Oncology and Translational Medicine
DOI 10.1007/s10330-018-0297-7

June 2019, Vol. 5, No. 3, P131–P136

ORIGINAL ARTICLE

Comparison of bone alignment and fiducial marker alignment for online cone-beam computed tomography-guided radiation therapy for prostate cancer

Hussein M. Metwally [1, 2] (✉)

[1] Clinical Oncology Department, Faculty of Medicine, Fayoum University, Cairo, Egypt
[2] Dar Al Fouad Hospital, Radiation Unit, Cairo, Egypt

Abstract

Objective The aim of the study was to evaluate the coverage of the prostate when prostatic implanted fiducial markers are used to verify setup of the patients in comparison to the pelvic bones while using cone-beam computed tomography (CBCT).

Methods Seventeen patients with prostate cancer were included. For each patient, daily online CBCT was done. CT planning was matched with CBCT with the help of fiducial markers (3–5 markers) and another matching with done the help of pelvic bony landmarks. Registration of clinical target volume (CTV) 1 including prostate plus seminal vesicles and CTV2 including prostate only was done and were used to confirm the target volume during the process of matching. Delineation of the rectum on every CBCT was done. Two automatic margin representing planning target volume (PTV) were created. PTV1 was generated by adding 1 cm in all directions (PTV1a) and 0.7 cm in the posterior direction (PTV1b). PTV2 was generated by adding 0.5 cm in all directions (PTV2a) and 0.3 cm in the posterior direction (PTV2b). PTV1a was prescribed to receive 46 Gy in conventional fractionation with a boost dose of 30 Gy to PTV1b. The same dose was prescribed to PTV2a and PTV2b. Calculation of the percentage of intersection between CTV1 and CTV2 created on CBCT with the original CTV scan was done. A comparison between the two CTVs (CTV1 and CTV2) mean dose and the original delineated CTV was done. Then a comparison to the mean dose of the original CTV of PTV1a, PTV2a (CTV1a and CTV2a), and for PTV1b and PTV2b (CTV1b and CTV2b). Calculation of the mean rectal dose and also V60, V70 and V74 was done on the delineated rectum on every CBCT, and then a comparison to the planned original rectal dose.

Results The created CTV1 and CTV2 intersection percentage with the original CTV1 and CTV2 significantly increased by 85% (range, 65%–95%, $P < 0.05$), when fiducial markers were used. The main difference of the received mean dose was significantly less in comparison to pelvic bone alignment (0.03% to 2% vs 0.03% to 11.6% for PTV1a, $P < 0.006$; 0.01% to 1.8% vs 0.03% to 10.2% for PTV2a, $P < 0.014$; 0.08 to 2.11 vs 0.04 to 11.29 for PTV1b, $P < 0.015$ and 0.01 to 1.79 vs 0.01 to 9.69 for PTV2b, $P < 0.004$). With the use of less PTV margins, significant decrease of the rectal mean dose, V60, V70 and V74 by $P < 0.004$, $P < 0.004$, $P < 0.0005$ and $P < 0.009$, respectively. Reduction of the CTV1a and CTV1b mean dose by 1.13% and 0.28% in comparison to the initial CTV1a and CTV2a.

Conclusion A significant improvement of prostatic cancer patients alignment when fiducial markers are used, with more homogenous dose distribution, and with significant decrease in PTV margins. The delivered rectal dose is significantly less allowing prostate dose escalation.

Received: 4 September 2018
Revised: 14 December 2018
Accepted: 27 December 2018

Key words: cone-beam computed tomography (CBCT); prostate cancer; bone alignment; fiducial marker alignment

✉ Correspondence to: Hussein M. Metwally. Email: khelshahat@yahoo.com

The dose received via external beam radiotherapy represents a curative treatment option for patients of all ages with prostate cancer [1–2].

Three-dimensional conformal irradiation techniques and intensity-modulated radiotherapy (IMRT) are being used increasingly in prostate cancer radiotherapy (RT) to minimize radiation dose to surrounding organs and to improve tumor control by dose escalation [3–5]. These new treatment techniques depend greatly on the precise design of margins during treatment planning. The margins must be large enough to encompass the planning target volume (PTV) within the prescription isodose line and account for patient setup variations and internal organ movement but must be small enough to limit the risk of injury to nearby critical structures.

Offline adaptive radiotherapy strategies [6–10] have been shown to be efficient and robust for designing patient-specific margins using a limited number of observations of patient setup error and internal organ motion.

The introduction of enhanced or new imaging systems in radiation oncology treatment rooms, such as an in-room kilovoltage X-ray system for bony landmark localization and markers [11–13], ultrasound imaging for prostate localization [14–17], or in-room computed tomography (CT) to provide three-dimensional volumetric patient data [18], provides opportunities for more proactive online image guidance based on bony anatomy or soft-tissue registration.

Cone-beam CT (CBCT), implemented onboard a medical accelerator, offers imaging guidance capabilities with great potential for significantly improving treatment accuracy [19].

Many studies have assessed the feasibility and accuracy of implanted gold seeds in the prostate and proved it to be an accurate, feasible, and safe method [20–24].

In this study, we used two different methods to assess accuracy and advantages of using implanted fiducial markers in the prostate with CBCT compared with that using bony landmarks.

Patients and methods

Patient population

In this study, we examined the data of 17 patients, with median age of 66 years, who were diagnosed with localized prostate cancer. The stage of disease ranged between T1c and T3a, with a mean Gleason score of 7 ng/mL. All patients were treated in the Institute of Claudius Regaud (Paris, France) between 2007 and 2008 with conformal external beam radiotherapy.

Fiducial marker implantation

Under local anesthesia, three to five fiducial markers were implanted in the prostate under ultrasound guidance. Implantation was performed at the same day of the planning CT. Patients also underwent pelvic magnetic resonance imaging (MRI) in the same treatment position to be used with the planning CT scan. No complication occurred in any of the patients during the procedure.

Target volume definition and dosimetric calculations

MRI images were registered to the planning CT scan using semiautomatic fusion system based on the position of the implanted fiducial markers (advantage windows planning system; Sun Nuclear Corporation and Philips, Neu-Isenburg, Germany). Subsequently the images were transferred to the pinnacle planning system (Philips Healthcare, Fitchburg, WI, USA).

On the planning CT scan, with the aid of registered MRI images, target volumes were defined, and the clinical target volume (CTV) 1 (prostate seminal vesicles), CTV2 (prostate), PTV1a, and PTV2a were automatically generated to include CTV1 and CTV2, respectively with a margin of 1 cm all around and 0.7 mm posteriorly.

Organs at risk were defined as follows: the rectal wall with a thickness of 5 mm extending 2 cm above and below PTV1a [25–27]. No special measures were taken for the rectum, but the patients were advised to evacuate the rectum before each session. Bladder wall was defined with a thickness of 7 mm, and the patients were also advised to have a semi-full bladder throughout all the treatment steps.

Dosimetric plans were generated using five fields with angles of (0°, 45°, 90°, 270°, and 315°) by initially using PTV1a at 46 Gy, followed by PTV2a at 30 Gy.

CBCT acquisition and image registration

All patients were treated using Varian linear accelerator equipped with online CBCT (OBI system; Varian Medical Systems, Inc., Palo Alto, CA, USA). CBCTs were acquired once weekly before treatment delivery throughout the whole treatment period. Only CBCTs with high quality were included in the study, resulting in an mean of five CBCTs for each patient. All CBCTs were transferred to the advantage windows planning system where semi-automatic fusion was performed for each CBCT with the original planning CT once using fiducial markers implanted inside the prostate and once using bony land markers as reference points for fusion. All fused images were transferred to the pinnacle planning system wherein the original contours for CTV1 and CTV2 were copied to each registered image and moved on each CT slice to fit the new prostate position acquired during treatment once with fiducial marker alignment and once with bony landmark alignment. The rectal wall was defined on each CBCT using the same protocol for the initial treatment plan.

CTV comparison

Three different methods were used in this study to evaluate the accuracy of patient repositioning.

The first method was to identify the percentage of intersection between generated CTVs on each CBCT for each patient and original CTV whether for CTV1 or CTV2. The initial planning CT scan, including contours of the initial CTVs and generated CTVs on each CBCT, were transferred to the pinnacle treatment planning system (Koninklijke Philips N.V., USA) where the percentage of intersection between the initial CTVs and generated CTVs were calculated for fiducial marker registration and bony landmark alignment.

The second method was to assess the dose delivered to CTV1 and CTV2 throughout the treatment period when using fiducial marker and bone alignment. The mean dose received by generated CTVs with the position acquired using fiducial marker and bone landmark alignment was calculated and compared with that of the initial CTVs.

The third method was to evaluate the accessibility of further PTV reduction when using fiducial marker alignment and its effect on the dose received by the rectum. A new PTV was generated around the initial CTV with 0.5 cm all around and 0.3 cm posteriorly (PTV1b and PTV2b) [28]. Another plan was generated using the same angle distribution similar to the initial plan but with the use of PTV1b and PTV2b. The mean dose received by the generated CTVs and V74, V70, and V60 for the rectum defined on the registered CBCTs were calculated and compared with the initial doses received by the initial CTVs and rectum.

Results

Percentage of intersection

Calculating the percentage of the volume intersection between CTVs generated on CBCTS and initial CTV showed that the percentage of intersection significantly increased by 85% (rang 65% to 95%) and 86% (range 63% to 95%) for CTV1 and CTV2, respectively, when using fiducial markers as the source for image registration ($P <$ 0.001; Fig. 1).

Dose calculation

The maximal variations of the mean dose delivered compared with the theoretical dose were significantly lower when using fiducial markers versus that using bony structures while using PTVa or PTVb for calculation.

For PTV1a and PTV2a, the range of variation for fiducial markers was 0.03%–2% and 0.01%–1.8%, whereas that for bone alignment was 0.03%–11.6% and 0.03%–10.2% ($P < 0.006$ and $P < 0.014$, respectively).

For PTV1b and PTV2b, we noted the same positive results in terms of fiducial marker alignment with a range of variation of 0.08–2.11 and 0.01–1.79 versus 0.04–11.29 and 0.01–9.69 ($P < 0.015$ and $P < 0.004$, respectively; Fig. 2).

Comparing the mean values of the mean dose, V74, V70, and V60 received by the contoured rectum on each CBCT with the initial theoretical doses planned to be received by the rectum dose showed that all the doses decreased significantly when using the smaller margin for the PTV with values of $P < 0.0042$, $P < 0.0009$, $P < 0.0005$, and $P < 0.0049$, respectively for volume dose. The mean dose received by the initial CTV1b and CTV2b decreased by 1.13% and 0.28%, respectively, compared with the mean dose received by the initial CTV1a and CTV2a. The percentage of reduction in dose delivered to the rectum was significantly greater than that of the CTV (57.27% versus 0.65%, $P < 0.0049$; Fig. 3).

Discussion

It is well known that the simulation CT image setup used for treatment planning is a snapshot of the patient's anatomy, although perhaps a most atypical one, because this is the first time a patient is introduced to the position in which RT is going to be performed. Systematic displacements in the prostate position between the simulation CT scan and daily RT sessions occur and can significantly affect the delivered radiation dose in patients with prostate cancer. Direct target localization methods, such as daily US alignment, CBCT with bone alignment, and electronic portal images with the use of intra-prostatic fiducial markers, are commonly used to make adjustments according to this uncertainty [4, 25, 29–37].

Many studies have shown that prostate dose escalation improves freedom from biochemical and clinical progression [38–41].

Using the modern techniques of radiation therapy provides an advantage of prostate dose escalation while decreasing the side effects of the treatment [42]. However, using these modern techniques gave rise to another problem with reduction in treatment field sizes.

In this study, we tried to evaluate the benefits achieved when combining the use of implanted fiducial markers with online CBCT. Having the CBCTs registered to the original planning CT scan allowed us to calculate doses for CTVs and rectums generated on the CBCTs.

Our results showed that the use of this combination can provide a more accurate method in daily patient repositioning than that while using CBCT with bone alignment. This technique allowed a more homogenous dose to be delivered to the CTV throughout the treatment period.

Moreover, we suggest that being more precise in daily alignment of the patient allows for further reduction in PTV volumes. Using a PTV with margins of 5-mm all

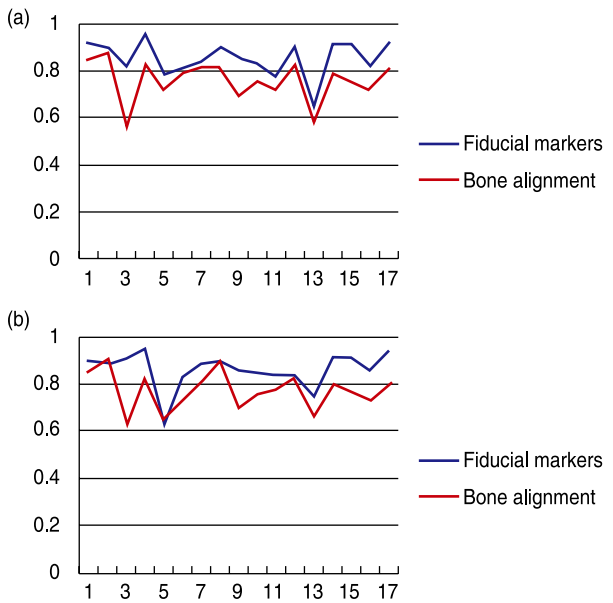

Fig. 1 Percentage of intersection for CTV1 (a) and CTV2 (b) when using fiducial markers and bone alignment

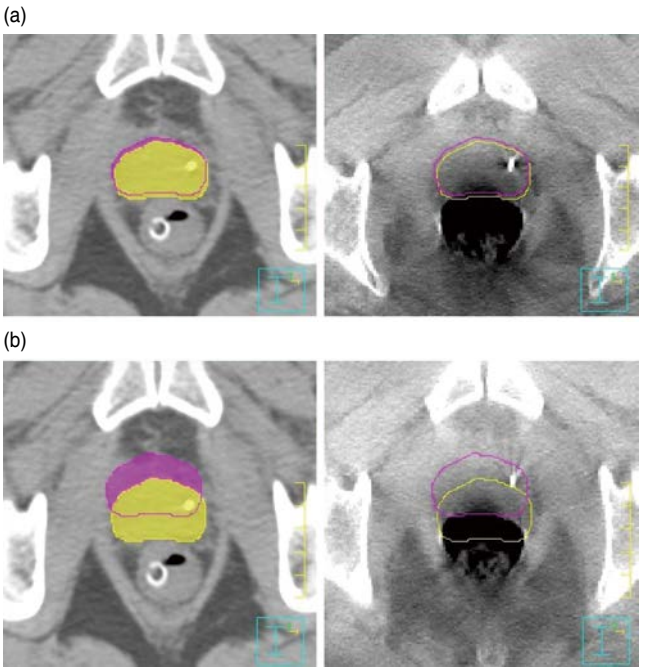

Fig. 2 Difference in CTV position with fiducial marker alignment (a) and bone alignment (b).

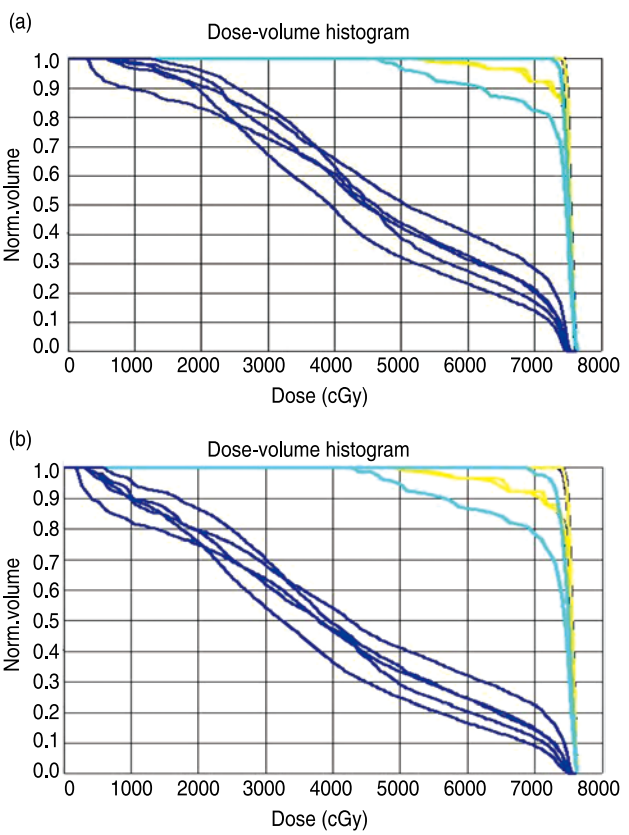

Fig. 3 Difference in dose received by the rectum and CTV with PTV1 (a) and PTV2 (b)

around and 3 mm posteriorly significantly reduced the dose received by the rectum with minimal reduction to the dose received by the CTV. We believe that the reduction in PTV will allow us to perform prostate dose escalation without exceeding the relative dose thresholds for rectal toxicity/NTCP [22, 42–45].

Daily online matching based on planning for the system is automated. The automated match is visually inspected in each case by the staff. The staff performs a manual match in case of any mismatch. The orthogonal image pairs taken in the first three sessions give an independent validation of the positioning accuracy with the automatic system. This validation demonstrates a sub-millimeter accuracy of the automatic system for matching. However, good accuracy is degraded by intra-fraction movements during the treatment time. Each treatment session takes approximately 8–10 min.

Another point addressed by this study is the accuracy in dose delivery to the seminal vesicles. Our results showed that the accuracy of treatment delivery always increased in terms of CTV intersection and homogenous dose delivery when only treating the prostate. We do believe that repositioning of the seminal vesicles is an important issue that needs more research.

The US-guided fiducial marker insertion for radiotherapy in the present study is well tolerated in the majority of patients with prostate cancer. The severity of most symptoms was Grade 1 or 2. The symptoms in the majority of patients last < 2 weeks.

Conclusion

A significant improvement of prostatic cancer patients alignment when fiducial markers are used, with more homogenous dose distribution, and with significant decrease in PTV margins. The delivered rectal dose is significantly less allowing prostate dose escalation.

Conflicts of interest

The author indicates no potential conflicts of interest.

References

1. Geinitz H, Zimmermann FB, Thamm R, *et al*. 3D conformal radiation therapy for prostate cancer in elderly patients. Radiother Oncol, 2005, 76: 27–34.
2. Nguyen TD, Poortmans PM, van der Hulst M, *et al*. The curative role of radiotherapy in adenocarcinoma of the prostate in patients under 55 years of age: a rare cancer network retrospective study. Radiother Oncol, 2005, 77: 286–289.
3. Pollack A, Zagars GK, Smith LG, *et al*. Preliminary results of a randomized radiotherapy dose-escalation study comparing 70 Gy with 78 Gy for prostate cancer. J Clin Oncol, 2000, 18: 3904–3911.
4. Pollack A, Zagars GK, Starkschall G, *et al*. Prostate cancer radiation dose response: results of the M. D. Anderson phase III randomized trial. Int J Radiat Oncol Biol Phys, 2002, 53: 1097–1105.
5. Yan D, Lockman D, Brabbins D, *et al*. An off-line strategy for constructing a patient-specific planning target volume in adaptive treatment process for prostate cancer. Int J Radiat Oncol Biol Phys, 2000, 48: 289–302.
6. Martinez AA, Yan D, Lockman D, *et al*. Improvement in dose escalation using the process of adaptive radiotherapy combined with three-dimensional conformal or intensity-modulated beams for prostate cancer. Int J Radiat Oncol Biol Phys, 2001, 50: 1226–1234.
7. Welsh JS, Patel RR, Ritter MA, *et al*. Helical tomotherapy: an innovative technology and approach to radiation therapy. Technol Cancer Res Treat, 2002, 1: 311–316.
8. van Herk M, Remeijer P, Rasch C, *et al*. The probability of correct target dosage: dose-population histograms for deriving treatment margins in radiotherapy. Int J Radiat Oncol Biol Phys, 2000, 47: 1121–1135.
9. Keller H, Tomé W, Ritter MA, *et al*. Design of adaptive treatment margins for non-negligible measurement uncertainty: application to ultrasound-guided prostate radiation therapy. Phys Med Biol, 2004, 49: 69–86.
10. Kitamura K, Shirato H, Shimizu S, *et al*. Registration accuracy and possible migration of internal fiducial gold marker implanted in prostate and liver treated with real-time tumor-tracking radiation therapy (RTRT). Radiother Oncol, 2002, 62: 275–281.
11. 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.
12. Zelefsky MJ, Crean D, Mageras GS, *et al*. Quantification and predictors of prostate position variability in 50 patients evaluated with multiple CT scans during conformal radiotherapy. Radiother Oncol, 1999, 50: 225–234.
13. Stroom JC, Koper PC, Korevaar GA, *et al*. Internal organ motion in prostate cancer patients treated in prone and supine treatment position. Radiother Oncol, 1999, 51: 237–248.
14. Beard CJ, Kijewski P, Bussière M, *et al*. Analysis of prostate and seminal vesicle motion: implications for treatment planning. Int J Radiat Oncol Biol Phys, 1996, 34: 451–458.
15. Roeske JC, Forman JD, Mesina CF, *et al*. Evaluation of changes in the size and location of the prostate, seminal vesicles, bladder, and rectum during a course of external beam radiation therapy. Int J Radiat Oncol Biol Phys, 1995, 33: 1321–1329.
16. Jaffray DA, Siewerdsen JH, Wong JW, *et al*. Flat-panel cone-beam computed tomography for image-guided radiation therapy. Int J Radiat Oncol Biol Phys, 2002, 53: 1337–1349.
17. 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.
18. Kupelian PA, Willoughby TR, Meeks SL, *et al*. Intraprostatic fiducials for localization of the prostate gland: monitoring intermarker distances during radiation therapy to test for marker stability. Int J Radiat Oncol Biol Phys, 2005, 62: 1291–1296.
19. Langenhuijsen JF, van Lin EN, Kiemeney LA, *et al*. Ultrasound-guided transrectal implantation of gold markers for prostate localization during external beam radiotherapy: complication rate and risk factors. Int J Radiat Oncol Biol Phys, 2007, 69: 671–676.
20. Poggi MM, Gant DA, Sewchand W, *et al*. Marker seed migration in prostate localization. Int J Radiat Oncol Biol Phys, 2003, 56: 1248–1251.
21. Shirato H, Harada T, Harabayashi T, *et al*. Feasibility of insertion/implantation of 2.0-mm-diameter gold internal fiducial markers for precise setup and real-time tumor tracking in radiotherapy. Int J Radiat Oncol Biol Phys, 2003, 56: 240–247.
22. Fokdal L, Honoré H, Høyer M, *et al*. Dose-volume histograms associated to long-term colorectal functions in patients receiving pelvic radiotherapy. Radiother Oncol, 2005, 74: 203–210.
23. Heemsbergen WD, Hoogeman MS, Hart GA, *et al*. Gastrointestinal toxicity and its relation to dose distributions in the anorectal region of prostate cancer patients treated with radiotherapy. Int J Radiat Oncol Biol Phys, 2005, 61: 1011–1018.
24. Koper PC, Jansen P, van Putten W, *et al*. Gastro-intestinal and genito-urinary morbidity after 3D conformal radiotherapy of prostate cancer: observations of a randomized trial. Radiother Oncol, 2004, 73: 1–9.
25. Létourneau D, Martinez AA, Lockman D, *et al*. Assessment of residual error for online cone-beam CT-guided treatment of prostate cancer patients. Int J Radiat Oncol Biol Phys, 2005, 62: 1239–1246.
26. Serago CF, Chungbin SJ, Buskirk SJ, *et al*. Initial experience with ultrasound localization for positioning prostate cancer patients for external beam radiotherapy. Int J Radiat Oncol Biol Phys, 2002, 53: 1130–1138.
27. Trichter F, Ennis RD. Prostate localization using transabdominal ultrasound imaging. Int J Radiat Oncol Biol Phys, 2003, 56: 1225–1233.
28. Artignan X, Smitsmans MH, Lebesque JV, *et al*. Online ultrasound image guidance for radiotherapy of prostate cancer: impact of image acquisition on prostate displacement. Int J Radiat Oncol Biol Phys, 2004, 59: 595–601.
29. Fuss M, Cavanaugh SX, Fuss C, *et al*. Daily stereotactic ultrasound prostate targeting: inter-user variability. Technol Cancer Res Treat, 2003, 2: 161–170.
30. Boda-Heggemann J, Köhler FM, Küpper B, *et al*. Accuracy of ultrasound-based (BAT) prostate-repositioning: a three-dimensional on-line fiducial-based assessment with cone-beam computed tomography. Int J Radiat Oncol Biol Phys, 2008, 70: 1247–1255.
31. Bylund KC, Bayouth JE, Smith MC, *et al*. Analysis of interfraction

prostate motion using megavoltage cone beam computed tomography. Int J Radiat Oncol Biol Phys, 2008, 72: 949–956.
32. Zhang M, Moiseenko V, Liu M, *et al*. Internal fiducial markers can assist dose escalation in treatment of prostate cancer: result of organ motion simulations. Phys Med Biol, 2006, 51: 269–285.
33. 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: 942–953.
34. Serago CF, Buskirk SJ, Igel TC, *et al*. Comparison of daily megavoltage electronic portal imaging or kilovoltage imaging with marker seeds to ultrasound imaging or skin marks for prostate localization and treatment positioning in patients with prostate cancer. Int J Radiat Oncol Biol Phys, 2006, 65: 1585–1592.
35. Van den Heuvel F, Fugazzi J, Seppi E, *et al*. Clinical application of a repositioning scheme, using gold markers and electronic portal imaging. Radiother Oncol, 2006, 79: 94–100.
36. 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.
37. Peeters ST, Heemsbergen WD, Koper PC, *et al*. Dose-response in radiotherapy for localized prostate cancer: results of the Dutch multicenter randomized phase III trial comparing 68 Gy of radiotherapy with 78 Gy. J Clin Oncol, 2006, 24: 1990–1996.
38. Zelefsky MJ, Fuks Z, Hunt M, *et al*. High dose radiation delivered by intensity modulated conformal radiotherapy improves the outcome of localized prostate cancer. J Urol, 2001, 166: 876–881.
39. 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: 1124–1129.
40. Mock U, Bogner J, Georg D, *et al*. Comparative treatment planning on localized prostate carcinoma conformal photon- versus proton-based radiotherapy. Strahlenther Onkol, 2005, 181: 448–455.
41. Bos LJ, van der Geer J, van Herk M, *et al*. The sensitivity of dose distributions for organ motion and set-up uncertainties in prostate IMRT. Radiother Oncol, 2005, 76: 18–26.
42. Wachter S, Gerstner N, Goldner G, *et al*. Rectal sequelae after conformal radiotherapy of prostate cancer: dose-volume histograms as predictive factors. Radiother Oncol, 2001, 59: 65–70.
43. Fiorino C, Cozzarini C, Vavassori V, *et al*. Relationships between DVHs and late rectal bleeding after radiotherapy for prostate cancer: analysis of a large group of patients pooled from three institutions. Radiother Oncol, 2002, 64: 1–12.
44. Foppiano F, Fiorino C, Frezza G, *et al*. The impact of contouring uncertainty on rectal 3D dose-volume data: results of a dummy run in a multicenter trial (AIROPROS01-02). Int J Radiat Oncol Biol Phys, 2003, 57: 573–579.
45. Vargas C, Martinez A, Kestin LL, *et al*. Dose-volume analysis of predictors for chronic rectal toxicity after treatment of prostate cancer with adaptive image-guided radiotherapy. Int J Radiat Oncol Biol Phys, 2005, 62: 1297–1308.

DOI 10.1007/s10330-018-0297-7
Cite this article as: Metwally HM. Comparison of bone alignment and fiducial marker alignment for online cone-beam computed tomography-guided radiation therapy for prostate cancer. Oncol Transl Med, 2019, 5: 131–136.