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International Journal of Current Research
Vol. 9, Issue, 12, pp.62730-62733, December, 2017

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

ISSN: 0975-833X

RESEARCH ARTICLE

ASSESSMENT OF POST IMPLANT MIGRATION OF ANCHOR TYPE GOLD FIDUCIAL MARKER IN CARCINOMA PROSTATE: A SINGLE INSTITUTION EXPERIENCE

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ARTICLE INFO

Article History:
Received 23rd September, 2017
Received in revised form
02nd October, 2017
Accepted 19th November, 2017
Published online 27th December, 2017

Key words:
Anchor-type gold fiducials,
Fiducial migration,
Planning CT scan,
Prostate cancer,
Radiotherapy.

ABSTRACT

Objective: Accuracy of target localization is of paramount importance in dose escalation of prostate cancer radiotherapy by Intensity Modulated Radiotherapy (IMRT) technique. Intraprostatic fiducial implantation is a standard procedure for localization of target volume. However, the possibility of fiducial migration confers uncertainty in radiotherapy planning. In this study, we have tried to evaluate whether there is significant migration of anchor type fiducials one week after their implantation when planning computed tomography (CT) scan is usually acquired.

Material and methods: We have analysed fiducial migration (FM) in 8 localized prostate cancer patients treated with IMRT. The median variation of Intermarker distances (IMD) between the apex, left and right fiducials were calculated to assess FM between day of implantation and day of planning CT acquisition.

Results: Between February 2015 and December 2016, 10 patients of prostate cancer were treated with IMRT based on fiducial markers. The FM came out to be 0.01, 0.03 and 0.1 cm respectively for apex-right, apex-left and left-right IMD.

Conclusions: FM was within 3 mm of our institutional Planning Target Volume (PTV) margins. Anchor type fiducials were found to be quite reliable for target volume localization and radiotherapy planning. Hence, planning CT scan can be taken on the day of fiducial implantation.

Citation: Narendra Kumar, Anindya Mukherjee, Gedela L Deepthi, Arun S Oinam, Renu Madan and Santosh Kumar. 2017. "Assessment of post implant migration of anchor type gold fiducial marker in carcinoma prostate: A single institution experience", *International Journal of Current Research*, 9, (12), 62730-62733.

INTRODUCTION

External beam radiation therapy is one of the most commonly used treatment options for prostate cancer. With the advent of Prostate Specific Antigen (PSA) screening, there has been an increase in the number of patients being diagnosed at an early age with localized disease. This has increased the concern of late effects seen with prostate cancer radiotherapy as they have longer survival period post radiotherapy. Due to this higher incidence of late effects in prostate cancer patients with higher doses of radiotherapy, conformity is very important in treatment delivery.

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Hence Intensity modulated radiotherapy (IMRT) is the standard of care in treatment of carcinoma prostate. Radiation dose escalation for prostate cancer improves biochemical and progression-free survival (Zelefsky *et al.,* 2001; Pollack *et al.,* 2002; Kuban *et al.,* 2011). However, with increasing doses, early and late side effects of treatment worsen (Zietman *et al.,* 2005; Peeters, 2005). Accurate target localization becomes essential to maximize radiation dose delivery to the tumor while decreasing normal tissue toxicity. The various methods available for daily tumor localization are ultrasound, implanted fiducial markers combined with Kilovoltage (KV) imaging, cone beam computed tomography (CBCT), and electromagnetic transponders. Of these methods, the process of using gold fiducial markers for prostate localization is well documented and used as standard practice in much radiation oncology departments (Greer *et al.,* 2006; Thompson *et al.,*

2005; Van der Heide *et al.,* 2007). It is a comparatively cheap, easy and reliable method of daily prostate localization and is also recommended in the recent Faculty of Radiation Oncology Genito-Urinary Group (FROGG) prostate cancer consensus guidelines (Wu *et al.,* 2001) for institutions implementing prostate image-guided radiation therapy (IGRT).As the prostate position is variable with respect to the bladder and rectal filling, accurate target localisation also helps us to make sure that our target is in our treatment area. There are two kinds of fiducials routinely used-seed and anchor type. With seed type of fiducials it was seen that they migrate after implantation and they need some time to get fixed into the tissue and minimal amount of migration also occurs during the course of treatment (Schallenkamp *et al.,* 2005). Gold anchor markers introduced by Naslund medical AB are claimed to have no possibility of migration after implantation and that CT based simulation can be done immediately after implantation (Naslund *et al.,* 2009). The purpose of present study is to estimate the amount of migration occurring with anchor type markers after implantation up to 1week.

MATERIALS AND METHODS

The study received approval from institutional ethical committee of Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh in June 2014. Thereafter, patients were accrued from July 2014 to July 2016. This prospective study enrolled patients of localised adenocarcinoma prostate who visited our clinic and had given informed written consent for fiducial implantation before radiotherapy. These patients underwent bowel preparation on the night before implantation and were started on prophylactic antibiotics one day before implantation. On the day of implantation patients were advised to come on empty stomach. The markers used were of anchor type and were implanted under trans-rectal ultrasound (TRUS) guidance using a 22 gauze needle with a diameter of 200 mm with a marker of 2 mm diameter. Initially patients were made to lie down in lithotomy position, after which the rectal probe was inserted and the desired position of the prostate identified. Once this was done, 3 markers were inserted-one at the apex and the other two at the base with a minimum distance of 1cm from each other to allow clear demarcation. All the three markers were placed within the prostate and at a distance of 5mm from the edge. The whole procedure was carried out under supervision of an urologist. Post implantation, an X-ray was taken in supine position to check the position of the markers, as shown in Figure 1. Finally, the patients were taken up for the pre- planning CT scan (Day 0 scan). They were simulated in supine position using a red footrest for immobilization. The pelvic area was scanned at 3mm intervals from the fourth lumbar vertebra up to the greater trochanter of the femur. The isocentre was placed near the center of the prostate and marked by anterior and lateral skin marks with alignment to in-room lasers. These patients underwent another CT scan one week after fiducial implantation for the purpose of radiotherapy planning (day 7 scan). The study was done by studying the position of the fiducial markers in both the Day 0 and Day 7 CT scans. The primary goal of the study was to estimate the fiducial migration in all three planes.For every patient, the reference point of origin was defined as a 'zero point' which was obtained from the intersection of the perpendicular line dropped from anterior border of cranial-most section of symphysis pubis with the line joining the centers of the femoral heads, as shown in Figures 2 and 3.

The *X*/*Y*/*Z* coordinates of on the Cartesian coordinate system can be calculated using a parametric equation as shown in *Appendix*. The positional coordinates of each fiducial were obtained in relation to this 'zero point'. From this data the distance between the every two fiducials were obtained-giving a total of 3 intermarker distances (IMD),viz. apex-right lateral IMD (dAR), apex-left lateral IMD (dAL), and that between right and left lateral fiducials (dRL). The fiducial marker (FM) migration was calculated by measuring the changes of IMDs between Day 0 and Day 7 scans. Then the median values of FM with their respective standard deviations were calculated using descriptive statistical models. Further subset analysis was done as a secondary endpoint of this study to see if migration in any plane is different from that in other planes.

RESULTS

Between February 2015 and December 2016, 10 patients of prostate cancer were treated with IMRT based on fiducial markers. All the patients were in the age group of 60-70yrs and 2 patients had T1 stage disease, 4 patients were T2 stage disease and the rest 4 had T3 disease. Of these 10 patients, we failed to implant all the 3 fiducial markers correctly within the prostate in 2 patients; hence the analysis was done in only 8 patients. The analysis done in these patients showed the median intermarker distance (IMD) variation or fiducial migration (FM) between the apex and right fiducial to be 0.01cm (Standard deviation, SD-0.13); the FM between left and right lateral fiducial was 0.03cm (SD-0.14) and the FM between left and right fiducial was 0.1cm (SD-0.08), as shown in Table 1.Though the median shifts are insignificant, the standard deviations obtained were large owing to the small sample size. Further, a subset analysis was done using non-parametric statistics. Kruskal Wallis one-way ANOVA was used since the sample size is less. By this we have seen that the shifts between the right-left fiducials are numerically greater but not statistically significant (P value>0.05).

Table 1. The displacement of markers based on intermarker distances (FM- Fiducial migration)

	FM_Apex & Right	FM_Apex & Left	FM_Left & Right
No. of patients	8	8	8
Median	0.01	0.03	0.1
Standard deviation	0.13038	0.14707	0.08350

Let P_i (x_i,y_i,z_i) be the co-ordinates for 3 points in Fig 3,
Where, i = 1 for left femur centre.
= 2 for right femur centre.
= 3 for anterior point of superior border of symphysis pubis.
= 0 for 'zero-point'

The relation of the perpendicular dropped from pubic symphysis to line joining the center of femoral heads is given by the direction cosine parametric equation: $P_3 \times [P_1 + t (P_2-P_1)] = 0$ from which the't' value can be found. Substituting't' in the following equations, co-ordinates of P_0 $(_0, _0, _0)$ can be calculated as below:

$x_0 = x_1 + t(x_2-x_1)$.
$y_0 = y_1 + t (y_2-y_1)$.
$z_0 = z_1 + t (z_2- z_1)$.

DISCUSSION

Prostate cancer is the second most common cancer in men worldwide. It is the fifth leading cause of cancer death in men. Widespread use of PSA for prostate cancer screening has further increased the cases of prostate cancer. Early patient identification also helps in decreasing the number of deaths due to prostate cancer because with adequate treatment, it is a completely curable disease as long as the disease is localised.

The optimal management of clinically localised prostate cancer can either be done with surgery, high dose external beam radiotherapy (EBRT) or interstitial radiotherapy. All have shown equivalent biochemical and disease free survival outcomes and the choice depends on the treating physician based on the patients' characteristics (Hanks, 1991). IMRT with daily positional verification has proven to be an effective method in controlling prostate cancer. Dose escalation in external-beam radiotherapy for localized prostate cancer improves the outcome, with lower prostate-specific antigen recurrence rates and lower late urinary tract toxicities (Zelefsky *et al.,* 2012). Due to close proximity of bladder and rectum to prostate, their day to day variations in filling can lead to significant displacement of prostate and alter the planned dose distribution (Klayton *et al.,* 2012) .This hampers the delivery of high dose to prostate due to increased bladder and rectal toxicity. Hence when higher doses are given, tumour localization is important to overcome the tumour miss and to reduce normal tissue toxicity which can occur due to variable bladder and rectal filling.

Initially target localization was used to be done by bone to bone matching on portal images. However the prostate position is not stable with respect to the bony anatomy; hence, the use of fiducial markers started. Intraprostatic fiducial markers in the form of gold seeds or coils are a reliable indicator of prostate position during the course of treatment (Dehnad *et al.,* 2003). The position of these markers detected by electronic portal imaging devices (EPIDs) can help us in accurate target localization by matching done on a daily basis. The other method of meticulous target localisation is by daily CBCT which allows soft tissue (both target and surrounding normal tissues) matching. But daily CBCT is quite time consuming and risks the patient with higher radiation exposure. Hence daily fiducial matching on EPID combined with CBCT once or twice a week seems to improve precision and effectiveness of prostate cancer treatment accuracy with no geographical miss and excessive workload (Adamczyk, 2012).

The use of gold fiducial markers for tumor localization has become widely popular because they can be easily seen on a digital radiograph and they remain relatively stable providing good alignment. There are various designs of gold fiducial marker markers available –sphere (seed), cylinder, coil and anchor type [11]. They have been studied and it has been seen that the chance of marker migration depends on the marker design and the organ. Although one marker is sufficient to reduce translational setup errors of the target, three markers are required to distinguish marker migration from true tumor motion (Jean-Briac *et al.,* 2008). As long as the three markers do not migrate in the same direction to the same extent, the position of the 3 markers can be used for tumor localization (Jean-Briac *et al.,* 2008). The individual marker migration can be detected by the change in the mutual distance between the markers. Usually planning CT is taken after one week of fiducial implantation to let the markers to stabilize and for any amount of edema to subside. Marker migration was studied with seed type of markers and quite a bit of significant marker migration was noted after implantation .This warrants a waiting period before a CT can be obtained for planning purposes (Poggi *et al.,* 2003). Recently anchor type markers have been introduced with apparently no significant migration after implantation and the vendors claimed that virtual simulation can be done immediately after marker implantation. These markers have cuts at 2mm increments which supposedly allow the marker to "sew" into the tissue providing superior attachment and reduced displacement (Naslund *et al.,* 2009). A study was done by Kukielka et al. with anchor type fiducial markers to see if any migration occurs after implantation by comparing the Day 0 and Day 7 CT scans. It showed that virtual simulation can be done immediately after marker implantation, as the period for marker stabilization is very less (Kukielka *et al.,* 2012). Since prostate position depends on rectal and bladder filling, it often happens that the actual prostate position changes with respect to the treatment isocentre. Therefore, we need our localization system to be highly accurate .We wanted to verify if there was really no migration with anchor type markers as claimed in some studies. If proved so, simulation could be done immediately after implantation thereby minimizing resource utilization in high volume centers like us and obviously save time. In our present study we have taken CT on the day of implantation and another CT was done after 1 week and the IMD have been compared .It was seen that none of the markers showed any evidence of significant migration. No IMD increased or decreased consistently and significantly over time. The amount of fiducial migration was within our PTV margins of 3mm.In subset analysis we have seen that the apex fiducial is comparatively more stable in relation to the other two fiducials, but it is not statistically significant due to the small size. Hence we can conclude based on this study that CT based simulation can be done immediately after anchor type fiducial marker implantation. Moreover, the need of daily CBCT is obviated and fiducial marker matching by EPID along with once a week CBCT seems quite satisfactory to reduce interfraction positional errors. However as the sample size is very small it can't be introduced into routine practice yet. Further studies on same lines can only affirm the findings of our study.

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