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ARE STILL FIDUCIAL MARKERS ALONE APPROPRIATE IN THE IMAGE GUIDED ERA FOR PROSTATE CANCER RADIOTHERAPY? A SINGLE INSTITUTION EXPERIENCE BASED ON A "WELL TRAINED" PATIENT SUBGROUP.

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ABSTRACT

Purpose: The purpose of this work is to assess the consistency of Fiducial Markers (FM) based IGRT in clinical practice and the magnitude of daily prostate gland displacements in a subgroup of patients carefully trained to maintain a constant and reproducible organ filling. **Methods**: A physician trained each patient in this selected 55 patients group, assuring a highly reproducible and well-administered self-preparation. Three FMs were implanted using a transrectal ultrasound technique. IGRT was achieved by daily single exposure MV portal images and, every 6 treatment sessions, double exposure portal images were acquired in order to evaluate differences in displacements between fiducial markers and bony structures. **Results**: There were no grade 3-4 complications (e.g. infections, bleeding or abscess) or significant patient reported discomfort related to FM insertion. Differences in displacements between FM and bony landmark resulted to be statistically significant ($p<0,05$), relating to a good self preparation. Displacement recorded during first five treatment sessions are not predictive of movement directions during remaining fractions. **Conclusions**: FMs give the opportunity, even in centers not equipped with in-room volumetric imaging systems, to perform IGRT. FMs-IGRT in combination to high quality patient rectal and bladder preparation allows an improvement of dose delivery and local control while reducing radiotherapy-related toxicity and overall treatment time. Images control has to be carried out every day in order to be clinically useful as displacements occur in random directions.

KEYWORDS: 1. Prostate Cancer, 2. Radiotherapy, 3. Fiducial Markers, 4. Rectal filling, 5. Bladder Filling.

INTRODUCTION

The role of radiation treatment (RT) in prostate cancer has increased in the last decade, since RT achieves a similar tumor probability control with a better toxicity profile when compared with radical surgery.[1] Nowadays, the use of advanced techniques such as intensity modulated radiation therapy (IMRT) has enabled the delivery highly conformal dose distribution, facilitating selective dose escalation while reducing dose to organ at risks (OARs) and radiation-induced morbidity.[2-3] Nevertheless, the accuracy of planned target volume (PTV) localization remains crucial as steep dose gradient may increase the risk of geographical miss.

Set-up errors and prostate gland motion relative to the pelvic bones are the dominant sources of uncertainty, with a range between 4 and 18 mm on day-to-day RT fraction.[4-5]

The integration of imaging in RT process has the ability to improve daily prostate localization, leading to a more precise dose delivery. Several Image-Guided Radiation Therapy (IGRT) technologies, such as implanted fiducial markers (FM), ultrasound (US), electronic portal imaging device (EPID), cone-beam CT (CBCT) and megavoltage CT (MVCT) have been employed in prostate cancer.

In order to minimize inter-fraction set-up uncertainties on-line fiducial-based IGRT, visualized on kV or MV images, have been traditionally used for daily image guidance and serve as a surrogate for soft tissue target volume verification and patient repositioning.[6-7]

Furthermore, implanted intraprostatic gold markers improve prostate localization and could allow a reduction of PTV safety margins[8-9] with the potential for morbidity reduction or late normal tissue toxicities.[10-12]

Our institution, start up in 2010, initiated transrectal fiducial markers insertion for IGRT in 2012 for selected low, intermediate and high risk prostate cancer patients submitted to radical conformal RT.

Using three implanted gold seeds, the purpose of this work, in an academic Department of Radiation Oncology not equipped with in-room volumetric imaging systems, is to assess the consistency of FMs based IGRT in clinical practice and the magnitude of daily prostate gland displacements in a subgroup of patients carefully trained to maintain a constant and reproducible organ filling.

MATERIALS AND METHOD

Between January 2012 and February 2015, 55 histologically proven by transrectal ultrasonography (TRUS)-guided biopsy localized prostate cancer patients who underwent FM placements in our Urological Department, were enrolled in this study.

Patients were chosen to take part in a specifically designed training course. A physician spent at least 60 minutes training each patient in this selected group, assuring a highly reproducible and well-administered self-preparation. The purpose of this careful and highly specific training was to ensure the lowest possible organ motion between each treatment session.

The clinical characteristics of patients population are shown in table 1. Patients were staged according to 7th edition (2009) American Joint Committee on Cancer staging classification system. Short (6 months) and long course (3 years) androgen deprivation therapy was performed in intermediate and high-risk cancer, respectively.[13]

Table 1. Tumor and treatment group characteristics

Age	**Average** **Range**	**73years** **56-79 years**
T stage	T1 T2 T3	8 42 5
Gleason Score	6 7 8-10	9 34 12
iPSA	0-10 11-20 >20	39 8 8
Risk category (D' Amico)	Low Intermediate High	5 29 21
Dose (Gy)	72 (2,4 Gy/day) 78 (2 Gy/day)	32 23
Follow-up since treatment completion	Shorter (<= 12 mo) Longer (> 12 mo)	25 30
Androgen deprivation	Yes No	50 5
Technique	3D IMRT	9 46

iPSA = initial PSA, Gy = Gray, 3D = Three Dimensional Radiotherapy, IMRT = Intensity-Modulated Radiation Therapy

Informed consent for implant in written form was obtained in all patients.

Patients were trained on preparation before FMs implant. Antiplatelet therapy is suspended 4 days before till 4 days after the procedure; antibiotics prophylaxis (fluoroquinolone) from the day before to 7 days after procedure is prescribed. Patients self-administered an enema the evening before and the morning of the procedure and, in order to fill the bladder, drank 500ml of water 30 minutes before the implant.

Three Qfix RT-4423K-17-3 Knurled Gold Fiducial Markers (1.2mm x 3mm in 17 gauge 20cm needles) were implanted using transrectal ultrasound guided technique in our Urological Department; the three gold markers were placed into the prostatic gland to allow triangulation and measurement of position in different planes (right prostate base, left mid-gland, and right apex). Complications occurred following the procedure were assessed by a physician.

Starting 3 days before the Computed Tomography (CT) scan for planning (AcqSim, Philips, the Netherlands) until the RT treatment end, patients adopted diet and preparation procedure. In detail, information sheets are discussed and handed to patients, reporting instructions on how to avoid food with too many fibers or fat, flatulent and mass producing; assume every day 2 charcoal tablet; to empty the rectum before the CT scan and every treatment session with the help of a self-administered enema. Patients are trained on how to fill the bladder before every RT session with a fluid amount based on the volume registered during the planning CT. Physicians made sure that every patient fully understood procedure.

All patients underwent a planning CT scan in supine position using Prostep (ProSTEP™ ABS, MEDIZINTECHNIK GMBH) immobilization device, filled bladder and empty rectum. The CT and the linear accelerator were equipped with identical models of a carbon index tables and immobilization devices. The CT simulation was performed without contrast medium. CT images were acquired with a 5 mm step spaced from L5 to 3 cm over the first gold seed, 3 mm from 3 cm over the first seed to 3 cm under the lowest one, 5 mm until the end of testicles. In the eventuality of a non-optimal and highly reproducible patient condition, such as an insufficient bladder filling or the presence of gas/fecal mass in rectum, planning CT was repeated until standards were matched. During CT scan was identified, using virtual simulation software, the isocenter inside the prostatic gland. Three skin tattoos, two laterals and one anterior, were carried out for set-up verification by alignment to mobile laser system. The CT images were transferred to the treatment planning system (Oncentra Master Plan v4.3, SP3, Nucletron B.V., Elekta Company, The Netherlands) to define the volumes of interest. The CTV consisted of the prostate ± seminal vesicles. For IGRT technique the PTV was generated by adding automatic expansion of CTV of 7 mm in cranio-caudal, lateral and anterior directions and 5 mm in posterior direction.

Selected Organ at Risks (OARs) were the femoral heads, bladder, rectum and penile bulb. Femoral heads were contoured from the cranial extremity to the small trochanter, including the femoral neck; penile bulb, bladder and rectum were outlined entirely. FMs were also contoured.

During the implementation phase, as staff completed the learning curve, first 9 patients out of 55 included in this study, were treated with 3D technique while the remaining 46 patients underwent IMRT-planned treatment. In 23 patients total radiation dose was 78 Gy with conventional fractionation schedule while in 32 cases IMRT was performed with moderate hypofractionation schedule (table 1).

Patients were treated with 3D technique using 5 individually shaped coplanar fields (gantry angle 0°, 45°, 90°, 270°, 315°) delivered with 10 or 18 MV beam photons energy produced by a linear accelerator (Synergy Platform; Elekta Atlanta, GA, USA) in daily fractions of 2 Gy.

In IMRT technique (Figure 1), all patients were treated with equally spaced 7-9 coplanar beams arrangement (7F-IMRT), 10 MV beam energy and direct Step & Shoot modality. Dose calculation was performed with the Plan Optimization Module (Raysearch Laboratories, Sweden) of our TPS. The dose was prescribed at the ICRU point. The optimization settings had the goal of covering greater than 95% of the PTV volume with the 95% of prescription dose limiting hotspots to 107% of the prescription dose. Collapsed-cone convolution methods were employed for final dose calculations.

To minimize the risk of gastrointestinal (GI) and genitourinary (GU) toxicities, QUANTEC (2010) dose-volume constraints were applied.[14]

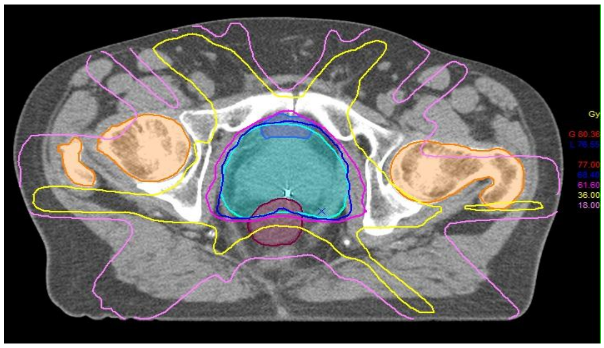

Figure 1. IMRT technique

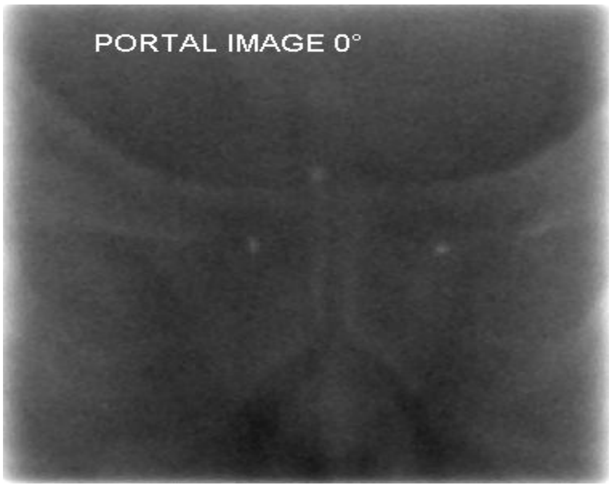

Figure 2A. DPI 0°

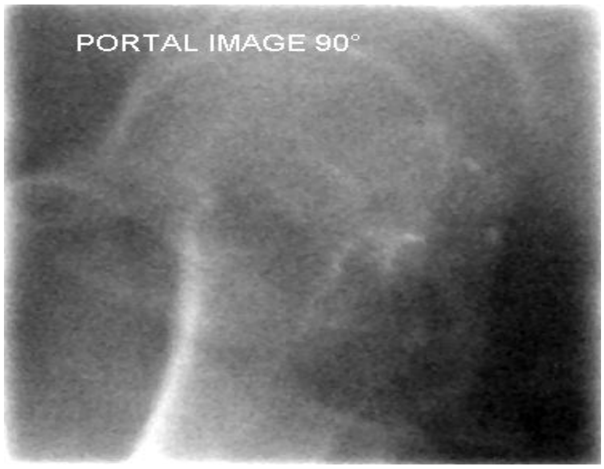

Figure 2B. DPI 90°

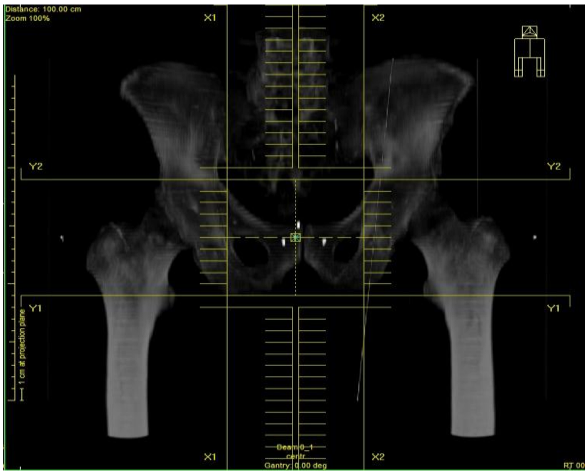

Figure 3A. DRR 0°

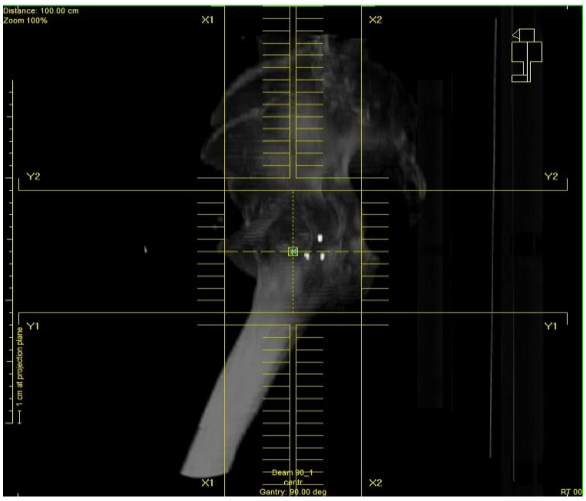

Figure 3B. DRR 90°

Starting from first RT fraction, before every single session, two orthogonal (0° and 90°) megavoltage Digital Portal Images (DPI) were acquired (Figures 2A-2B) using an electronic portal imaging device (EPID).

Daily single exposure DPI were obtained using 6MV photons beam with a field size of 10x10 cm and superimposed with the reference images (Digitally Reconstructed Radiograph, DRR) generated from the Treatment Planning System (TPS) (Figures 3A-3B) while every 6 treatment sessions, double exposure DPI images (20x20 cm field size) were acquired.

With the use of an I-VIEW system (Elekta Atlanta, GA, USA), a comparison between gold seeds position on DPI and DRR was carried out. Taking into account system's sensitiveness, we established a 3 mm threshold for table position correction.

Acute radiation toxicities were assessed weekly using RTOG/EORTC scoring system.

Differences in mean between seeds and bone structures movements along cranio-caudal, lateral and anterior directions were compared using two-sided *t*-test. One-sample t-test was used for comparison of movements of seed between each other. Computations were performed with the STATA statistical package, release 13.1 (STATA Corp, College Station, TX). All *p* values were two-sided, and $p < 0.05$ was considered statistically significant.

RESULTS

None severe FM implants related complications such as infections, bleeding or abscess were reported. Minor rectal bleeding, dysuria or hematuria affected less than 10% of implanted patients and were self limiting. Patients reported that discomfort related to implant procedure has been inferior to standard diagnostic 12-core biopsy.

GI and GU high grade toxicity (>G2) were 5.45% and 1.82%, respectively. Results are shown in table 2.

Table 2. Acute toxicity in treatment group.

ACUTE TOXICITY		
	GI	**GU**
G0	22	12
G1	22	28
G2	8	14
G3	3	1
G4	0	0
TOTAL	55	55

RTOG/EORTC scoring system. GI=gastro-intestinal; GU=genito-urinary

A total of 4214 (3714 regarding seeds and 500 of bony structures) DPI were acquired during this study. Due to technical reasons 32 images related to FMs were excluded from the analysis. Acquisition and matching of daily DPI-DRR increased the overall treatment time of about 5 minutes per patient.

Patients positioning has been corrected, according to FMs, 1533 times out of 1857 total treatment sessions.

In Figure 4 is shown the box plot of seeds and bones in latero-lateral and craniocaudal directions at 0°. The mean value and standard deviation of seeds movement in latero-lateral direction is found to be – 0,81 ± 3,3 mm; meanwhile mean value and standard deviation of bony structure is 1,3 ± 3,3 mm. The found difference, despite being little, is statistically significant (t-Student p=0,03).

In the same way considering cranio-caudal direction, mean value and standard deviation turned out to be 0,5 ± 3,9 mm for seeds and -0,18 ± 2,9 mm for bones; even in this case, despite being less than a millimeter, results are statistically significant (t-Student p=0,01).

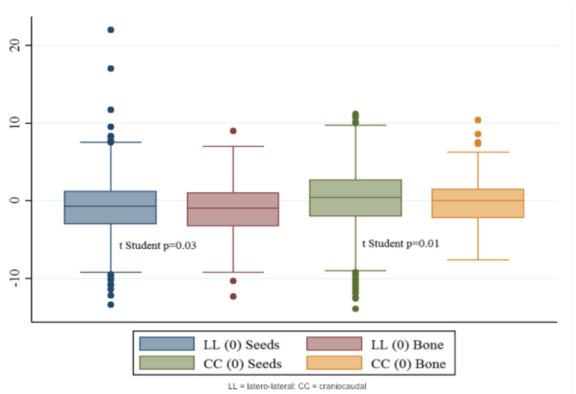

Figure 4. Seeds and bones shifts in CC and LL directions at 0°

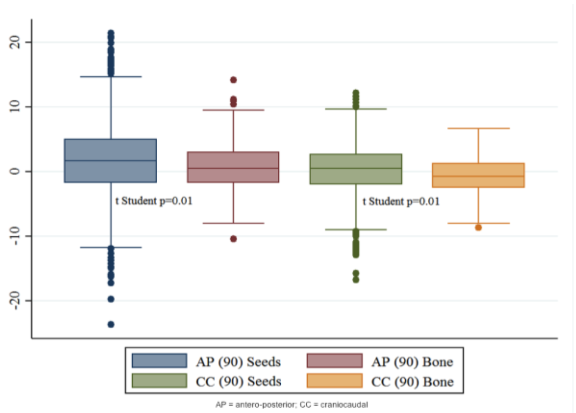

Figure 5. Seeds and bones shifts in AP and CC directions at 90°

Similarly in Figure 5, box plot of movements in antero-posterior and cranio-caudal directions, in relation to 90° projection, is displayed. In detail, in antero-posterior direction mean value and standard deviation appeared to be 1,7 ± 5,3 mm when considering seeds movement and 0,8 ± 4,1 mm for bony structures; also in this case difference reaches statistical significance (t-Student p=0,01), even if limited.

In cranio-caudal direction mean value and standard deviation result to be 0,44 ± 3,9mm and -0,64 ± 2,9mm for seeds and bones respectively; results are statistically significant in this case as well (t-Student p=0,01).

In table 3 are shown shift percentages based on FM displacements and grouped by dimension. The vast majority of target movements resulted to be inferior to 5 millimeters. The worst-case scenario involves the AP dimension at 90° angle.

Table 3. Shifts percentages grouped by proportion of displacements.

Dimension	Proportion of displacements <3 mm (%)	Proportion of displacements <5 mm (%)	Proportion of displacements <7 mm (%)	Median in absolute value (mm)
LL 0° angle	64,6	85,9	95	2
CC 0° angle	57,8	78,6	90,4	2,25
AP 90° angle	41,2	65,5	80,9	3,5
CC 90° angle	57,6	79,4	91,5	2,35

LL = latero-lateral, CC = cranio-caudal, AP = antero-posterior

In Figure 6 are shown results from the analysis between FMs movements during first five treatment session and movements registered during the entire treatment course. Considering latero-lateral and antero-posterior directions, results did not reach statistical significance (p=0,87 and p=0,95, respectively). Regarding cranio-caudal direction, found difference is instead statistically significant (p=0,01).

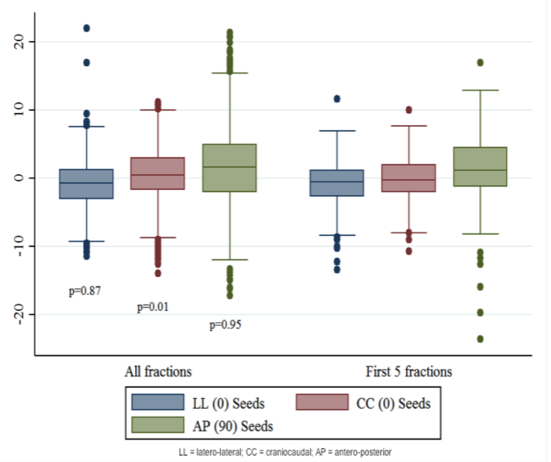

Figure 6. Movement recorded during first five treatment session compared to movements recorded during whole treatment course

DISCUSSION

Radiotherapy has benefited from great technical advance during last years. IGRT is now approaching routine use, as it basically increases the therapeutic ratio by reducing the CTV-PTV margins.[15] A successful radiation treatment relies on a precise dose delivery to the target allowing for dose escalation, while sparing normal surrounding tissues.

Accurate target localization remains a crucial factor in order to grant a high precision treatment and lower the risk of generating geographical misses. Interfraction and intrafraction target movements are contributing factors to both random and systematic errors and can be partially corrected with the introduction of daily image guidance or tumor tracking.

A widely accepted and cost-effective method to improve prostate localization before each treatment session, is the use of implanted FMs, alone in a department not equipped with onboard imaging, or combined with other image guidance technique.[16-17]

We did not detect any major complication derived from FM's implant; no clinically relevant short and long term changes were reported in QoL due to FMs implantation. Even if some authors choose not to discontinue antiplatelet therapy[18-20] we maintained the withdrawal of antiplatelet drugs considering it simpler and safer to apply. In the same way we choose to maintain the antibiotics prophylaxis in consideration of transrectal implant procedure in order to minimize possible complications rate.[21]

In our study, IGRT was achieved by daily online verification of gold seeds in the prostate gland, analyzing orthogonal DPI. To determine FMs position patients received every day 6 Monitor Unit (MU), resulting in a total administered dose to PTV on each day of 4,26 cGy. Kan et al.[22] reported that each standard mode pelvis Cone Beam Computed Tomography (CBTC) had an effective dose of 22,7 mSv and daily usage can deliver a substantial amount of dose to critical organs; small bowel and rectum can receive an additional dose up to 1.4 to 2.2 Gy in 35 fractions and increase the effective dose of circa 800 mSv, which could induce an additional secondary cancer risk of 4%.

As a part of internal quality assurance protocol, we evaluated the stability of knurled gold seeds in 10 patients by measuring on weekly CT scans the distance between each marker (Inter-marker distance). The recorded unpublished data showed neither statistically significant marker displacement nor seed loss, justifying the routinely use of these type of FMs. All that considered we can uphold that US guided FMs implant, in terms of implant-related morbidity, is a feasible and safe procedure, as it already was demonstrated by many studies.[23-24]

In our opinion, FMs give the opportunity to carry out a moderate hypofractionation schedule with a substantial reduction of overall treatment time and a relevant enhancement in dose delivery precision by the use of an highly conformal dose distribution technique.

Considering that prostatic gland has no link to bony structures, its position mainly depends to surrounding organs; greater part of this position is determined by bowel and rectum filling.

The aim of this study was to analyze if maintaining a reproducible filling of said organs could reduce gland motions, giving the opportunity to reduce treatment margins. FMs position, acting as surrogate of prostate localization, is determined either by daily set-up and surrounding organs filling, while bony landmarks represent set-up only. Every patient resulted to be capable of carrying out a good self preparation, in order to keep under control organs filling and consequently the preparation level each patient underwent 2 CT scan during treatment course, bladder filling resulted to be constant during treatment in contrast to what found by other authors.[25] Our rectal preparation protocol was well tolerated in accordance to other publications.[26]

Results shown in Table 3, suggest that even if a good preparation is carried out, the rectal volume affects considerably the position of prostate.

Patients positioning has been corrected, according to daily FMs position, 1533 times out of 1857 total treatment sessions with a cut-off in shift in order to correct patient's position settled to 3 mm, in other terms FMs were useful in determining patient set-up in 83% of treatment sessions. Set-up and organ position data obtained from FMs and from bony structures images differ more than 3 mm in at least one projection in 66% of times and in 26,4% of times for more than 6 mm.

Treatment margins were set to 7 mm in isotropic except 5 mm at prostate-rectal interface as IGRT with grossly reduced margins was found out to be a predictor of poorer biochemical outcome, leading to recurrence in 42% vs 9% in non IGRT patients at 5 years.[27]

Some studies demonstrated that the accuracy of FMs, compared to other guidance technique, did not differ more than 3-4 mm underlining the good organ localization FMs can provide, especially with the use of kV imaging.[28-29] Unfortunately, in our Department kV image is not available, and daily DPI are acquired with the primary MV photons beam that are lower in quality and more troublesome to interpret. Gill et al.[30] reported that if a 3 mm threshold were to be applied to both EPI and KVI (kV Imaging) units, there would still be 27% more actual couch shifts on KVI units than on EPI units. Pisani et al.[31] studied the interobserver alignment of an anthomorphic phantom with a known translational shift when imaged with both kV and MV beams; they found that interobserver alignment was more variable with megavoltage imaging than KVI. Even if EPI are objectively less accurate than KVI, the reported differences in median absolute displacement between the two technologies is no more than 1 mm, validating EPI as an accurate tool for IGRT in prostate cancer patients.[29] When operating the choice of margins extension, rapid intrafractional movements must be kept in consideration. Intrafraction motion of prostate have been investigated in various series, standard deviation are quite comparable ranging around 1 mm in LR directions and 3 mm in SI or AP direction.[32] The LINAC available in our Department doesn't provide any automated couch shift, correction of patient position is carried out manually by technicians, that increases both residual treatment error and treatment time with an added risk of patient movement.[33]

Differences in shift measured between gold seed and bony structures turned out to be statistically significant despite being little in value; those results can be referred to a well controlled organ motion, tiny differences in displacement can relate to constant surrounding organs filling and therefore to a good patients self-preparation.[34]

Constant organ filling can also be related to low treatment toxicity levels, in more detail acute RTOG/EORTC GI and GU score higher than G2 has been reported in only 5.45% and 1.82%, respectively. 45 out of 55 patients underwent a follow-up prolonged enough (>6 months) to assess late treatment toxicity, only 1 (2,22%) high grade (>G2) has been reported referring to GU symptoms and none (0%) GI.

Even if organ shifts are kept low, their path cannot be foreseen because it occurs in random directions, that considered portal imaging has to be carried out every day, this causes a slight increase in treatment session time, we however quantified that time consumption in no more than 5 minutes.

Data collected therefore suggest that constant organ filling cannot replace FM based image guidance. The use of highly conformal volumes made possible by IMRT requires, in our opinion, a precise knowledge of target position, otherwise risk of causing high toxicity by missing treatment target is substantial.

CONCLUSIONS

Fiducial Markers based IGRT-IMRT allows the localization of the prostate gland during radiotherapy. Implant procedure is a simple, safe and well tolerated technique, severe complications are uncommon and marker migration is not clinically significant.

High quality self preparation can reduce prostate displacement, but cannot substitute the accuracy of target localization given by daily image guidance. Images control has to be carried out every day in order to be clinically useful as displacements occur in random directions.

Finally, as high dose gradient technique and hypofractionation schedule requires an accurate daily target localization, in our opinion the implementation of Fiducial based IGRT can, in a cost-effective way, improve dose delivery in a Department of Radiation Oncology not equipped with in-room volumetric imaging systems.

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