# Prostate Cancer Stereotactic Body Radiation Therapy with Image-guided Radiation Therapy (IGRT) Technique with Three-Dimensional Transperineal Ultrasound for IGRT Tracking of the Prostate

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## Abstract

**Introduction** Ultrahypofractionated radical radiotherapy for prostate cancer, also known as stereotactic body radiation therapy (SBRT), is an unprecedented modality of prostate radiotherapy and is still used very sparsely in Brazil. The use of fiducial implants and spacers may make it even more difficult to implement prostate SBRT on a large scale in Brazil. We describe a completely non-invasive technique for the treatment of localized prostate cancer with stereotactic body radiotherapy.

**Materials and Methods** This is a case series study with 9 patients and 48 SBRT fractions analyzed. In our treatment protocol, we use the Elekta Versa-HD linear accelerator (Elekta, Stokholm, Sweden), a transperineal ultrasound (TPUS) with tracking and synchronization capabilities (Clarity 4D ultrasound system, Elekta), and the Monaco Planning System (Elekta). Displacements were measured in the three axes (lateral, longitudinal, and vertical). The discrepancy between the initial ultrasound location of the prostate and the location of the cone beam has also been documented.

**Results** The mean displacements were 2.02 mm, 3.12 mm, and 2.93 mm for the lateral, longitudinal, and vertical directions, respectively. The data show that treatment was interrupted in 14 of the 48 treatment fractions (29.17%), 8 (57%) with displacements greater than 5 mm and 6 (43%) with displacements between 3 and 5 mm.

The initial TPUS image-guided radiation therapy (IGRT) and its mean displacements for localization with the cone-beam computed tomography (CBCT) were 1.3 mm, 1.9 mm, and 1.5 mm, for the lateral, longitudinal, and vertical directions, respectively. Using van Herk formula, a margin of 7.3 mm in the lateral directions, 9.35 mm longitudinally, and 7.74 mm vertically, would be required.

**Conclusion** Here we describe an SBRT technique for prostate cancer that is completely non-invasive and allows for a high level of accuracy. Transperineal 3D ultrasound

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provides real-time position data to the prostate that can be used to gate the SBRT treatment, allowing for smaller, more personalized planning target volume (PTV) margins even without fiducial markers or spacers, which may be more applicable for low- and middle-income countries.

## Introduction

Prostate cancer is a highly prevalent cancer worldwide, and it also has a high incidence in Brazil. Data from the Brazilian National Cancer Institute (Instituto Nacional de Câncer [INCA], in Portuguese) estimate more than 72 thousand new cases in 2024 in this country.[1]

Radiation therapy has been used to treat prostate cancer efficiently for many decades. More recently, hypofractionated regimens have been gaining popularity due to recent studies showing efficacy, low toxicity rates, and the fact that they are 50% (or more) shorter than conventional fractionated radiotherapy.[2]

A subtype of the hypofractionated regimen is ultrahypofractionation, also known as stereotactic body radiotherapy (SBRT), which is characterized by doses equal to or greater than 5 Gy per fraction, usually with a total of 5 fractions.[3]

In many cancer centers, prostate SBRT is usually done with the use of fiducial markers and spacers.[4,5]

Commercial fiducials are not approved by the National Health Surveillance Agency.[6] Even if they were approved, the incremental costs of using these products would likely make radiotherapy almost inaccessible in Brazil, aggravating the Brazilian bottleneck in access to cancer treatment.[7]

The current study describes a completely noninvasive prostate SBRT technique using transperineal ultrasound for intrafraction prostate screening.

This technique would likely make prostate SBRT more accessible to low- and middle-income countries and decrease waiting lists in radiotherapy departments by reducing the number of fractions.

## Materials and Methods

We have developed a transperineal ultrasound (TPUS)-based workflow for SBRT. Here we describe the dislocations of our first 9 patients treated with TPUS and ultrahypofractionation. It is a case series of prospective, consecutive cases. The selection criteria were patients with localized prostate cancer following hypofractionated radiotherapy for prostate cancer (hypo-RT-PC)[8] or metastatic[9] study criteria eligible for ultrahypofractionated radiotherapy. The exclusion criteria were the same as those used in these trials. The National Comprehensive Cancer Network (NCCN) risk groups were used (►**Fig. 1**)[10]

Most patients were treated with 5 fractions. All patients underwent computed tomography simulation (CT-Sim) before treatment with a planning TPUS (►**Fig. 2**), using a dedicated computed tomography, Somatom Definition AS (Siemens AG, Munich, Germany), 20-channels, large bore. During CT-SIM, a TPUS scan was generated. The CT-SIM was then fused with TPUS images and diagnostic magnetic resonance imaging (MRI) (►**Fig. 3**). The clinical target volume (CTV) was contoured as the prostate with or without the proximal third of the seminal vesicles, based on CT-MRI fusion, and the final CTV count was uploaded into the Clarity 4D ultrasound system (Elekta, Stokholm, Sweden) for image-guided radiation therapy (IGRT) (►**Fig. 4**). The planning target volume (PTV) is defined as the CTV plus a margin of 3 to 4 mm posteriorly and 5 mm in all other dimensions. The urethra was circumvented as an organ at risk (OAR) identified on MRI or by a pediatric relief bladder tube used during the simulation and was to receive less than 95% of the prescribed dose, but more than 35 Gy (urethra-sparing approach).[11] That means that with a prescription of 40 Gy in 5 fractions, the urethra avoidance region should receive more than 35 Gy but less than 38 Gy. The treatment planning was done by Monaco system (ELEKTA) and patients typically received two arcs with volumetric modulated arc therapy (VMAT) technique, with a flattening filter free (FFF) 6 MV photons.

The Monaco planning system was used to plan all patients' treatment to receive two volumetric modulated arc therapy (VMAT) arcs, with a flattening filter free (FFF) of 6 MV photons.

For treatment, the probe of the TPUS was positioned by the therapists with the aid of a physicist. The patients were positioned according to the SBRT protocol and aligned to the skin tags using lasers in the treatment room. The prostate was first located by ultrasound and then a kilovoltage (kV)-cone beam CT (CBCT) was performed to confirm the position of the prostate as well as the volumes of the rectum and bladder (preparation). The CBCT correction was the gold standard and TPUS IGRT was used for the initial localization. Once the prostate was localized by CBCT, the TPUS tracking was initiated and lasted until the end of the treatment. This whole procedure was repeated for each fraction. The displacements were recorded and are presented in ►**Table 1**. During intrafraction tracking by US, the beam was gated automatically if the target moved more than 3 mm for more than 5 seconds, or manually if it moved more than 5 mm, at any of the 3 orthogonal coordinates. The localization procedure would be repeated if the displacement of more than 3 mm was persistent and consistent. Between the first and second treatment arcs, an intrafraction CBCT was performed, during the first arc while the beam was on ad was used to corroborate US data and re-check bladder and rectum volumes. (Intrafraction, Elekta).

In our study, we considered a displacement of 3 mm to be significant, since our lowest margin could be 3 mm, but any displacement of more than 5 mm was considered unacceptable.

 

| Risk Groups (NCCN) | Clinical/Pathologic features | | |
|---|---|---|---|
| Very low | Has all of the following:<br>• T1c<br>• Grade Group 1<br>• PSA <10 ng/mL<br>• Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/coree<br>• PSA density <0.15 ng/mL/g | | |
| Low | Has all of the following but does not qualify for very low risk:<br>• T1–T2a<br>• Grade Group 1<br>• PSA <10 ng/mL | | |
| Intermediate | Has all of the following:<br>• No high-risk group features<br>• No very-high-risk group features<br>• Has one or more intermediate risk factors (IRF): T2b–T2c Grade Group 2 or 3 PSA 10–20 ng/mL | Favorable intermediate | Has all of the following:<br>• 1 IRF<br>• Grade Group 1 or 2<br>• <50% biopsy cores positive |
| | | Unfavorable intermediate | Has one or more of the following:<br>• 2 or 3 IRFs<br>• Grade Group 3<br>• >50% biopsy cores positive |
| High | Has no very-high-risk features and has at least one high-risk feature:<br>• T3a OR<br>• Grade Group 4 or Grade Group 5 OR • PSA >20 ng/mL | | |
| Very high | Has at least one of the following: • T3b–T4<br>• Primary Gleason pattern 5<br>• 2 or 3 high-risk features<br>• >4 cores with Grade Group 4 or 5 | | |

**Fig. 1** National Comprehensive Cancer Network prostate cancer risk groups. Adapted from: NCCN Prostate Cancer Guidelines.

To calculate the PTV using the Van Herk formula ($M = 2.5\Sigma + 0.7\sigma$),[12] a delineation error of 2.5 mm was considered as systematic,[13] and the set-up error was obtained by the standard deviation of the means of the displacements obtained in the cone beams performed before the beginning of the treatment. To calculate the random error, the standard deviation of the means of the intrafraction displacements was obtained.

This study respected the ethical principles contained in the Declaration of Helsinki.

This project was approved by a research ethics committee and registered in Plataforma Brasil under CAAE number. 64273317.9.0000.5533

## Results

The mean displacements were 2.02 mm, 3.12 mm, and 2.93 mm in the lateral, longitudinal, and vertical directions, respectively.

Treatment was interrupted in 14 of the 48 treatment fractions (29.17%), 8 with displacements greater than 5 mm and 6 with displacements between 3 and 5 mm. The largest displacement observed was 12.27 mm. In other words, in 16.66% of the fractions, the target would have exceeded the PTV margin, causing some loss of coverage.

Analyzing the directions, 11 of the 17 displacements (64.7%) capable of interrupting the treatment ($> 3$ mm) occurred in the vertical direction, 4 in the lateral direction, and another 2 in the longitudinal direction. Not all dislocations $> 3$ mm resulted in interruption as long as they lasted less than 5 seconds.

We compared the location of the TPUS with the CBCT and the complete data are shown in ►**Table 2**. The percentage of CBCT displacement above 7 mm was only 7.6%, meaning that a 7 mm PTV for a treatment with TPUS IGRT alone would be adequate for 92.4% of all treatment fractions.

Using Van Herk formula ($M = 2.5\Sigma + 0.7\sigma$), a margin of 7.3 mm would be required in the lateral directions, 9.35 mm

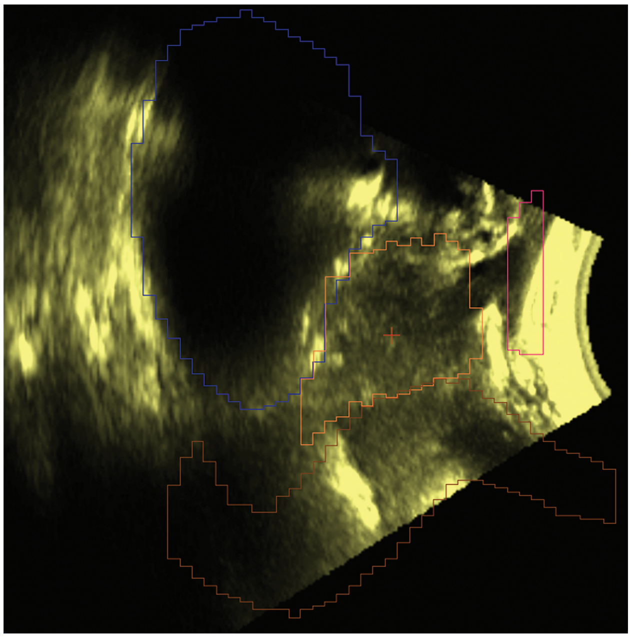

**Fig. 2** Transperineal ultrasound image acquired during simulation.

in the longitudinal direction, and 7.74 mm in the vertical direction, respectively, where Σ represents the systematic uncertainty and σ the random uncertainty.

## Discussion

Stereotactic body radiation therapy is a fractionation modality that has been gaining more and more acceptance in the treatment of prostate cancer.

Several approaches can be taken to reduce the possibility of acute and late toxicity, such as spacers, urethral preservation techniques, and reduced PMTC margins. Whenever the margins of the PTV are reduced, the possibility of geographical missing increases. An alternative to mitigate this risk is to apply intrafraction monitoring, and here we describe our protocol with the TPUS Clarity 4D system, which allows intrafraction monitoring and gating.[14]

A PTV of 7 mm would likely be suitable for a TPUS IGRT without CBCT, since the discrepancy between initial localization in TPUS and correction by CBCT was below 2 mm on average. In the lateral, longitudinal, and vertical axes, the mean displacements were 2.02 mm, 3.12 mm, and 2.93 mm, respectively, but some displacements were greater, with a maximum of 11.2 mm in the longitudinal direction in only 1 patient and in only 1 day of treatment. The percentage of displacement above 7 mm was only 7.6%.

The outliers must have other reasons for a discrepant movement, other than change in volume of bladder and rectum. One of those was discomfort in set-up positioning or a full bladder eliciting muscular contraction. Particularly

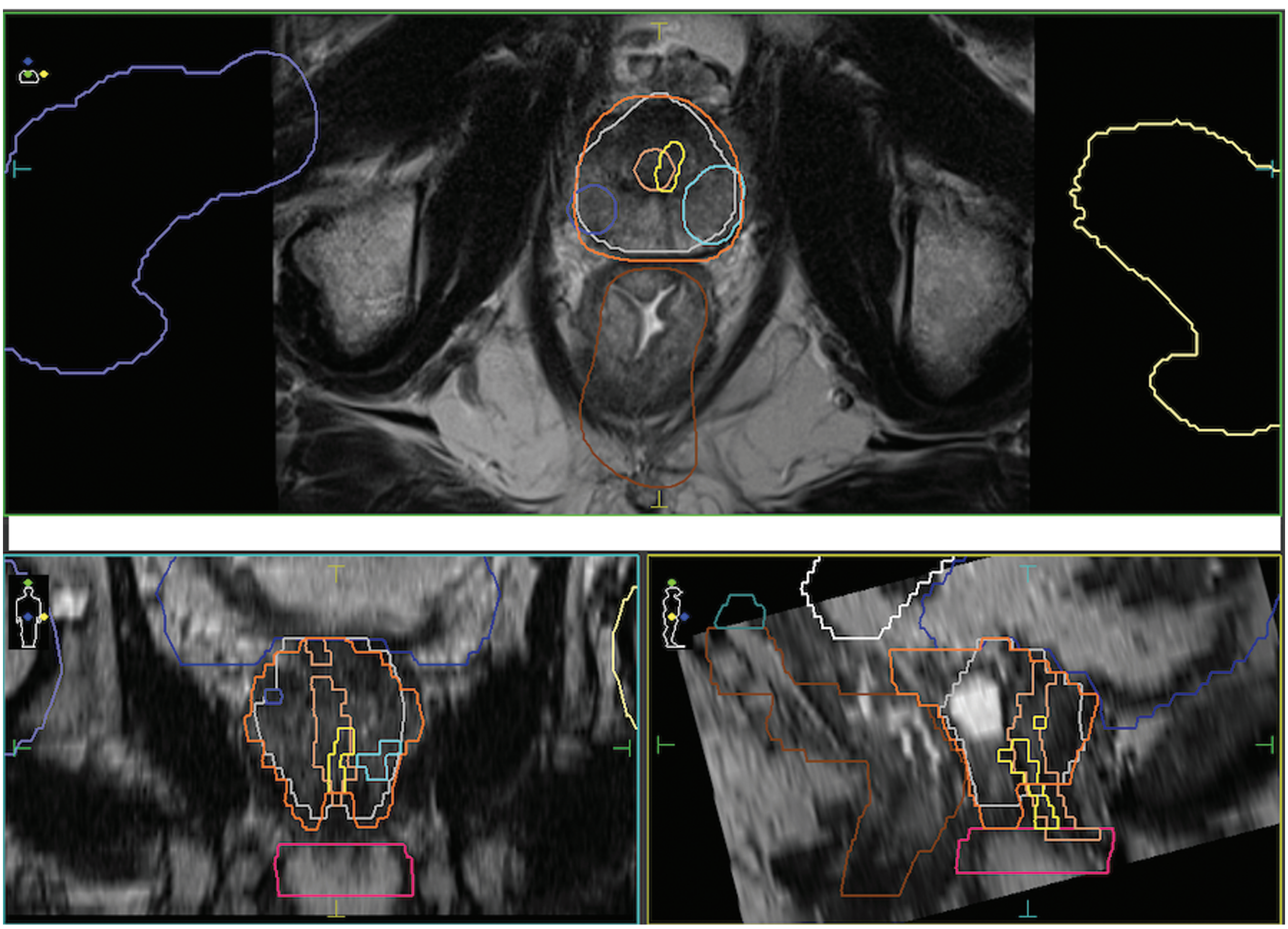

**Fig. 3** Magnetic resonance imaging scan fusion with computed tomography scan.

 

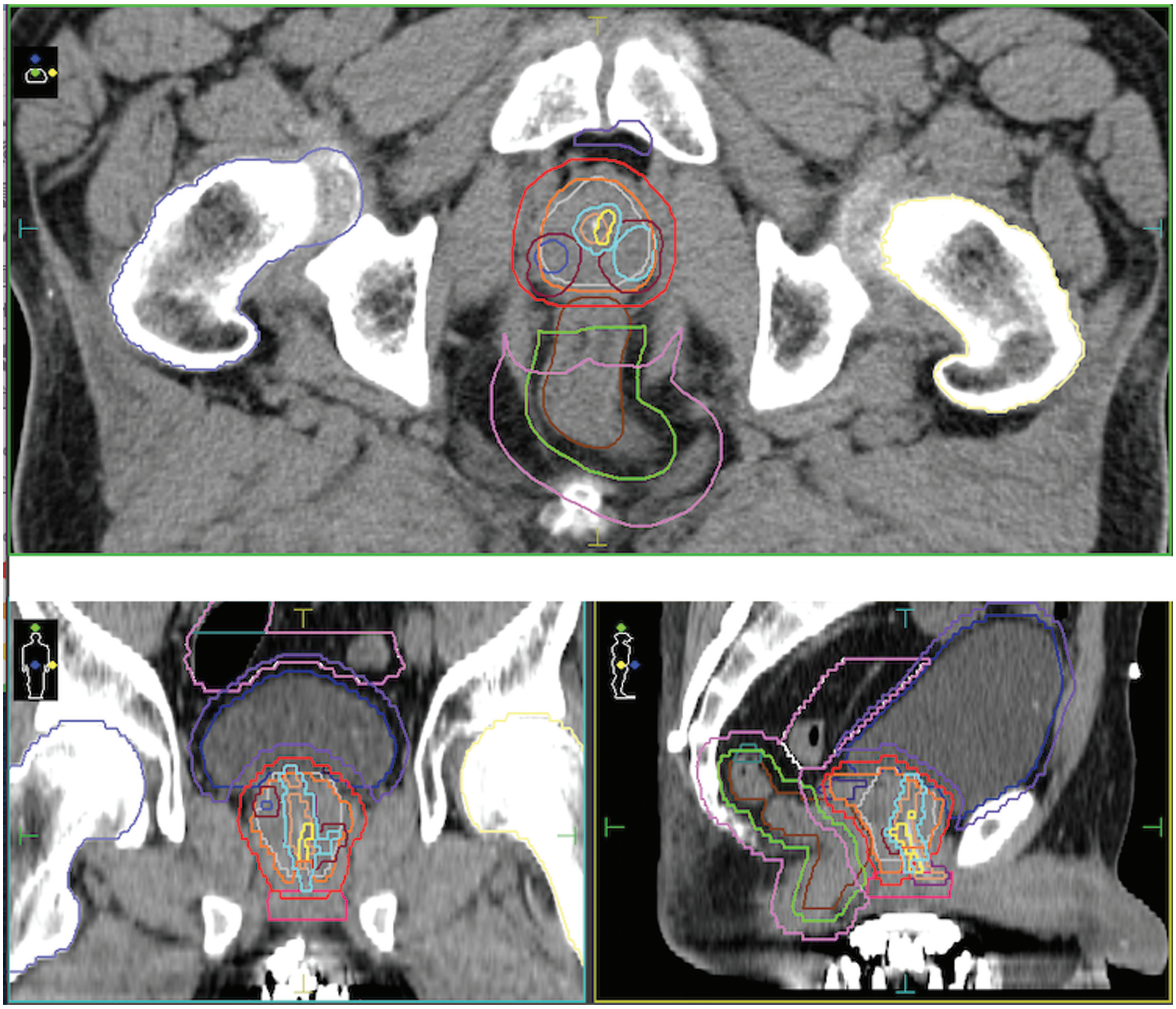

**Fig. 4** Contouring.

**Table 1** Maximum (max) prostate displacements during transperineal ultrasound tracking (mm)

| Patient | Direction | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 |
|---|---|---|---|---|---|---|---|
| A | $X_{max}$ | 2.12 | 2.83 | 1.64 | 2.12 | 2.36 | |
| | $Y_{max}$ | 2.87 | 2.64 | 10.45 | 3.08 | 1.41 | |
| | $Z_{max}$ | 1.58 | 1.79 | 1.11 | 2.75 | 1.44 | |
| B | $X_{max}$ | 1.66 | 1.68 | 1.22 | 1.03 | 1.56 | 1.45 |
| | $Y_{max}$ | 5.65 | 12.27 | 3.69 | 1.37 | 2.28 | 1.82 |
| | $Z_{max}$ | 2.59 | 2.52 | 1.38 | 0.83 | 1.12 | 1.25 |
| C | $X_{max}$ | 3.70 | 1.12 | 1.38 | 1.09 | 1.52 | |
| | $Y_{max}$ | 2.57 | 1.59 | 7.57 | 2.17 | 3.05 | |
| | $Z_{max}$ | 0.30 | 0.97 | 1.03 | 0.73 | 1.39 | |
| D | $X_{max}$ | 7.38 | 2.42 | 2.23 | 5.49 | 2.16 | |
| | $Y_{max}$ | 2.90 | 2.48 | 2.68 | 5.28 | 2.67 | |
| | $Z_{max}$ | 3.33 | 0.96 | 2.02 | 2.57 | 2.58 | |
| E | $X_{max}$ | 2.47 | 0.71 | 3.62 | 1.41 | 0.77 | |
| | $Y_{max}$ | 2.27 | 3.55 | 1.85 | 6.04 | 1.17 | |
| | $Z_{max}$ | 1.64 | 1.34 | 1.58 | 2.57 | 0.57 | |

(*Continued*)

 

**Table 1** (*Continued*)

| Patient | Direction | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 |
|---|---|---|---|---|---|---|---|
| F | $X_{max}$ | 0.61 | 0.61 | 0.89 | 0.86 | 0.77 | |
| | $Y_{max}$ | 0.89 | 0.43 | 0.80 | 2.00 | 0.51 | |
| | $Z_{max}$ | 0.38 | 0.53 | 0.72 | 0.83 | 0.97 | |
| G | $X_{max}$ | 0.87 | 1.84 | 1.23 | 0.95 | 0.52 | 0.55 |
| | $Y_{max}$ | 0.98 | 1.74 | 2.28 | 1.06 | 1.04 | 0.94 |
| | $Z_{max}$ | 1.01 | 0.92 | 1.37 | 0.73 | 1.66 | 0.67 |
| H | $X_{max}$ | 1.09 | 0.69 | 0.74 | 1.22 | 0.95 | |
| | $Y_{max}$ | 0.96 | 0.69 | 1.07 | 0.90 | 0.72 | |
| | $Z_{max}$ | 0.51 | 0.53 | 0.70 | 0.67 | 0.32 | |
| I | $X_{max}$ | 1.73 | 0.56 | 1.24 | 2.10 | 2.19 | 0.78 |
| | $Y_{max}$ | 2.38 | 2.43 | 2.34 | 2.80 | 6.32 | 2.40 |
| | $Z_{max}$ | 2.07 | 1.77 | 2.35 | 2.18 | 3.49 | 1.59 |

**Table 2** Values for displacement discrepancy between the transperineal ultrasound and the kilovoltage cone beam (mm)

| Patients | Direction | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 |
|---|---|---|---|---|---|---|---|
| A | Lateral | 3.10 | 2.50 | 1.80 | 0.10 | 3.50 | |
| | Longitudinal | 0.70 | 6.20 | 2.10 | 3.30 | 8.20 | |
| | Vertical | 2.00 | 5.20 | 3.80 | 5.10 | 3.70 | |
| B | Lateral | 3.00 | 0.80 | 5.00 | 0.80 | 2.90 | 3.80 |
| | Longitudinal | 1.20 | 3.70 | 1.80 | 0.20 | 1.60 | 0.00 |
| | Vertical | 6.00 | 7.40 | 0.00 | 0.40 | 0.90 | 0.00 |
| C | Lateral | NI | NI | 0.60 | 1.10 | 2.1 | |
| | Longitudinal | NI | NI | 0.90 | 2.30 | 0.8 | |
| | Vertical | NI | NI | 0.40 | 1.60 | 3.3 | |
| D | Lateral | 3.40 | 5.00 | 1.5 | 1.4 | 1.50 | |
| | Longitudinal | 1.00 | 11.20 | 1.5 | 3.2 | 0.20 | |
| | Vertical | 0.10 | 4.40 | 4 | 4 | 3.20 | |
| E | Lateral | 0.1 | 0 | 1.90 | 4.90 | 3.80 | |
| | Longitudinal | 1.9 | 0 | 0.90 | 0.60 | 7.40 | |
| | Vertical | 0.9 | 0 | 8.90 | 8.60 | 3.30 | |
| F | Lateral | 1.1 | 4.5 | 1.90 | 1.40 | 2.90 | |
| | Longitudinal | 3.9 | 7.8 | 1.90 | 3.60 | 0.10 | |
| | Vertical | 0.5 | 6.2 | 3.50 | 5.60 | 0.60 | |
| G | Lateral | 2.2 | 0.2 | 0.90 | 3.90 | 0.80 | 3.00 |
| | Longitudinal | 6.6 | 2 | 8.20 | 6.20 | 6.30 | 9.60 |
| | Vertical | 5.4 | 8.5 | 1.10 | 0.00 | 3.10 | 0.70 |
| H | Lateral | 2.90 | 2.30 | 0.30 | 1.20 | 3.80 | |
| | Longitudinal | 2.40 | 4.70 | 2.60 | 4.20 | 2.90 | |
| | Vertical | 3.90 | 2.50 | 2.50 | 0.30 | 0.90 | |
| I | Lateral | 0.30 | 1.80 | 2.90 | 1.90 | 1.00 | 1.90 |
| | Longitudinal | 0.10 | 0.30 | 1.30 | 0.30 | 2.60 | 3.50 |
| | Vertical | 8.30 | 4.70 | 2.30 | 7.10 | 0.50 | 3.00 |

 

obese patients could press the TPUS probe between their legs, thus provoking false prostate movements in the system.

One strategy implemented later on was to make the patient comfortable before initiating prostate tracking and starting the simulation with an intermediate bladder volume.

Inserting fiducials and spacers is time-consuming and expensive.

Implementing TPUS tracking has its own challenges but once your team gains expertise, the process is fast, accurate, non-invasive, and probably cheaper than inserting fiducials and/or spacers. Overall, the TPUS probe was an easy and intuitive tool to use compared to other IGRT systems. When using TPUS as IGRT the accuracy increases with the learning curve.[15–18]

The main limitation of our study is our low number of patients.

## Conclusion

In the present study, we describe our completely non-invasive technique for prostate SBRT using TPUS as tracking system without fiducials or spacers, which may be more affordable for developing countries. The average changes are small, although some individual changes are big enough to warrant a screening system if the PTV margins are small, which is typically the case in prostate SBRT planning.

### Authors' Contribution

IM: collection and assembly of data, conception and study design, data analysis and interpretation, manuscript writing, provision of study materials or patient, final approval of the manuscript; AM: conception and study design, data analysis and interpretation, manuscript review and editing and final approval of the manuscript.

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### Clinical Trials

None.

### Conflict of Interests

The authors have no conflict of interests to declare.

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