	-0.65
Average standard deviation (SDp)	1.33	1.39	1.46	1.79	1.65	1.56
Systematic error (Σp)	0.36	0.59	0.76	0.59	0.82	0.81
Random error (σp)	1.38	1.44	1.55	1.87	1.75	1.67
AP - Anterior-Posterior direction, SI - Superior-Inferior direction, ML - Medial-Lateral direction, M - average population shifts, SD - average standard deviation, Σp - population systematic error, σp - population random error.						

Table 2: Results of intra-fractional shifts based on evaluating either bony anatomy or fiducial marker registration.

When registering to bony anatomy, 45.13% of all intra-fractional shifts in the AP direction were in the posterior direction, 33.63% in the anterior direction, and in 21.24% of all cases, no shift was necessary. In the SI direction, 61.06% of all shifts were in the inferior direction, 18.58% in the superior direction, and in 20.35% of cases, no shift was required. In the ML direction, 50.44% of shifts were towards the patient's left, 27.43% to the right, and in 22.12%, no shift was required. Registration on fiducial markers yields qualitatively similar results.

Determining Safety Margins for Inter-Fractional Shifts

Table 3 shows safety margins derived from inter-fractional shifts according to van Herk formula. When registering to bony anatomy, the margins in the AP, SI and ML directions are 9.44 mm, 6.65 mm and 6.02 mm, respectively.

	Safety margins calclulated from inter-fractional shifts					
	Bony anatomy				**Fiducial markers**	
Direction [mm]	**AP**	**SI**	**ML**	**AP**	**SI**	**ML**
PTV - CTV margin	9.4	6.7	6	10.4	14.19	8.5
AP - Anterior-Posterior direction, SI - Superior-Inferior direction, ML - Medial-Lateral direction.						

Table 3: Safety margins derived from inter-fractional shifts according to van Herk formula.

When registering to fiducial markers, safety margins in the AP, SI and ML directions are 10.41 mm, 14.19 mm and 8.50 mm, respectively.

Determining Safety Margins for Intra-Fractional Shifts

1. Table 4 shows safety margins derived from intra-fractional shifts according to van Herk formula. When registering to bony anatomy, the margins in the AP, SI and ML directions are 1.88 mm, 2.47 mm and 3.00 mm, respectively. When registering to fiducal markers in prostate, the margins in the AP, SI and ML directions are 2.79 mm, 3.27 mm and 3.19 mm, respectively.

	Safety margins calculated from intra-fractional shifts					
	Bony anatomy			**Fiducial markers**		
Direction [mm]	AP	SI	ML	AP	SI	ML
Safety margin	1.9	2.5	3	2.8	3.27	3.2
AP - Anterior-Posterior direction, SI - Superior-Inferior direction, ML - Medial-Lateral direction.						

Table 4: Safety margins derived from intra-fractional shifts according to van Herk formula.

	Correlation factor between inter-fractional and intra-fractional movements of bone structures and fiducial markers		
Direction [mm]	**AP**	**SI**	**ML**
Correlation of inter-fractional movement between bony structures and fiducial markers	0,67 ($p < 0.005$)	0,61 ($p < 0.005$)	0,94 ($p < 0.005$)
Correlation of intra-fractional movement between bony structures and fiducial markers	0,06 ($p = 0.420$)	0,30 ($p < 0.005$)	0,66 ($p < 0.005$)
AP - Anterior-Posterior Direction, SI - Superior-Inferior direction, ML - Medial-Lateral direction, rxy - correlation factor.			

Table 5: Total values of correlation factors between inter-fractional and intra-fractional movements of bone structures and fiducial markers.

From the Table 5 we can see that correlation factors comparing between inter-fraction motion of bony anatomy and fiducial markers show the mean correlation (r=0.40-0.69) in AP and SI directions, while the correlation factor in ML direction is r=0.94 and represents a strong positive correlation.

The values of p show statistically significant correlation in intra-fractional movements in SI ($p < 0.001$) and ML ($p < 0.001$) directions, whereas for the movements in the AP direction differences were not statistically significant ($p = 0.42$).

Discussion

In an IGRT setup values for safety margins can be obtained by applying van Herk formula to the intra-fractional positional shifts based on registration of bony anatomy and fiducial markers. Systematic and random errors due to inter-fractional motion is minimised by daily imaging and patient repositioning. The usage of the on-line correction method allows us the reduction of the overall setup error (systematic and random) down to approximately 1 mm [13]. Inter-fractional motion enters the estimate for safety margins in the case when on-line patient imaging and repositioning is not used. The estimate for safety margins can be further improved by including the uncertainty in contouring of the target and the OARs. It has been shown that other uncertainties, e.g. the uncertainties in contouring the fiducial markers and the movement of fiducial markers inside the prostate are less important than the errors in patient setup and the prostate motion [20]. It is known that the prostate position with respect to the bony anatomy can vary [21].

In a study of the influence of inter-fractional motion of prostate by Kupelian et al. [16], the authors found out that daily variations in the rectum and bladder volume result in significant variation in dose distribution during the treatment. By implanting fiducial markers into the prostate and using Electronic Portal Imaging (EPI) system we can assure that the treatment field does not miss the target [4]. Analyses of fiducial marker movement within the prostate have shown that this movement is insignificant, in the sub- millimetre range [22,23].

In our study, mean values (M_p) and Standard Deviations (SD) of inter-fractional motion in AP, SI and ML directions were -1.06 ± 2.4 mm, 0.18 ± 1,52 mm and 1.69 ± 1.96 mm, respectively. This is consistent with the M_p values in the AP direction in the study by Nedervan et al. [24], although the values for the systematic and random error in this study are smaller in all directions. The values

obtained for inter-fractional motion with reference to the bony anatomy are also consistent with the results obtained by Ikeda et al. [25], who obtained -2.0 mm for the M_p value in the AP direction. The values of Σ obtained in this study are in all directions comparable with the values, obtained in a study which examined the impact of the no-action-level (NAL) protocol for reducing systematic error [26]. The values of Σ_p obtained in this study in the AP (3.09 mm), SI (2.23 mm) in ML (1.72 mm) directions are consistent with the results of other studies using the same patient positioning system (reference points and isocentric lines) [24,27]. The magnitude of the inter-fractional prostate motion in the AP direction is important, as shifts in the posterior direction can induce an increase in rectal toxicity. The shifts in AP direction obtained in this study are also comparable with the studies in which the patients were positioned in prone position, and in which a thermoplastic mask was used for patient fixation [24,25]. Analysing inter-fractional motion, using fiducial markers as reference, yields larger values for Mp than using bony anatomy as reference [28,29]. The largest difference between the values for inter-fractional motion based on bony anatomy and fiducial markers is in the SI direction (M_p=0.18 mm vs. M_p=4.12 mm), which is consistent with other studies [28].

Using an on-line image-guided setup correction protocol is the only way to reduce both the systematic and the random inter-fraction setup error resulting from the motion of prostate and bony structures. The magnitude of the safety margin is related to the frequency of the IGRT procedure [29,30]. Based on the results of this study, employing daily imaging and setup correction would significantly reduce inter-fractional shifts which arise due to irreproducibility of the exact patient setup.

Inter-fractional shifts are mostly influenced by the variation in bladder and rectum volume during the treatment course. The impact is most pronounced in prostate shifts in AP and SI directions, as has been shown by Magnetic Resonance Imaging (MRI) [16]. A standardised procedure for consuming a given amount of liquid before each treatment session has an important role in assuring a reproducible bladder volume, as it reduces the displacement of target and organs at risk from their position during the initial set-up. Employing such a protocol reduces large inter-fractional shifts, but does not eliminate prostate motion completely [31].

Mean values (Mp) and Standard Deviations (SD) of inter-fractional shifts based on fiducial markers show an agreement with the results obtained by Schallenkamp et al., [32] as do the results of SD of intra-fractional fiducial marker displacement, the largest being in the AP direction (±1.79 mm), being followed by SI (±1.65 mm) and MLdirections (±1.56 mm) [5]. The values obtained for Σ_p of intra-fractional displacement in SI and AP directions are also comparable with the published values [5,33]. The smallest and the largest values of σ for intra-fractional displacement were found in the ML and AP directions, respectively, which is consistent with a study in which they used an endo-rectal balloon [34]. Overall, intra-fractional displacements of fiducial markers were found to be smaller than the inter-fractional displacements, which is in agreement with the published results [15,35], even though an ultrasound system for prostate localization was used in the first study.

The values of Σ_p obtained in this study are comparable with the published values for intra-fractional shift in the AP direction, while the random errors obtained are smaller than those reported in similar studies [5,29]. A study of intra-fractional motion of prostate fiducial markers employing fluoroscopic imaging before and after each treatment session found out that the most pronounced motion M_p is in the SI direction, which is in agreement with our findings [36]. Smaller values of SD and random errors also result in a smaller value for the safety margin.

The value for the CTV-PTV safety margin based on the inter-fraction motion of bony anatomy are comparable with the results of Litzenberg et al. [27] who suggest the values of 8.2 mm (ML), 12.5 mm (SI), and 5.7 mm (AP). In our study, the values obtained for the safety margin in the ML and SI directions are slightly smaller, while a slightly larger safety margin is needed in the AP direction. A study by Beltran et al. [37] which suggests the values of 7.3 mm (ML), 8.1 mm (SI) and 10.5 mm (AP) matches our results in the SI and ML directions even better.

Using intra-fractional motion of bony anatomy as the basis for the CTV-PTV safety margin yields the values of 1.88 mm (AP), 2.47 mm (SI) and 3.0 mm (ML). Similar studies which examined the clinical implications of intra-fractional prostate motion recommend a 3 mm safety margin [5,15,27]. The analysis of the intra-fractional motion based on fiducial markers in this study confirms that a 3 mm safety margin is safe for the clinical practice. Melancon et al. [38] have also concluded that the value of 3 mm is sufficient to compensate for the intra-fractional prostate motion, while other studies [27,32] suggest the values of 3.4 mm (AP and SI), and 2.7 mm (ML), which is similar to the results we obtained.

The values of correlation factors between inter- and intra-fraction motion in a given direction obtained in this study show a low correlation (r = 0.20-0.39) between inter- and intra-fraction motion of bony anatomy in the AP and ML directions and negligible correlation (r = 0.01-0.19) in all other cases, indicating that generally there is no correlation between inter- and intra-fraction motion of bony structures. In a similar study [35] the authors found still negligible (0.191) yet statistically significant correlation between inter- and intra-fraction motion in SI-direction, and even lower and statistically insignificant values in other directions. The correlation between inter-fraction motion of bony anatomy and fiducial markers in this study was found to be medium (r = 0.40-0.69) and statistically significant in the AP and ML directions and very high (r = 0.94) and statistically significant in the SI direction. The latter is comparable with the results of another study [37], in which the authors found high positive correlation (r = 0.79).

Evaluation of geometric errors during the treatment process, in particularly monitoring patient position and patient's organ positions, represents a necessary part of the radiotherapy practice. Both factors influence the accuracy of dose delivery, which is limited by the target motion, body inhomogeneity, beam geometry and set-up errors.

Applying the van Herk formula on the results of the intra-fraction motion of fiducial markers, we obtained the following values for CTV-PTV safety margin: 2.8 mm (AP), 3.3 mm (SI) and 3.2 mm (ML), which can be approximated by isotropic margin of 3 mm. When using the intra-fraction motion of bony anatomy as the basis, we arrive at somewhat smaller values: 1.9 mm (AP), 2.5 mm (SI) and 3.0 mm (ML). This indicates that an independent intra-fraction prostate motion relative to the bony anatomy exists, but using exclusively bony anatomy as a reference is not sufficient, as has been noted before. The analysis of intra-fraction motion of fiducial markers can serve as a basis of safety margin reduction when employing an on-line IGRT protocol.

The results are based on a population-wide statistics of the studied cohort and assuming that daily on-line IGRT protocol for patient set-up is used. Using IGRT allows reducing the systematic and random set-up errors of both prostate and bony anatomy to a minimal level. These results are in agreement with other published recommendations which suggest a 3 mm CTV-PTV safety margin to compensate for the intra-fraction motion of bony anatomy and fiducial markers. Van Herk formula assures a minimum CTV coverage of 95% of the prescribed dose at least 90% of the time. Reducing safety margin to this minimal value allows reducing of OAR toxicity and less side effects of radiotherapy treatment.

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References

1. Cancer in Slovenia 2014. Ljubljana: Institute of Oncology Ljubljana, Epidemiology and Cancer Registry, Cancer Registry of Republic of Slovenia, 2017.
2. Kragelj B, Borštnar S, Sedmak B (2009) Urogenital cancer: Prostate cancer. In: Novaković et al., Editors. Oncology: Research, diagnosis and treatment of cancer. Ljubljana: Mladinska knjiga. 347-356.
3. Thariat J, Hannoun-Levi JM, Myint AS, Vuong T in Gérard JP (2013) Past, present, and future of radiotherapy for the benefit of patients. Nat Rev Clin Oncol 10: 52-60.
4. Grabec D, Gačnik U in Kragelj B (2011) Precise irradiation of locally advanced high-risk prostate cancer. Oncology 1: 10-13.
5. Aubry JF, Beaulieu L, Girouard LM, Aubin S, Tremblay D, et al. (2004) Measurements of intrafraction motion and interfraction and intrafraction rotation of prostate by three-dimensional analysis of daily portal imaging with radiopaque markers. Int J Radiat Oncol Biol Phys 60: 30-39.
6. Peeters ST, Heemsbergen WD, van Putten WL, Slot A, Tabak H, et al. (2005) Acute and late complications after radiotherapy for prostate cancer: Results of a multicenter randomized trial comparing 68 Gy to 78 Gy. Int J Radiat Oncol Biol Phys 61: 1019-1034.
7. The Royal College of Radiologists (2012) On target: ensuring geometric accuracy in radiotherapy. London: The Royal College of Radiologists: 10-15.
8. Hukku S, Halder S (2004) Image guided radiation therapy. Apollo Medicine 1: 146-147.
9. Amelio D, Winter M, Habermehl D Jäkel O, Debus J, et al. (2013) Analysis of inter- and intrafraction accuracy of a commercial thermoplastic mask system used for image-guided particle radiation therapy. J Radiat Res 54: 69-76.
10. Gupta T, Narayan Anand C (2012) Image-guided radiation therapy: Physician's perspectives. J Med Phys 37: 174-182.
11. Xu F, Wang J, Baits S, Xu QF in Shen YL, Zhong RM (2008) Interfractional and intrafractional setup errors in radiotherapy for tumors analyzed by cone-beam computed tomography. Chinese J Cancer 27: 372-376.
12. Stroom JC, Kroonwijk KL, Koper PCM, van Dieren EB, Heijemn BJM (2000) Detection of internal organ movement in prostate cancer patients using portal images. J Med. Phys 27: 452-461.
13. Van der Vight LP, van Lin ENJT, Spitters-Post I, Visser AG, Louwe RWJ (2009) Off-line setup corrections only marginally reduce the number of on-line corrections for prostate radiotherapy using implanted gold markers. Radiother Oncol 90: 359-366.
14. Chow JCL, Jiang R, Markel D (2009) The effect of intrafraction prostate motion on IMRT plans: a dose-volume histogram analysis using a Gaussian error function model. J Appl Clin Med Phys 10: 79-95.
15. Britton KR, Takai Y, Mitsuya M, Nemoto K, Ogawa Y, et al. (2005) Evaluation of Inter- and Intrafraction Organ Motion during Intensity Modulated Radiation Therapy (IMRT) for Localized Prostate Cancer Measured by a Newly Developed On-board Image-guided System. Radiat Medicine 23: 14-24.
16. Kupelian PA, Langen KM, Zeidan OA (2006) Daily variations in delivered doses in patients treated with radiotherapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 66: 876-882.
17. Chen Z, Yang Z, Wang J, Hu W (2016) Dosimetric impact of different bladder and rectum filling during prostate cancer radiotherapy. Radiat Oncol 11: 103.
18. Van Herk M (2004) Errors and Margins in Radiotherapy. Seminars in Radiation Oncology 14: 52-64.
19. Remeijer P, van Herk M (2006) Imaging for IMRT. In: Bortfeld T, Schmidt-Ullrich R, De Neve W, Wazer DE, editors. Image-Guided IMRT. Springer-Verlag Berlin Heidelberg: 19-30.
20. Dehnad H, Nederveen AJ, van der Heide UA, van Moorselaar RJ, Hofman P, et al. (2003) Clinical feasibility study for the use of implanted gold seeds in the prostate as reliable positioning markers during megavoltage irradiation. Radiother Oncol 67: 295-202.
21. De Courvoisier R, Tucker SL, Dong L, Mohan R, Cheung R, et al. (2005) Increased risk of biochemical and local failure in patients with distended rectum on the planning CT for prostate cancer radiotherapy. Int J Radiat Oncol Biol Phys 62: 965-973.
22. Poggi MM, Gant DA, Sewchand W, Warlick W (2003) Marker seed migration in prostate lokalization. Int J Radiat Oncol Biol Phys 56: 1248-1254.

23. Pouliot J, Aubin M, Langen KM, Liu YM, Pickett B, et al. (2003) (Non)-migration of radiopaque markers used for on-line localization of the prostate with an electronic portal imaging device. Int J Radiat Oncol Biol Phys 56: 862-866.

24. Nederveen AJ, van Heide UA, Dehnad H, van Moorselaar RJ, Hofman P. et al. (2002) Measurements and clinical consequences of prostate motion during a radiotherapy fraction. Int J Radiat Oncol Biol Phys 53: 206-214.

25. Ikeda I, Mizowaki T, Sawada Y, Nakata M, Norihisa Y, et al. (2014) Assessment of interfractional prostate motion in patients immobilized in the prone position using a thermoplastic shell. J Radiat Res 55: 168-174.

26. De Boer, van Os MJH, Jansen PP, Heijmen BJM (2005) Application of the no action level (NAL) protocol to correct for prostate motion based on electronic portal imaging of implanted markers. Int J Radiat Oncol Biol Phys 61: 969-983.

27. Litzenberg DW, Balter JM, Hadley SW, Sandler HW, Willoughby TR, et al. (2006) Influence of intrafraction motion on margins for prostate radiotherapy. Radiat Oncol Biol Phys 65: 548-553.

28. Jani KR, Bhavsar D, Gajjar S, Patel V, Krishnappan C, et al. (2011) Daily Evaluation of prostate position by gold marker based image guided radiotherapy (IGRT) in prostate cancer patients. Int J Radiat Oncol Biol Phys 7: S766.

29. Graf R, Wust P, Budach V in Boehmer D (2009) Potentials of on-line repositioning based on implanted fiducial markers and electronic portal imaging in prostate cancer radiotherapy. Radiat Oncol 4: 13.

30. Kupelian PA, Langen KM, Willoughby TR, Zedian OA, Meeks SL (2008) Image-guided radiotherapy for localized prostate cancer: Treating a moving target. Semin Radiat Oncol 18: 58-56.

31. Langen KM, Willoughbry TR, Meeks SL, Santhanam A Cunningham A, et al. (2008) Observations on real-time prostate gland motion using electromagnetic tracking. Int J Radiat Oncol Biol Phys 71: 1084-1090.

32. Schallenkamp JM, Herman MG, Kruse JJ, Pisansky TM (2005) Prostate position relative to pelvic bony anatomy based on intraprostatic gold markers and electronic portal imaging. Int J Radiat Oncol Biol Phys 63: 800-811.

33. Kotte A, Hofman P, Lagendijk J, van Vulpen M, van der Heide UA (2007) Intrafraction motion of the prostate during external-beam radiation therapy: analysis of 427 patients with implanted fiducial markers. Int J Radiat Oncol Biol Phys 69: 419-425.

34. Steiner E, Georg D, Golden G, Stock M (2013) Prostate and patient intrafractional motion: Impact on treatment time-dependent planning margins for patients with endorectal balloon. Int J Radiat Oncol Biol Phys 86: 755-761.

35. Huang E, Dong L, Chandra A, Kuban DA, Rosen II, et al. (2002) Intrafraction prostate motion during IMRT for prostate cancer. Int J Radiat Oncol Biol Phys 53: 261-268.

36. Shimizu S, Shirato H, Kitamura K, Shinohara N, Harabayashi T, et al. (2000) Use of an implanted marker and real-time tracking of the maker for the positioning of prostate and bladder cancers. Int J Radiat Oncol Biol Phys 48: 1591-1597.

37. Beltran C, Herman MG in Davis BJ (2008) Planning target margin calculations for prostate radiotherapy based on interfraction and intrafraction motion using four localization methods. Int J Radiat Oncol Biol Phys 70: 289-295.

38. Melancon AD, O'Daniel JC, Zhang L, Kudchadker RJ, Deborah A, et al. (2007) Is a 3-mm intrafractional margin sufficient for daily image-guided intensity-modulated radiation therapy of prostate cancer? Radiother Oncol 85: 251-259.