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Original Article

Computed tomography based evaluation of prostatic fiducial marker migration between the periods of insertion and simulation

Prostatik fidusiyal işaretleyicilerin yerleştirilme ve simülasyon dönemleri arasındaki migrasyonunun bilgisayarlı tomografi ile değerlendirilmesi

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ABSTRACT

Objective: The aim of this study was to determine whether significant fiducial marker migration occurs between the periods of prostatic marker insertion and computed tomography (CT) performed for radiotherapy planning and if a waiting period is necessary.

Material and methods: Thirty-nine patients with prostate adenocarcinoma underwent fiducial marker insertion before radiotherapy between June 2013 and December 2015. Three markers were inserted by one radiologist under the guidance of transrectal ultrasonography. All patients underwent CT three hours after insertion to confirm the number and position of fiducial markers. Radiotherapy planning CT was performed on an average of 11 days (range 7-20) after insertion. CT images were imported into treatment planning system to analyze the position of fiducial markers. Point- based marker match algorithm was used to find the distance of marker migration. The mean and maximum distances between each fiducial markers were calculated.

Results: The mean distance of migration was 1.029±0.42 mm (range 0.23-1.93 mm) and the maximum distance was 1.361±0.59 mm (range 0.25-2.74 mm). The distance of marker migration was not statistically significant for the groups organized according to the timing of marker insertion, prostate volume, patient age, prostate specific antigen level and Gleason score.

Conclusion: According to our results significant fiducial marker migration did not occur during the interval between insertion and treatment planning CT. It should be taken into consideration that performing simulation on the same day as marker insertion might prevent increased cost and delayed radiation therapy by saving the patients from extra visits to the clinic.

Keywords: Computed tomography; fiducial marker; migration; prostate cancer; radiation therapy.

ÖZ

Amaç: Bu çalışmanın amacı, prostatik fidusiyal işaretleyicilerin, yerleştirilme ve radyoterapi planlama tomografisi çekilmesi dönemleri arasında anlamlı bir migrasyon gösterip göstermediklerini ve bir bekleme süresinin gerekip gerekmediğini belirlemekti.

Gereç ve yöntemler: Haziran 2013 ve Aralık 2015 tarihleri arasında prostat adenokarsinomu tanılı 39 hastaya radyoterapi öncesi prostatik fidusiyal işaretleyici yerleştirildi. Aynı radyolog tarafından ultrasonografi eşliğinde transrektal yoldan üç adet işaretleyici yerleştirildi. Tüm hastalara işlemden üç saat sonra işaretleyicilerin sayı ve yerini doğrulamak için bilgisayarlı tomografi (BT) çekildi. Radyoterapi planlama tomografisi işlemden ortalama 11 gün (7-20 gün) sonra yapıldı. BT görüntüleri, fidusiyal işaretleyicilerin pozisyonunu analiz etmek için tedavi planlama sistemine transfer edildi. İşaretleyici migrasyonunun mesafesini hesaplamak için nokta bazlı işaretleyici eşleştirme algoritması kullanıldı. Her bir fidusiyal işaretleyici arasındaki ortalama ve maksimum mesafeler hesaplandı.

Bulgular: Ortalama migrasyon mesafesi 1,029±0,42 mm (0,23-1,93 mm) ve maksimum migrasyon mesafesi 1,361±0,59 mm (0,25-2,74 mm) olarak hesaplandı. Fidusiyal işaretleyici migrasyonu ile planlama tomografisi arasındaki süre, prostat hacmi, hasta yaşları, prostat spesifik antijen seviyeleri ve Gleason skorları arasında istatistiksel olarak anlamlı ilişki gözlenmedi.

Sonuç: Bizim sonuçlarımıza göre, fidusiyal işaretleyici yerleştirilmesi ile planlama tomografisi arasındaki sürede fidusiyal işaretleyicilerde anlamlı migrasyon saptanmadı. Simülasyonun, işaretleyici yerleştirilmesi ile aynı gün yapılmasının, hastaların kliniğe tekrarlayan ziyaretlerini önleyerek radyoterapinin gecikmesini ve maliyet artışını engelleyeceği göz önünde bulundurulmalıdır.

Anahtar Kelimeler: Bilgisayarlı tomografi; fidusiyal işaretleyici; migrasyon; prostat kanseri; radyoterapi.

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Introduction

Prostate cancer is the most common cancer and the second most common reason of cancer death in men.[1] Radical prostatectomy, external beam radiotherapy (EBRT) and brachytherapy are different options in the treatment of localized prostate cancer.[2] During the past decade, substantial developments have been made in EBRT and the main objective has become irradiating smaller volumes with much higher radiation doses.[3] These improvements allowed maximizing the radiation dose for the tumor with restricting toxicity to the rectum and bladder.[2] However, it may be difficult to localize the prostate gland for irradiation because the prostate does not stay in the same location during the radiotherapy process.[4] Variable bladder volume and rectal capacity as well as respiration may lead to prostate displacement up to 2 cm which results in improper radiotherapy.[2-4] This may cause inaccurate dose coverage of the prostate, especially with smaller planning target volume margins. In current treatment courses to account for prostate motion, ensure accurate delivery of high-dose radiation, and localize the prostate easily and exactly, image-guided 3-dimensional conformal radiation therapy is used with implanted fiducial markers since the last decade.[2] Implantation of fiducial markers is minimally invasive, well-tolerated procedure not associated with significant complications.[5] Because the fiducial markers are surrogates for the position of the prostate gland, the positional stability of these markers is crucial which has been questioned.

Studies have shown that migration of fiducial markers may occur during the radiation therapy.[6-13] It is not clear whether clinically significant fiducial marker migration happens immediately after insertion because of prostatic swelling or bleeding. To allow for an initial migration or settling of the fiducial markers, computed tomography (CT) for radiotherapy planning is generally performed several days after marker insertion. If fiducial marker migration occurs after the treatment planning CT, then it can result in inaccurate treatment targeting and difficulty in treatment. Also this situation may result in increased cost and delayed radiotherapy because of recurrent patient visits.[6] The aim of this study was to determine whether significant fiducial marker migration occurs within the interval between the prostatic marker insertion and radiotherapy treatment planning CT and if a waiting period is necessary.

Material and methods

Thirty-nine patients with localized prostate adenocarcinoma who underwent fiducial marker insertion before radiotherapy between June 2013 and December 2015 at our institution were retrospectively analyzed. Marker insertion procedure was performed by the same radiologist at our center. Gold markers were inserted transrectally with the patient in a dorsal lithotomy position with the aid of ultrasonography under mild general anesthesia without endotracheal intubation. Three fiducial markers (1.2x3 mm; CIVCO, Orange City, Iowa) were inserted using a preloaded sterile needle (30 cm, 17G) into the right base, left deep mid-gland and right apex of the prostate in a triangle shape. If the patients were under anticoagulant therapy, the anticoagulant drugs were stopped one week before insertion. Patients were advised to fast after midnight and underwent rectal enema a few hours before the procedure. Antibiotic prophylaxis was done with 1000 mg intravenous cefazolin during the procedure followed by 500 mg oral ciprofloxacin at every 12 hours for 5 days. Three hours after insertion, the patients underwent anteroposterior (AP) and lateral X-Ray of the pelvis (Figure 1) to confirm the number and position of the markers which were immediately verified with CT (Figure 2).

Radiotherapy planning CT was performed within an average of 11±2.4 days (range 7-20 days) after fiducial marker insertion. Patients underwent rectal enema and were asked to drink at least

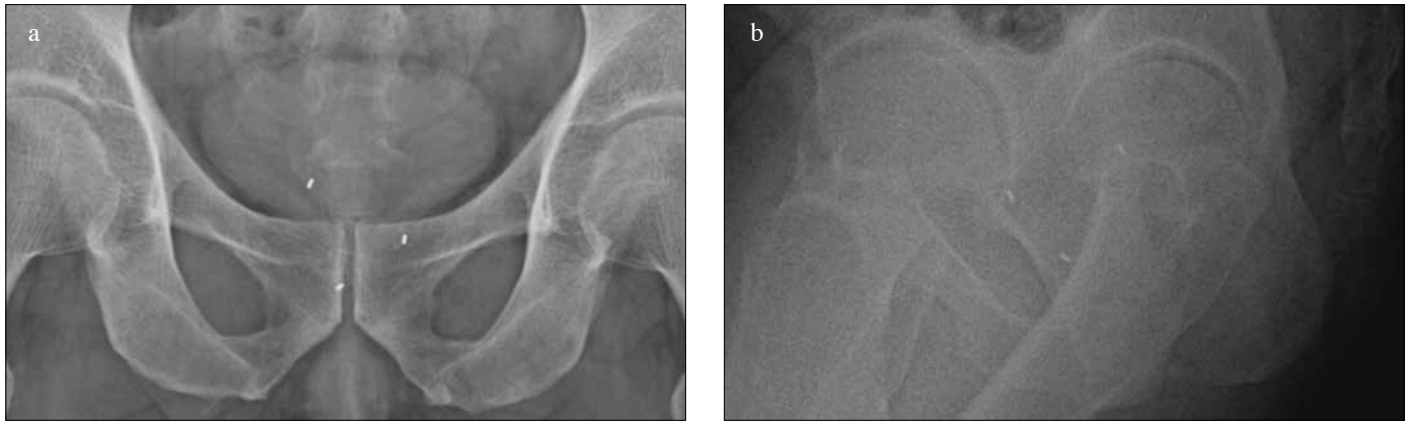

Figure 1. a, b. Two-dimensional X-Ray of the pelvis demonstrating three prostatic gold markers in a triangle position on AP (a) and lateral (b) views

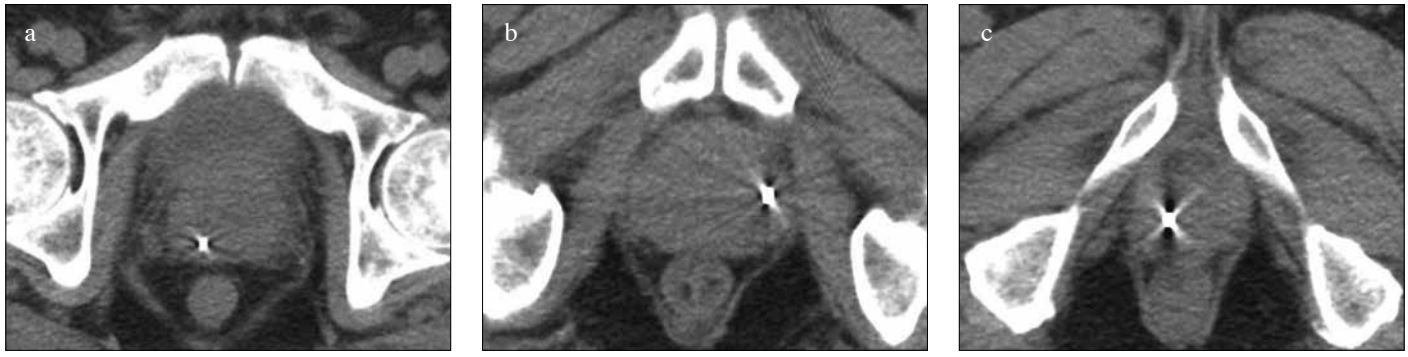

Figure 2. a-c. Axial CT images demonstrating inserted gold markers in the right base (a), left deep mid-gland (b) and right apex (c) of the prostate

500 mL of water before the planning CT. The slice thickness of the CT was 2 mm. CT images obtained from the days of insertion up to radiotherapy planning were imported into the Eclipse treatment planning system (TPS, Varian Medical Systems, Palo Alto, CA, USA) to analyze the position of fiducial markers. Point- based marker match algorithm through rigid translations and rotations was used to find the distance of migration. After registration, the mean and maximum distances between each fiducial markers were recorded. Patients were divided into two groups: those who had CT simulation 11 days before (the median time from fiducial marker insertion to treatment planning CT) or after radiotherapy planning.

Each patient signed an informed consent before fiducial marker insertion, computed tomographic examination and radiotherapy respectively. Because ours was a dosimetric study, we did not get approval of the ethics committee. Our study has been prepared in accordance with the principles of Helsinki declaration.

Statistical analysis

Two-tailed Student t-test and Anova was used to compare the groups. P≤0.05 was considered statistically significant. IBM Statistical Package for the Social Sciences (IBM SPSS Statistics; Armonk, NY, USA) version 20.0 for Windows was used for statistical analysis. The factors that may affect marker migration including prostate volume, patient age prostate specific antigen (PSA) levels and Gleason scores were also evaluated.

Results

Median patient age was 70 years (range; 55-83 years). PSA levels were <10 ng/mL in 10 (25.6%), 10-20 ng/mL in 16 (41.0%) and >20 ng/mL in 13 patients (33.4%). Median prostate volume was 55.8 cc (range; 28.59-130.71 cc). Gleason scores were 3-6 in 15 (38.5%), 7 in 15 (38.5%) and 8-10 in 9 patients (23.1%). The patient characteristics are described in Table 1. The average time from fiducial marker insertion to treatment planning CT was 11±2.4 days (range 7-20 days). The patients were grouped according to the time of marker implantation and there were 26 patients (66.7%) whose markers were implanted at or before 11 days in 26 (66.7%), and 11 days after in 13 (33.3%) patients . The mean and maximum distances of marker migration were calculated as 1.029±0.42 mm (range; 0.23-1.93 mm) and 1.361±0.59 mm (range; 0.25-2.74 mm), respectively. Seven of 39 patients had a maximum distance of >2 mm. For the time groups (at or before 11 days and after 11 days), mean distances were 1.014±0.40 mm and 1.057±0.55 mm respectively without any statistically significant difference (p=0.90).

Table 1. Patient characteristics

Median age	70 years (range 55-83)
PSA	Patients, n
<10 ng/mL	10 (25.6%)
10-20 ng/mL	16 (41.0%)
>20 ng/mL	13 (33.4%)
Gleason score	
3-6	15 (38.5%)
7	15 (38.5%)
8-10	9 (23.1%)
Prostate volume	Median 55.8 cc (range 28.59-130.71)

PSA: prostate-specific antigen

For the patients whose prostate volumes were ≤55.8 cc or more than this value, mean distances were 1.014±0.37 mm and 1.044±0.47 mm, respectively without any statistically significant difference (p=0.82). The patients were also grouped according to their ages and the mean distances for the patients ≤70 or >70 years of age were 0.959±0.34 mm and 1.128±0.51 mm respectively without a statistically significant intergroup difference (p=0.22). The patients were grouped according to the risk groups based on PSA levels and Gleason scores. For the patients whose PSA levels were <10 ng/mL, 10-20 ng/

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mL and >20 ng/mL; mean distances were 1.145±0.52 mm, 1.070±0.35 mm and 0.887±0.40 mm respectively, without a statistically significant intergroup difference (p=0.18). For the patients whose Gleason scores were 3-6, 7, and 8-10; mean distances were 1.195±0.45 mm, 1.008±0.39 mm and 0.786±0.27 mm respectively, without a statistically significant intergroup difference (p=0.16).

Discussion

Different possible reasons are described for intraprostatic fiducial marker migration. The fiducial marker may be in a small pool of blood just after the placement and a few days may be needed for the organization of the hemorrhage to become fixed into the gland.[9] Poggi et al.[10] studied 9 patients with 5 fiducial markers each and reported an average migration of 1.2±0.2 mm for markers, just as Aubin et al.[11] who revealed similar findings on 7 patients with 3 markers each. Litzenberg et al.[12] studied 10 patients with 3 markers through their radiation treatment and reported marker migration ranging from 0.7 to 1.7 mm. Kupelian et al.[7] obtained similar results in 56 patients with 3 markers each. In our study of 39 patients, the mean and maximum distances of marker migration were 1.029±0.42 mm and 1.361±0.59 mm, respectively, which were similar with the above- mentioned studies. Chung et al.[13] and Delouya et al.[9] investigated the rating of the quality of the matching procedure and importance of fiducial marker migration for the matching accuracy. Delouya et al.[9] aimed to determine a cut-off value of marker migration which results in difficult or inaccurate matches. They included 31 patients (only 8 patients had planning CT just after marker insertion) and found an mean migration of 1.2±0.6 mm. They determined that migration of less than 2 mm does not affect the matching quality significantly and suggested that if the marker migration from the planning CT to the first day of the radiotherapy was more than 2 mm, it is necessary to perform a new planning CT or to adapt the planning target volume margins, so matching would be more proper if the planning CT was performed several days after marker insertion. Tiberi et al.[14] investigated marker migration in 37 patients who were treated for prostate cancer with concurrent androgen deprivation therapy (ADT) and radiotherapy. They reported a mean migration of 0.8±0.3 mm which was less than the mean migration (1.2±0.6 mm) found by Delouya et al.[9] in patients treated without ADT. This result was also discordant with the findings of Pouliot et al.[15] concerning 11 patients 8 of which received concurrent ADT. Three of these 8 patients showed a reduction in intermarker distance of approximately 6 mm within 52 days due to a global reduction in prostate volume. Kumar et al.[6] has specifically evaluated fiducial marker migration following insertion and 7 days after in 100 patients and found a mean distance of 0.78±0.45 mm. In their study, 99 of 100 patients had migration less than 2 mm therefore they concluded that clinically significant migration does not occur immediately after insertion as well as marker insertion technique, prostate size and marker location do not affect migration considerably.

In our study of 39 patients, the median time from fiducial marker insertion to treatment planning CT was 11 days. The mean and maximum distances of marker migration were 1.029±0.42 mm and 1.361±0.59 mm, respectively which were not significantly different relative to the previous studies.[6-12] The distance of marker migration was not statistically significant for the groups organized according to the timing of marker insertion, prostate volume, patient age, PSA level and Gleason score. Seven of 39 patients had a maximum distance of more than 2 mm which was accepted as clinically significant marker migration.[6,9]

A number of limitations exited in our study, first it was a retrospective study. The study has also small sample size. The migration during treatment, effects of migration on matching difficulty during treatment and effects of androgen deprivation therapy on migration were not examined. The definition of distance for marker migration was another limitation of our study.

In conclusion, our study suggests that significant fiducial marker migration does not occur between insertion and treatment planning CT. Therefore, radiotherapy planning CT and simulation can be performed on the same day after insertion to prevent increased cost and delayed radiotherapy by saving the patients from extra visits to the clinic without significant concern for marker migration.

Ethics Committee Approval: Authors declared that the research was conducted in compliance with Ethical Principles for Medical Research Involving Human Subjects stated in the World Medical Association Declaration of Helsinki "" (amended in October 2013).

Informed Consent: Written informed consent was obtained from patient who participated in this study.

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