Ann Med Res

Current issue list available at AnnMedRes

Annals of Medical Research

journal page: www.annalsmedres.org

Prostate gland localization with fiducial markers

Hatice Onder[a,*], Gul Kanyilmaz[b]

[a] *Ataturk Public Hospital, Department of Radiation Oncology, Aydın, Turkey*
[b] *Necmettin Erbakan University, Meram School of Medicine, Department of Radiation Oncology, Konya, Turkey*

ARTICLE INFO

Keywords:
Prostate cancer
Radiotheraphy
Fiducial markers

Received: Sep 20, 2021
Accepted: Mar 25, 2022
Available Online: May XX, 2022

DOI:
10.5455/annalsmedres.2021.09.546

Abstract

Aim: Prostate gland inter-intra fraction organ motion cause uncertainties on both target organ definition and risky organ doses. The aim of this study is to determine axis shifts between gold markers and pelvic bony structures by using electronic portal images and factors which affects these shifts at prostate cancer patients who had gold marker implantation before radiotheraphy.

Materials-methods: This study involved 31 patients with prostate cancer who had placement of gold markers into the prostate gland before radiotheraphy. In the course of treatment, electronic portal images were used for field control with guidance of gold markers every other day. Treatment fields determined by using bony structures and gold markers respectively. Lateral, longitudinal and vertical axis shifts (minimum, mean, maximum) between gold markers and pelvic bony structures were evaluated and the factors which attracted these shifts were examined.

Results: We assessed a total of 1683 electronic portal images, and we determined axis shifts between gold markers and bony structures mean laterally minimum 0.3 (0-3)mm, mean 0.4 (0.5-3.2)mm, maximum 3.2 (1-6)mm; longitudinally minumum 0.5 (0- 4) mm, mean 2.4 (0.8-8.4) mm and maximum 6.1 (2-12) mm; vertically minumum 0.5 (0- 2) mm, mean 1.8 (0.4-4) mm and maximum 4.3 (1-7). The relation between maximum lateral axis shift values and using hormone-replacement theraphy; minimum vertical axis shift values and body mass index were statiscally significant (p=0.02, p=0.03).

Conclusion: We established a statistically significant relation between lateral axis shift maximum values and using hormone-replacement theraphy; minimum vertical axis shift values and body mass index(p=0.02, p=0.03). Treatment margin must be determined carefully, especially in patients who have elevate body mass index and use hormone theraphy, if gold markers can not be used.

Introduction

Radiotheraphy (RT) is one of the main component of prostate cancer treatment. In recent 20 years, RT doses were escalated to 72-86 Gray (Gy) from 66-70 Gy with using new RT techniques such as intensity modulated radiation theraphy (IMRT), image guided radiation theraphy (IGRT) and volumetrik modulated arc threaphy (VMAT). Biochemical and clinical progression free survival and overall survival were increased with dose escalation, furthermore acute and late side effects showed an increase [1-5]. Prostate gland is a movable organ in pelvic bony structures. Rectum and bladder fullness affect prostate gland movement. Soft tissue matching is more important for prostate localization during RT. Target volume registration with electronic portal image (EPI) or cone beam computer tomography (CBCT) by using bony structures as refference is inadequate. Prostate gland localization with EPI is impossible while it's feasible with CBCT but high scan doses (5-15 cGy) is required and soft tissue matching enhances treatment time and increases the risk of intrafractional set up mistakes [6].

Interfractional set up mistakes can be qualify with IGRT for prostate cancer treatment, both dose escalation and toxicity reduction can be done with this technique [7-9]. For this technique, prostate gland movements must be followed closely. Fiducial marker (FM) placement to prostate gland is one of the standart technique for monitoring organ motion. It is an invaziv procedure and there are some risks such as blooding and infection , but it is fast and tolerable frequently [10-14]. FMs are visible with kilovolt (kV) or megavolt (MV) imaging [15].

For planning target volume (PTV) margin, patient posi-

*Corresponding author:
Email address: dr.haticeyildiz@hotmail.com (Hatice Onder)

tion changes, beam sequences and organ movements must be taken into consideration. It is possible to reduce toxicities with FM by clinical target volume (CTV) and PTV margin reduction [16].

In this study, we aimed to compare the accuracy of portal image based set up corrections with fiducial markers and pelvic bony structures seperately, to evaluate prostate gland motion by measuring the axis shifts between pelvic bony structures and FMs. Also we aimed to see the factors which possibly affects prostate gland motion.

Materials and Methods

This was a single institutional and retrospective study. 31 localize prostate cancer patients who had definitive RT in our department age ≥18, nonmetastatic, no prior history of prostatectomy and had FMs for prostate localization were involved in this study. All patients had three gold seeds in the prostate that were placed by an urologist under transrectal ultrasound 10 days before planning computer tomography (CT). Gold seeds were placed into base, middle and apex of prostate gland with an angle of 45 degree. All patients were scanned at supine position with a full bladder, empty rectum with Siemens Spring Power CT. Patients were asked to drink 1000 ml of water half an hour before CT scan . CT scans were optained in a slice thickness of 3 mm. CT images were transferred to planning system (Eclips version 8.9. (CTV] (prostate and seminal vesicals] and PTV (CTV+1 cm all directions and 6 mm for posterior direction] were determined. All patients were treated with lineer accelerator (Varian clinical IX /120 MLC with 0.5 cm thickness] by IMRT technique (using pencil beam algoritm with 6MV photon energy] a total dose of 74-78 Gy .Patients treatment field registrations were done every other day with EPI (Varian portal vision; 2 MU, 6MV, 15x15 cm field size at gantry 0-90 and treatment field) by using makers as refference during treatment.

In this study, we examined a total of 1683 EPIs of 31 patients retrospectively from offline rewiew. There was lateral, anterior-posterior and treatment field EPIs of all patients.We did field registration both with guidance of gold markers and pelvic bony structures respectively and measured the axis shifts between these methods . Maximum, minimum, mean values of the axis shifts at lateral, vertical and longitudinal directions between gold markers and pelvic bony structures were estimated to report the amount of the prostate gland motion. We researched the factors which may affect these shifts like age, tumor stage, body mass index, hormonal treatment, initial prostate volume. This research was approved by the institutional ethic board of Bulent Ecevit University (Protocol number: 33479383/22) at 18/04/2019 and conducted according to the ethical principles of the declaration of Helsinki.

Statistical methods

Statistical analyses were analyzed by Statistical Package for Social Sciences software, v 13.0 (SPSS, Chicago, IL, USA). Patient, disease, and treatment characteristics were performed by descriptive statistics. The minumun value, maximum value, mean value, proportion value, ranges, and standard deviation values were specified. Categorical variables were analyzed by Pearson's Chi-square test, and continuous variables were analyzed by ANOVA test and independent samples T-test. A two-sided p-value of ≤0.05 was considered to be statistically significant.

Table 1. Patient Characteristics

	median	range
Age	71	(54-83)
RT dose	76 Gy	(74-78)
BMI	27.6 kg/m^2	(21.5-34.6)
PSA	8	(0.55-47)
	Patient number	Percentage(%)
Hormonal treatment		
Yes	22	77
No	9	23
T Stage		
T1	1	3.2
T2a	8	25.8
T2b	10	32.3
T2c	12	38.7
Gleason score		
3+3	17	54.8
3+4	8	25.8
4+3	3	9.7
4+4	2	6.5

Results

Median patient age was 71 years (54- 83). Median RT dose was 76 (74-78) Gy. 22 patients (%71) had hormonotheraphy (HT) with RT. Mean body mass index (BMI) was 27.6. BMI of 22 patients (%71) was above the normal value. Mean prostat spesific antigen (psa) was 11.57, median psa was 8. (Patients demographics described at Table 1)

We assessed a total of 1683 EPIs, and we determined axis shifts between gold markers and bony structures mean laterally minimum 0.3 (0-3)mm, mean 0.4 (0.5-3.2)mm, maximum 3.2 (1-6)mm; longitudinally minumum 0.5 (0- 4) mm, mean 2.4 (0.8-8.4) mm and maximum 6.1 (2-12) mm; vertically minumum 0.5 (0- 2) mm, mean 1.8 (0.4-4) mm and maximum 4.3 (1-7). Maximum axis shifts between pelvic bony structures and gold markers were 12.7 and 6 mm at longitudinal, vertical and lateral directions respectively

Factors which may affect these shifts like age, tumor stage, BMI, hormonal treatment, gleason skor and initial prostate volume were researched. The relation between maximum value of lateral axis shift values and using HT; minimum vertical axis shift values and body mass index were statistically significant (p=0.02, p=0.03).

At single variable analysis, an inverse proportion between all directions axis shifts and initial prostate volumes was assessed. We detected that, while initial prostate volume was increasing, the axis shifts at all directions was decreasing. This relationship was statistically significant at only lateral minimum and longitudinal minimum values (p:0.01 and p:0.004).

Discussion

The success and effectiveness of prostate cancer radiotherapy depend on the accuracy of dose distribution [17]. With the use of higher doses, biochemical failure rates decreased, while side effects increased [18]. Biochemical control rates improved by %15-20 at the doses of 74-81 Gy [5]. Biochemical tumor control also improved overall survival and reduced the development of distant metastases. As compared with three-diemensional conformal radiation theraphy (3D-CRT), toxicities were reduced with IMRT and this reduction was much more with IGRT [17].

Prostate gland location changes in the pelvic bony structures due to the filling of rectum and bladder. The modalities for locating the prostate gland during RT are pretreatment transabdominal ultrasound localization, FMs, CBCT and in room helical CT [19, 20] .CBCT is one of the most popular method that can be used to determine prostate gland localization. But higher imaging doses are required for CBCT and the other disadvantage of this method is that; interobserver variations are much more as compared with FM using [21]. Moseley at al. emphasized that FM and CBCT are comperable for prostate gland localization during RT. Prostate gland can not be viewed with standart portal imaging techniques but FM implantation allows for prostate localization with portal imaging. Additionally, CTV-PTV margin can be decreased by using FMs. Dose distribution and prostate movements can be determined correctly. Accurate dose and precise target definition faciliates dose escalation without of toxicity [22]. Also, FM implantation can perform successfully with acceptable toxicity, even though it is an invasive modality [16]. The common complications with FMs are hematuria, rectal bleeding and fever [14, 23, 24]. In our study, after transrectal gold markers implantation, 2 patients had clinical infection evidences and they treated with antibiotics successfully. Rectal bleeding and hematuria were not seen in any patient.

There are some types of FMs as gold markers, pollymer markers and electromagnetic markers. Gold and Pollymer FMs are the most commonly used. Gold FMs can be viewed at CT and CBCT but there are more artifacts arround the markers. Pollymer FMs have minimal artifacts but they can not be seen at EPI . They are appropriate for kV imaging. If EPI or MV imaging will use, gold markers can be clearly defined at lateral and anterior-posterior portal image [25].

In the current study, gold FMs were used. We assessed the axis shifts between pelvic bony structures and gold markers. We also determined interfractional motion of prostate. Maximum axis shifts were 12, 7 and 6 mm at longitudinal, vertical and lateral directions respectively. The mean value of maximum shifts were 6.1 mm, 4.3 mm and 3.2 mm at longitudinal, vertical and lateral directions respectively. According to literature, the motion of prostate at vertical and longitudinal directions is significantly larger than motion at lateral direction [26]. Schallenkemp at al. determined the shifts between pelvic bony structures and FMs with daily portal imaging and they showed 2.5 mm, 3.7 mm and 1.9 mm mean shifts at vertical, longitudinal and lateral directions, respectively [27]. Their results were in accordance with our results. Similarly, Van der Heide at al. researched 453 prostate motions between treatments with FMs. They determined $>$ 3 mm shift %34 at vertical, %35 at longitudinal and %9 at lateral directions [28]. Skarsgard at al. examined interfractional prostate motion with EPI and FM, they emphasized 3.7 mm, 3.7 mm and 3.6 mm PTV margin was optimum at vertically, longitudinally and laterally respectively [29]. Our study results comfirmed all these outcomes.

Possible factors that might affect prostate movement were also examined in this study. The effects of BMI, initial prostate volume, HT use, age, and tumor size on prostate gland motion were investigated. The relation between maximum lateral axis shift values and using HT; minimum vertical axis shift values and body mass index were statistically significant. There are many studies investigated a relationship between BMI and prostate gland motion. Stintaroh at al. displayed negative correlation between BMI and prostate motion at anterior-posterior direction and positive correlation at lateral direction [30]. Set up errors were much more with overweight patients because there was higher shifts at markers on the skin [31]. But some studies reported that interfractional prostate motion at craniocaudal direction was lesser with obes patients [32]. This was probably about male form obesity. Abdominal fatty tissues put pressure on the prostate at caudal and dorsal directions. This limits the prostate gland motions. According to some previus studies, there was no relationship between BMI and prostate shifts except left-right shifts [33]. Many studies reported increased left-right shifts at obes patients [32, 34].

HT had a shrinking effect on prostate gland and shrinking effect was most prominent with HT during the first 3 months [35]. We did not evaluate HT using time interval in our study. Another restrictiveness of this study was that, we did not determine intrafractional prostate shifts, rotational prostate motion and marker fixation. According to previus studies rotational prostate motions had a minimum effect on prostate localization as compared with translational corrections [36]. Prostate gland rotational motion was very small and more than 15 degrees rotations were due to patients movements [37].

The lack of measurement of intrafractional prostate movement was the shortcoming of this study. Past studies showed that intrafractional prostate shifts were smaller than interfractional shifts [26]. It was known that this movement increases as the daily treatment period increases. Another lack of this study was that the positions of the markers were not evaluated. But according to literature, markers were well fixed and they moved all together probably due to prostate shrinking [28]. The movement was usually less than 1 mm [27].

In conclusion, prostate gland localization during RT is required for the success and effectiveness of prostate cancer radiotherapy. Daily portal imaging with FMs is an effective method to determine the position of prostate gland during RT. PTV margins must be created carefully wtih patiens who have not FM, especially in overweight patients and patients who have HT.

References

1. Zelefsky MJ, Levin EJ, Hunt M, et al. Incidence of late rectal and urinary toxicities after three-dimensional conformal radiotherapy and intensity-modulated radiotherapy for localized prostate cancer. Int J Radiat Oncol Biol Phys. 2008;70:1124-9
2. Michalski JM, Yan Y, Bruner DW, et al. Preliminary toxicity analysis of 3-dimensional conformal radiation therapy versus intensity modulated radiation therapy on the high-dose arm of the Radiation Therapy Oncology Group 0126 prostate cancer trial, Int J Radiat Oncol Biol Phys. 2013;87:932-8.
3. Dearnaley DP, Jovic G, Syndikus I, et al. Escalated-dose versus control-dose conformal radiotherapy for prostate cancer: long-term results from the MRC RT01 randomised controlled trial. Lancet Oncol. 2014;15:464-73
4. Kuban DA, Tucker SL, Dong L, et al. Long-term results of the M. D. Anderson randomized dose-escalation trial for prostate cancer. Int J Radiat Oncol Biol Phys. 2008;70:67-74
5. Beckendorf V, Guerif S, Le Prisé E, et al. 70 Gy versus 80 Gy in localized prostate cancer: 5-year results of GETUG 06 randomized trial. Int J Radiat Oncol Biol Phys 2011;80:1056-63.
6. Hoogeman MS, Nuyttens JJ, Levendag PC, et al. Time dependence of intrafraction patient motion assessed by repeat stereoscopic imaging. 2008;70:609-18.
7. Gill S, Thomas J, Fox C, et al. Acute toxicity in prostate cancer patients treated with and without image-guided radiotherapy. Radiat Oncol 2011 Oct 28;6:145
8. Rudat V, Nour A, Hammoud M, et al. Image-guided intensity-modulated radiotherapy of prostate cancer: Analysis of interfractional errors and acute toxicity. Strahlenther Onkol. 2016;192:109-17
9. Drozdz S, Schwedas M, Salz H, et al. Prostate cancer treated with image-guided helical TomoTherapy® and image-guided LINAC-IMRT : Correlation between high-dose bladder volume, margin reduction, and genitourinary toxicity. Strahlenther Onkol 2016;192:223-31
10. Welsh JS, Berta C, Borzillary S, et al. Fiducial markers implanted during prostate brachytherapy for guiding conformal external beam radiation therapy. Technol Cancer Res Treat.2004;3:359-64.
11. Dehnad H, Nederveen AJ, van der Heide UA, et al. Clinical feasibility study for the use of implanted gold seeds in the prostate as reliable positioning markers during megavoltage irradiation. Radiother Oncol. 2003;67:295-302.
12. Shinohara K, Roach M. Technique for implantation of fiducial markers in the prostate. Urology. 2008 ;71:196-200.
13. Linden RA, Weiner PR, Gomella LG, et al. Technique of outpatient placement of intraprostatic fiducial markers before external beam radiotherapy. Urology.2009;73:881-6.
14. Igdem S , Akpinar H, Alço G, et al. Implantation of fiducial markers for image guidance in prostate radiotherapy: patient-reported toxicity. Br J Radiol. 2009;82:941-5.
15. McVicar N, Popescu IA, Heath E. Techniques for adaptive prostate radiotherapy. Phys Med. 2016;32:492-8.
16. Ghaffari H, Navaser M, Mofid B, et al. Fiducial markers in prostate cancer image-guided radiotherapy. Med J Islam Repub Iran. 2019;33:15.
17. Rastogi M, Nanda SS, Gandhi AK, et al. Pelvic bone anatomy vs implanted gold seed marker registration for image-guided intensity modulated radiotherapy for prostate carcinoma: Comparative analysis of inter-fraction motion and toxicities. J Egypt Natl Canc Inst. 2017;29:185-190.
18. Zelefsky MJ, Fuks Z, Leibel SA. Intensity-modulated radiation therapy for prostate cancer. Semin Radiat Oncol.2002;12:229-37.
19. Stephans KL, Xia P, Tendulkar RD, et al. The current status of image-guided external beam radiotherapy for prostate cancer. Curr Opin Urol.2010;20:223-8.
20. Soete G, Verellen D, Storme G. Image guided radiotherapy for prostate cancer. Bull Cancer.2008;95:374-80.
21. Moseley DJ, White EA, Wiltshire KL, et al. Comparison of localization performance with implanted fiducial markers and cone-beam computed tomography for on-line image-guided radiotherapy of the prostate. Int J Radiat Oncol Biol Phys.2007 ;67:942-53.
22. Weg ES, Pei X, Kollmeier MA, et al. Dose-Escalated Intensity Modulated Radiation Therapy for Prostate Cancer: 15-Year Outcomes Data. Adv Radiat Oncol. 2019 ;4:492-499.
23. Gill S, Li J, Thomas J, et al. Patient-reported complications from fiducial marker implantation for prostate image-guided radiotherapy. Br J Radiol. 2012 ;85:1011-7.
24. Loh J, Baker K, Sridharan S, et al. Infections after fiducial marker implantation for prostate radiotherapy: are we underestimating the risks?. Radiat Oncol. 2015;10:38.
25. Osman SOS, Russell E, King RB, et al. Fiducial markers visibility and artefacts in prostate cancer radiotherapy multi-modality imaging. Radiat Oncol. 2019;14:237.
26. Byrne TE. A review of prostate motion with considerations for the treatment of prostate cancer. Med Dosim Fall 2005;30:155-61.
27. Schallenkamp JM, Herman MG, Kruse JJ, et al. Prostate position relative to pelvic bony anatomy based on intraprostatic gold markers and electronic portal imaging. Int J Radiat Oncol Biol Phys. 2005;63(3):800-11.
28. van der Heide UA, Kotte AN, Dehnad H, et al. Analysis of fiducial marker-based position verification in the external beam radiotherapy of patients with prostate cancer. Radiother Oncol. 2007;82:38-45.
29. Skarsgard D, Cadman P, El-Gayed A, et al. Planning target volume margins for prostate radiotherapy using daily electronic portal imaging and implanted fiducial markers. Radiat Oncol. 2010;5:52.
30. Maruoka S, Yoshioka Y, Isohashi F, et al. Correlation between patients' anatomical characteristics and interfractional internal prostate motion during intensity modulated radiation therapy for prostate cancer. Springerplus. 2015;4:579.
31. Millender LE, Aubin M, Pouliot J, et al. Daily electronic portal imaging for morbidly obese men undergoing radiotherapy for localized prostate cancer. Int J Radiat Oncol Biol Phys. 2004;59:6-10.
32. Thompson AL,Gill S, Thomas J, et al. In pursuit of individualised margins for prostate cancer patients undergoing image-guided radiotherapy: the effect of body mass index on intrafraction prostate motion. Clin Oncol (R Coll Radiol).2011 ;23:449-53.
33. Brown A, Tan A, Cooper S, et al. Obesity does not influence prostate intrafractional motion. J Med Radiat Sci. 2018;65:31-38.
34. Noel C, Parikh PJ, Roy M, et al. Prediction of intrafraction prostate motion: Accuracy of pre- and post-treatment imaging and intermittent imaging. Int J Radiat Oncol Biol Phys 2009; 73: 692–8.
35. Onal C, Topkan E, Efe E, et al. The effect of concurrent androgen deprivation and 3D conformal radiotherapy on prostate volume and clinical organ doses during treatment for prostate cancer. Br J Radiol. 2009;82:1019-26.
36. Redpath AT, Wright P, Muren LP. The contribution of on-line correction for rotational organ motion in image-guided radiotherapy of the bladder and prostate. Acta Oncol. 2008;47:1367-72.
37. Boda-Heggemann J, Lohr F, Wenz F, et al. kV cone-beam CT-based IGRT: a clinical review. Strahlenther Onkol.2011;187:284-91.