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Displacements of fiducial markers in patients with prostate cancer treated with image guided radiotherapy: A single-institution descriptive study

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ABSTRACT

Aim: To describe daily displacements when using fiducial markers as surrogates for the target volume in patients with prostate cancer treated with IGRT.

Background: The higher grade of conformity achieved with the use of modern radiation technologies in prostate cancer can increase the risk of geographical miss; therefore, an associated protocol of IGRT is recommended.

Materials and methods: A single-institution, retrospective, consecutive study was designed. 128 prostate cancer patients treated with daily on-line IGRT based on 2D kV orthogonal images were included. Daily displacement of the fiducial markers was considered as the difference between the position of the patient when using skin tattoos and the position after being relocated using fiducial markers. Measures of central tendency and dispersion were used to describe fiducial displacements.

Results: The implant itself took a mean time of 15 min. We did not detect any complications derived from the implant. 4296 sets of orthogonal images were identified, 128 sets of images corresponding to treatment initiation were excluded; 91 (2.1%) sets of images were excluded from the analysis after having identified that these images contained extreme outlier values. If IGRT had not been performed 25%, 10% or 5% of the treatments would have had displacements superior to 4, 7 or 9 mm respectively in any axis.

Conclusions: Image guidance is required when using highly conformal techniques; otherwise, at least 10% of daily treatments could have significant displacements. IGRT based on fiducial markers, with 2D kV orthogonal images is a convenient and fast method for performing image guidance.

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1. Background

Prostate cancer is the leading cause of cancer incidence and the third cause of cancer mortality among Colombian males.[1] The role of radiation treatment in prostate cancer has increased in the last decade, since radiotherapy achieves a similar tumor probability control with a better toxicity profile when compared with radical prostatectomy.[2] Nowadays, the use of modern radiation techniques in prostate cancer treatment is widely recognized as a gold standard.[3] IMRT enhances conformity, which allows increasing doses administered to the tumor while diminishing doses administered to organs at risk.[4]

The higher grade of conformity achieved with IMRT can increase the risk of geographical miss[5]; therefore, a protocol of IGRT is recommended when using IMRT or other highly conformal techniques. It is well known that bony structures and tumor target volumes may have significant displacements in relation to the skin tattoos traditionally used for patient setup in conventional treatments; therefore, highly conformal techniques should be performed under new conditions such as IGRT protocols. IGRT applied on daily treatments can translate into a decrease in the margins required for PTV, which will finally turn into a reduced radiation dose for organs at risk and a consequent decreased toxicity.[6]

In traditional IGRT treatments, the patient can be daily aligned with conventional radiographs. This strategy reduces the geometric uncertainties, since it guarantees that bony structures are located in the same position. However, the tumor volume may have significant displacements in relation to the bony structures; hence, daily IGRT based on bony structures is not the ideal solution.[7,8] IGRT based on daily Cone Beam CT (CBCT) warrants that daily tumor anatomy coincides with the anatomy of the treatment plan; yet, it demands longer acquisition times and expertise in image fusion and co-registration. An intermediate alternative is to use fiducial markers inserted on the prostate as a surrogate of the tumor volume.[9] Fiducial markers have been traditionally considered as valid surrogates of a tumor volume, considering that seed migration after implantation is inferior to 1 mm.[10] When using fiducial markers, the image guidance can be performed based both on CBCT or conventional X-rays.[11]

2. Aim

The aim of this study is to describe daily displacements when using three fiducial markers as surrogates for the target volume in patients with prostate cancer treated with IGRT, and to determine the optimal margin required around the CTV based on our own practice.

3. Materials and methods

3.1. *Patients*

Data of 128 patients with primary prostate cancer treated with on-line IGRT and daily repositioning based on fiducial markers were included. Every patient with prostate cancer and an implanted fiducial marker was included in the study regardless of risk classification, age, use of hormonal therapy, or treatment technique (IMRT or 3D-conformal). Patients with hip replacement or with increased risk of toxicity derived from the implant (patients that had previously developed infections in prostate biopsies, under anticoagulation therapy, with a prosthetic heart valve, previous infectious endocarditis, or heart valve disease) were excluded from the study. Patients with treatments that included pelvic lymph nodes were also excluded from the study.

3.2. *Fiducial markers implant*

An oral and rectal enema and a clear liquid diet were prescribed the day previous to the insertion of fiducials. Antimicrobial prophylaxis was administered with oral ciprofloxacin, starting before the implant, twice a day for three days. Three cylindrical gold seeds were implanted guided by a transrectal ultrasonography using a biopsy needle and a brachytherapy template. Different kinds of seeds were used along the course of the study. Unstriated seeds 0.78 mm diameter and 5 mm in length were initially used, longer unstriated seeds of 8 mm were used afterwards, and finally, most of the patients were implanted with striated seeds of 0.78 mm diameter and 8 mm in length (we subjectively considered that the definitive position of the seed implant was easier to achieve when using striated seeds). The insertion of the seeds was designed in order to create two triangles: the first one in the antero-posterior projection with its base located on the prostate apex, and the other one on the lateral projection with its base located on the posterior wall of the prostate.

3.3. *Simulation and volume delineation*

A CT scan was acquired one week after seed implantation. An oral and rectal enema and a clear liquid diet were prescribed the day previous to the planning CT scan. Bladder contrast was used in all patients. Patients were simulated in a supine position with a foam immobilization device placed below the knees and a universal feet support cushion. The pelvic area was scanned at 3 mm intervals from the fourth lumbar vertebra up to the greater trochanter of the femur. The obtained image data sets were imported into the Eclipse® treatment planning system. The Clinical Target Volume was defined accordingly to the recommendations of the European Organization for Research and Treatment of Cancer (EORTC).[12] PTV was defined by using a tridimensional CTV expansion of 8 mm. Organs at risk were delineated according to international guidelines and included the rectum,[13] bladder[14] and femoral heads.

3.4. *Radiotherapy treatment planning*

IMRT or 3D conformal radiotherapy was prescribed. Dosimetric objectives for the PTV were: V90% ≥ 100% (100% of the PTV volume must receive at least 90% of the prescribed dose), V95% ≥ 95%, V107% ≤ 2%. Dosimetric objectives for bladder and rectum were V40Gy ≤ 60% (the volume of the rectum that receives 40 Gy must be inferior to 60%), V60Gy ≤ 40%, V70Gy ≤ 20%, V75Gy < 15%. Femoral heads were restricted to receive a maximal dose of 50 Gy. The prescribed dose varied between 72 Gy and 78 Gy in 36 to 39 daily fractions, respectively, according to the D'Amico risk classification and the radiation oncologist criteria. Five to seven fields were used. IMRT was administered using the sliding-window technique. The treatment was performed with Varian Clinac IX, equipped with a 120 Millenium Multileaf Collimator (MMLC-120), and an On Board Image (OBI) device capable of performing 2D kV images and 3D CBCT.

3.5. *IGRT treatment*

The patients were asked to arrive to their daily treatments with a full bladder and an empty rectum. Daily on-line IGRT was performed using the OBI device, with 2D kV orthogonal images. These images were fused and co-registered with the Digitally Reconstructed Radiograph (DRR) obtained from the simulation CT, using the anatomy-matching software On-Board Imager version 1.4. Fusion and co-registration were based on fiducial markers. Image fusion and registration were performed by a trained radiation therapist without the presence of a radiation oncologist. However, as a protocol in our institution, off-line review is routinely performed by a radiation oncologist. Prostate displacement and patient setup deviations during daily treatment were manually detected in the X, Y and Z directions, and corrected by automatic coach movements. Rotational deviations inferior to 2 degrees for the roll, pitch or yaw were not corrected. The patient was repositioned when rotational deviations were subjectively considered high.

3.6. *Statistical methods*

A retrospective, consecutive study was designed. Daily displacement of the fiducial markers was considered as the difference between the position of the patient when using skin tattoos and the position of the patient after being relocated using fiducial markers. We assumed that the displacement of the fiducial markers encompasses both the isocenter and prostate displacement. Hence, the mean displacement of the fiducial markers reflects setup errors and interfractional prostate movements. The atypical extreme values for fiducial markers displacements were identified and analyzed using descriptive graphic analyses.

3.7. *Calculation of theoretical optimal margins for PTV*

Individual systematic and random errors were calculated for each patient as the mean and the standard deviation of daily displacements of the fiducial markers. The systematic error for the whole series of patients was calculated as the mean of the individual systematic errors. The random error for the whole series of patients was calculated as the quadratic mean of individual variances.[11] The theoretical margin size was calculated by adding the result of multiplying the systematic error by 2.5 and the random error by 0.7. This theoretical margin was calculated in order to ensure that 90% of the patients receive at least 95% of the prescribed dose.[15]

Table 1 – Descriptive statistics on fiducial markers displacements (absolute values in cm) in 4077 prostate cancer treatments with IGRT based on fiducial markers.

	Fiducial markers displacement (absolute values in cm)		
	X	Y	Z
Mean	0.34	0.30	0.32
Standard deviation	0.30	0.28	0.28
25th percentile	0.1	0.1	0.1
Median	0.3	0.2	0.3
75th percentile	0.5	0.4	0.5
95th percentile	1.0	0.8	0.9
Maximum	1.6	2	1.4

4. Results

Between May 2009 and January 2011, 128 prostate cancer patients were treated with IGRT based on fiducial markers. The procedure itself took a mean time of 15 min. We did not detect any complication derived from the implant. Taking and analyzing the daily kV images increased the overall treatment time in about 3 min per patient. 4296 sets of orthogonal images were identified, 128 sets of images corresponding to treatment initiation were excluded; 91 (2.1%) sets of images were excluded from the analysis after having identified that these images contained extreme outlier values in one or more coordinates that we assumed to correspond in the majority of cases to errors in tattoo laser aligning. Besides, the images related to treatment initiation, a mean of 32.5 sets of orthogonal images were performed to every patient along the radiation treatment.

The mean absolute displacement of fiducial markers was close to 3 mm in all directions, with a maximal value of 2 cm in Y direction. Although the maximal absolute displacement of 2 cm was identified in the Y-axis, the axis with the highest mean absolute displacement was X (Table 1 and Fig. 1). The graphic analysis demonstrated that a non despicable

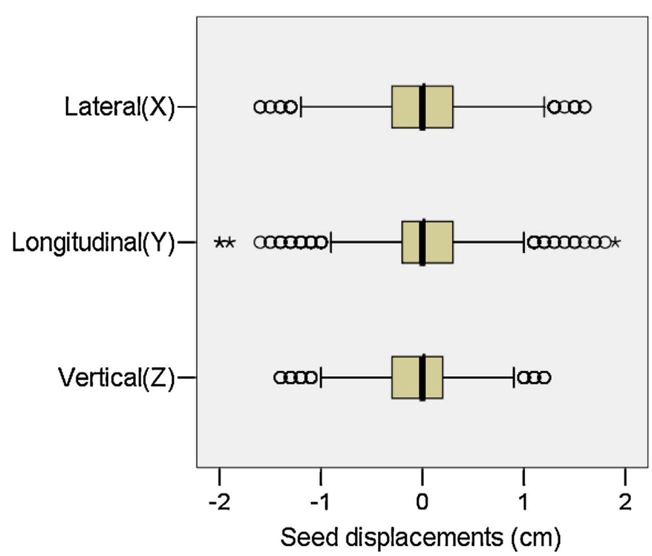

Fig. 1 – Boxplot describing fiducial markers displacements (real numbers in cm) in 4077 prostate cancer treatments with IGRT based on fiducial markers.

percentage of patients exhibited a very high setup error in the three axes (outliers represented by white circles in Fig. 1) and despite having excluded most of the extreme outliers, there were still a percentage of patients with extremely high setup errors in the Y axis (extreme outliers represented by solid stars in Fig. 1). Analysis of percentiles 75th, 90th and 95th showed that if IGRT had not been performed, 25% of the treatments would have had displacements superior to 4 mm in any of the three axes, 10% of the treatments would have had displacements superior to 7 mm in any axis, and 5% would have had displacements superior to 9 mm in any axis. The displacement of the fiducial markers proved to be strongly symmetric in the X-axis, while mildly asymmetric in the Y and Z-axis, with a predominance of greater displacements in the inferior direction in Y, and in posterior direction in Z (asymmetry coefficient of 0.007, −0.113 and −0.094 for X, Y and Z, respectively). Kurtosis coefficient demonstrated highly concentrated data in all the three axes, showing the highest values in Y (kurtosis coefficient value of 0.58, 1.75 and 0.32 for X, Y and Z, respectively).

The mean systematic errors of fiducial markers displacement were −0.04 mm in X, 0.27 mm in Y, and −0.37 mm in Z. The random errors were 4.0 mm in X, 3.1 mm in Y, and 3.6 mm in Z. Based on systematic and random errors, in this cohort of prostate cancer patients treated with IGRT based on fiducial markers, the theoretical margin that would be required in order to ensure that 90% of the patients receive at least 95% of the prescribed dose would be 2.7 mm in X, 2.9 mm in Y, and 1.5 mm in Z.

5. Discussion

Geographical misses in modern radiation treatments can be due to several factors. Early mistakes in the definition of the target volume can be translated into systematic geographical misses. Random or systematic geographical misses can take place when inappropriate margins are assigned for the planning target volumes, since these margins must properly consider both interfractional and intrafractional target movements. Mistakes on target definition should be progressively lower since delineation guidelines have been issued for several tumors in the last years. However, geographical misses due to interfractional or intrafractional target movement can only be diminished with the introduction of daily image guidance, maintenance of the traditional margins, or with the use of tumor tracking.

In our study, we found mean and systematic errors of -0.04 ± 4 mm in X, 0.27 ± 3.1 mm in Y, and -0.37 ± 3.6 mm in Z. These values are similar to those obtained in two similar studies with a smaller sample of patients. The first study found mean and systematic errors of 0.6 ± 1.5 mm in X, -0.25 ± 2.51 mm in Y, and 0.51 ± 2.45 mm in Z.[16] The second study found slightly higher mean errors with similar values for random errors of 1.1 ± 1.4 mm in X, 1.9 ± 2.3 mm in Y and 2.3 ± 2.7 mm in Z.[17] Our study allowed us to prove that if IGRT had not been performed, nearly 10% of the daily treatments would have had displacements superior to 7 mm in any axis. This would have been translated into geographical misses capable of compromising the outcome, since we currently use an 8 mm margin for the CTV in all directions. According to this data, in our own practice, the margin required in order to ensure that 90% of the patients receive at least 95% of the prescribed dose, would be inferior to 3 mm in any direction. These findings are consistent with two other studies in which image-guided marker alignment required a margin of less than 4 mm in any axis.[18,19]

However, theoretical margins obtained from fiducial marker displacements can only account for geometric uncertainties. Intrafractional movements caused by pulsating arteries, bowel movements or changes in bladder filling are not considered by traditional margins. The traditional values for intrafractional movements of the prostate during non-rotational IMRT sessions are close to 3 mm.[20] Hence, considering that our required margin for diminishing geometric uncertainties would be near 3 mm, and that we should add at least 3 mm in order to consider intrafractional movements, we have decided to reduce the currently used margin of 8 mm in all directions, to 7 mm in X and Y, and to maintain 8 mm in the Z direction, considering that most patients have significant displacements in the posterior direction.

Even though from a theoretical point of view, IGRT would allow to decrease margins and reduce geographical miss, so far, the clinical benefit in terms of tumor control or toxicity of the IGRT has not been established. A recently approved Phase II-III clinical trial that randomized patients in three arms: radiation treatment without image guidance, radiation treatment with image guidance and conventional margins, and radiation treatment with image guidance and margin reduction should throw some light on this subject. This protocol is currently recruiting, and has completed 88% of the planned sample.[21]

The use of IGRT means an increase in the dose of administered radiation; however, if the mean dose derived from a CBCT is close to 7 cGy or near 1.2 cGy when using portal images, it is estimated that the total administered dose would be 245 cGy when using daily CBCT or 42 cGy when using daily portal images.[22] It would correspond to administering the equivalent to one session of treatment in the case of daily IGRT with CBCT; however, these doses are not fully administered to the tumor, neither to the normal tissues, since the type of voltage required for kV images will deposit most of the radiation dose in the surface. In this scenario, the benefit of the use of IGRT decreasing the risk of geographical miss and reducing the required margins overcomes the possible disadvantage of a potentially increased risk of radiation induced tumors.

An IGRT approach based on CBCT increases the dose administered to healthy tissues when compared with IGRT based on 2D kV orthogonal images.[22] This is of particular relevance in prostate cancer patients considering, that the overall survival is expected to exceed 60% even in the worst-case scenario. We consider that the dose administered in IGRT to healthy tissues is a relevant matter for prostate cancer patients. The use of IGRT based on fiducial markers with 2D kV orthogonal images have several advantages over other techniques: the implant procedure has virtually no complications (potential complications derived from the implant such as infection, bleeding, seed migration, and urinary retention have not been reported), IGRT based on fiducial markers requires standard expertise in image fusion and co-registration, it does not need the constant presence of the radiation oncologist, it allows the same precision that would be obtained with CBCT, and it has the advantage of decreasing the acquisition time and the dose administered to healthy tissues with CBCT. Other forms of IGRT, such as ultrasound guided radiotherapy, require the presence of a well trained professional, may take more time to analyze, and, as recent reports show, it could not be as accurate and reproducible as required.[23]

6. Conclusion

IGRT is required when using highly conformal techniques; otherwise, at least 10% of daily treatments could have significant displacements. IGRT based on fiducial markers, with 2D kV orthogonal images is a convenient and fast method for performing IGRT in comparison with CBCT-based IGRT. This method allows quicker treatment administration, with the added value of lower radiation exposure. The procedure itself is safe and fast, with no complications derived from the implant, and a mean time for the implant of just 15 min. This IGRT technique allowed us to reduce the setup errors (considering both isocenter and prostate displacement), and to decrease the margin size by 1 mm, in the X and Y directions. Reductions in margin size can potentially translate into reduced toxicities.

Authors' contributions

RC study design, data analysis, data interpretation, draft of the manuscript. IB, JV study design, data acquisition, elaboration of the manuscript final version. FT, JA, AG, study design, elaboration of the manuscript final version. All authors read and approved the final manuscript.

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Conflict of interest

None declared.

REFERENCES

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. *GLOBOCAN 2008, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]*. Lyon, France: International Agency for Research on Cancer; 2010. Available in: http://globocan.iarc.fr [cited 17.05.11].
2. Mendenhall WM, Nichols RC, Henderson R, Mendenhall NP. Is radical prostatectomy the "gold standard" for localized prostate cancer? *Am J Clin Oncol* 2010;**33**(October (5)):511–5.
3. Button MR, Staffurth JN. Clinical application of image-guided radiotherapy in bladder and prostate cancer. *Clin Oncol (R Coll Radiol)* 2010;**22**(October (8)):698–706.
4. Staffurth J. Radiotherapy Development Board. A review of the clinical evidence for intensity-modulated radiotherapy. *Clin Oncol (R Coll Radiol)* 2010;**22**(October (8)):643–57.
5. Yoon M, Kim D, Shin DH, et al. Inter- and intrafractional movement-induced dose reduction of prostate target volume in proton beam treatment. *Int J Radiat Oncol Biol Phys* 2008;**71**(July (4)):1091–102.
6. Dawson LA, Sharpe MB. Image-guided radiotherapy: rationale, benefits, and limitations. *Lancet Oncol* 2006;**7**(October (10)):848–58.
7. Adamczyk M, Piotrowski T, Adamiak E. Evaluation of combining bony anatomy and soft tissue position correction strategies for IMRT prostate cancer patients. *Rep Pract Oncol Radiother* 2012;**17**(February (2)):104–9.
8. Paluska P, Hanus J, Sefrova J, et al. Utilization of cone-beam CT for offline evaluation of target volume coverage during prostate image-guided radiotherapy based on bony anatomy alignment. *Rep Pract Oncol Radiother* 2012;**17**(May (3)):134–40.
9. Pang G, Beachey DJ, O'Brien PF, Rowlands JA. Imaging of 1.0-mm-diameter radiopaque markers with megavoltage X-rays: an improved online imaging system. *Int J Radiat Oncol Biol Phys* 2002;**52**(February (2)):532–7.
10. Poggi MM, Gant DA, Sewchand W, Warlick WB. Marker seed migration in prostate localization. *Int J Radiat Oncol Biol Phys* 2003;**56**(August (5)):1248–51.
11. Osei EK, Jiang R, Barnett R, Fleming K, Panjwani D. Evaluation of daily online set-up errors and organ displacement uncertainty during conformal radiation treatment of the prostate. *Br J Radiol* 2009;**82**(January (973)):49–61.
12. Boehmer D, Maingon P, Poortmans P, et al. EORTC radiation oncology group. Guidelines for primary radiotherapy of patients with prostate cancer. *Radiother Oncol* 2006;**79**(June (3)):259–69.
13. Michalski JM, Gay H, Jackson A, Tucker SL, Deasy JO. Radiation dose-volume effects in radiation-induced rectal injury. *Int J Radiat Oncol Biol Phys* 2010;**76**(March (3 Suppl.)):S123–9.
14. Viswanathan AN, Yorke ED, Marks LB, Eifel PJ, Shipley WU. Radiation dose-volume effects of the urinary bladder. *Int J Radiat Oncol Biol Phys* 2010;**76**(March (3 Suppl.)):S116–22.
15. van Herk M, Remeijer P, Rasch C, Lebesque JV. The probability of correct target dosage: dose-population histograms for deriving treatment margins in radiotherapy. *Int J Radiat Oncol Biol Phys* 2000;**47**(July (4)):1121–35.
16. Graf R, Wust P, Budach V, Boehmer D. Potentials of on-line repositioning based on implanted fiducial markers and electronic portal imaging in prostate cancer radiotherapy. *Radiother Oncol* 2009;**April (4)**:13.
17. Munoz F, Fiandra C, Franco P, et al. Tracking target position variability using intraprostatic fiducial markers and electronic portal imaging in prostate cancer radiotherapy. *Radiol Med* 2012;**117**(September (6)):1057–70.
18. Tanyi JA, He T, Summers PA, et al. Assessment of planning target volume margins for intensity-modulated radiotherapyof the prostate gland: role of daily inter- and intrafraction motion. *Int J Radiat Oncol Biol Phys* 2010;**78**(December (5)):1579–85.
19. Kudchadker RJ, Lee AK, Yu ZH, et al. Effectiveness of using fewer implanted fiducial markers for prostate target alignment. *Int J Radiat Oncol Biol Phys* 2009;**74**(July (4)):1283–9.
20. Boda-Heggemann J, Köhler FM, Wertz H, et al. Intrafraction motion of the prostate during an IMRT session: a fiducial-based 3D measurement with cone-beam CT. *Radiother Oncol* 2008;(November (3)):37.
21. UK Clinical Research Network: Portfolio Database. Available in: http://public.ukcrn.org.uk/Search/StudyDetail.aspx?StudyID=8592 [cited 01.06.11].
22. Murphy MJ, Balter J, Balter S, et al. The management of imaging dose during image-guided radiotherapy: report of the AAPM Task Group 75. *Med Phys* 2007;**34**(October (10)):4041–63.
23. Robinson D, Liu D, Steciw S, et al. An evaluation of the clarity 3D ultrasound system for prostate localization. *J Appl Clin Med Phys* 2012;**13**(July (4)):3753.