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Intraoperative Registered Ultrasound and Fluoroscopy (iRUF) for dose calculation during prostate brachytherapy: improved accuracy compared to standard ultrasound-based dosimetry

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Abstract

Background and Purpose—Intraoperative transrectal ultrasound dosimetry during low-dose-rate prostate brachytherapy is imprecise due to sonographic distortion caused by seed echoes and needle tracks that obscure seed positions or create false signals as well as traumatic edema. Here we report the results of a pilot study comparing a combined ultrasound and fluoroscopy-based seed localization method (iRUF) to standard ultrasound-based dosimetry (USD).

Material and Methods—Eighty patients undergoing permanent Pd-103 seed implantation for prostate cancer were prospectively enrolled. Seed implantation was performed using standard USD for intraoperative dose tracking. Upon implant completion, six x-ray images were intraoperatively acquired using a mobile C-arm and transverse ultrasound images of the implanted prostate were also acquired. Three-dimensional seed locations were reconstructed from x-ray images and registered to the ultrasound for iRUF dosimetry. Day 1 CT/MRI scans were performed for post-implant dosimetry. Prostate and urethral dosimetric parameters were separately calculated for analysis on iRUF, USD, and CT/MRI data sets. Differences and similarities between dosimetric values measured by iRUF, USD, and CT/MRI were assessed based on root mean squared differences, intraclass correlation coefficients (ICC), and Wilcoxon signed rank test.

Results—Data from 66 eligible patients were analyzed. Compared to CT/MRI, iRUF dosimetry showed higher correlation with overall ICC of 0.42 (0.01 for USD) and significantly smaller root

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Conflict of interest statement A US patent has been filed for the fluoroscopy-based implant reconstruction algorithm.

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mean squared differences (overall 16.5 vs 21.5 for iRUF and USD) than USD for all prostate and urethral dosimetric parameters examined. USD demonstrated a tendency to overestimate dose to the prostate when compared to iRUF.

Conclusions—iRUF approximated post-implant CT/MRI prostate and urethral dosimetry to a greater degree than USD. A phase II trial utilizing iRUF for intraoperative dynamic plan modification is underway, with the goal to confirm capability to minimize and correct for prostate underdosage not otherwise detected.

Keywords

prostate brachytherapy; intraoperative dosimetry; fluoroscopy; C-arm; registration

Introduction

Permanent prostate brachytherapy is a highly effective method for treating patients with localized prostate cancer, and emerging data are establishing its role and value as a key element in the management of patients with locally advanced disease [1], [2]. Optimal placement of sources is the key to achieving adequate dose to the prostate while minimizing toxicity to normal tissues [3]. While an initial treatment plan is created with optimal positions of the sources prior to the implantation, actual sources may not be placed to the intended positions due to dynamic changes occurring during implantation such as needle deviation, tissue deformation, and prostatic edema [4]. Each source's position is typically estimated at the time of deposition based on the visualized needle tip on sagittal ultrasound, a technique often called *real-time dosimetry* (herein referred to as ultrasound-based dosimetry or USD). Although the real-time dosimetry approach may seem to work well, this method does not update source position after the time of placement, and therefore does not account for changes occurring during the implant [5].

To overcome the limitations of the real-time dosimetry approach, a *dynamic dosimetry* approach that identifies implanted sources repeatedly and adapts to the dynamic character of implants has been advocated [6]. However, localizing implanted sources in current transrectal ultrasound (TRUS)-guided procedure is challenging as they are not consistently visible on ultrasound and the echogenicity of needle tracks and calcifications may appear similar to that of sources. Prior work has demonstrated that improved dosimetric results can be achieved by combining another imaging modality, most commonly x-ray imaging with TRUS for intraoperative source localization. Recently, Ishiyama et al. [7] and Westendorp et al. [8] reported that intraoperative dosimetry based on O-arm CT or C-arm cone-beam CT showed higher predictive power for 1-month CT-based post-implant dosimetry than USD, demonstrating the utility of intraoperative CT imaging in combination of TRUS for improving dosimetry prediction. Unfortunately, these approaches require equipment that is not commonly available or significantly alter the current brachytherapy workflow, e.g., requiring a surgical suite with an isocentric fluoroscopic simulator, CT scanner or CT-capable C-arm, or transporting the patient to a separate room for CT scanning prior to completion of brachytherapy [7]–[12].

In contrast to the prior methods, we have developed an intraoperative Registered Ultrasound and Fluoroscopy system (iRUF) which utilizes a mobile C-arm that is widely available in most hospitals [13]. Our method involves reconstruction of seeds from a few x-rays and their spatial registration to TRUS. A clinical study was performed to demonstrate the feasibility of our approach, as well as to explore for differences in dosimetry between iRUF and USD methods.

Materials and Methods

In this study, we compared iRUF or USD vs. ‘ground truth’ CT/MRI fusion dosimetry on prostate cancer patients who were treated by low-dose-rate permanent interstitial implant. The implant was performed using the standard USD method, i.e., real-time dosimetry strategy, where planning ultrasound images were acquired intraoperatively and treatment plan created manually using VariSeed 8.0 (Varian, Palo Alto, CA, USA). Pd-103 seeds were placed using a hybrid approach with both pre-loaded stranded sources as well as loose seeds via Mick applicator (Mick Radio-Nuclear Instruments, Mount Vernon, NY, USA); loose seeds were coated with synthetic bioabsorbable polymer (AnchorSeed, Theragenics Corp, Buford, GA, USA) to prevent seed slippage. Seed positions were interactively updated by a physicist with input from the physician in the treatment planning system (TPS) based on TRUS visualization. With each seed position confirmed at time of placement either by visualization of the seed itself or the needle tip on the TRUS image, and the dose was visualized and superimposed on the prostate contour.

iRUF system consists of four components: (1) seed and fiducial segmentation, (2) fiducial detection and pose estimation, (3) seed reconstruction, and (4) registration to TRUS images, and follows a simple workflow (see Fig. 1). The system has been prototyped with graphical user interface using MATLAB (MathWorks, Natick, MA, USA), and runs on a stand-alone workstation. A brief description of each component and the workflow follows. Full details have been described in our prior publications [13]– [17].

Image acquisition and preprocessing

Transverse TRUS images were acquired intraoperatively using a BK Pro-Focus US scanner (BK Medical, Peabody, MA, USA) to image the prostate. Although only three x-ray images are required for seed reconstruction, six x-ray images were taken for research purposes within a 20° cone around the anterior-posterior axis without changing the positioning of the patient using an OEC 9800 or 9900 non-isocentric mobile C-arm (GE Healthcare, Milwaukee, WI, USA) to image the seeds and an x-ray tracking fiducial (see Fig. 2a). The tracking fiducial was attached to the template by a mechanical bridge or a flexible arm and placed above the patient's pelvic area so that it could be captured along with seeds in the same x-ray images. The TRUS probe was removed during the x-ray scan to avoid occlusion of seeds by the probe. TRUS images were acquired at 1 mm intervals except for two cases which had 2.5 mm intervals. X-ray and TRUS image acquisition was performed once at the end of the procedure and takes approximately 2 minutes. iRUF dosimetry was computed offline. The C-arm was calibrated to compute the focal length, image center, and image distortion parameters using a calibration phantom before the procedure started [13], [18].

The patient's x-ray images were corrected for image distortions using the precomputed calibration parameters.

Segmentation and pose estimation

Most mobile C-arms do not have an encoder and therefore do not provide information about where the images are acquired. To compute x-ray image pose, we initially used a Fluoroscope TRACKing fiducial (FTRAC) [19] that consists of 9 beads, 3 lines, and 2 ellipses (all radio-opaque) for the first 16 patients. While FTRAC provided excellent tracking accuracy, its many features often occluded the seeds, making seed segmentation challenging. For the latter 64 patients, we simplified FTRAC and used a points-based fiducial with only 9 seed-like radio-opaque markers [13]. With this fiducial, the seed-like markers can be segmented just like seeds, thus making the autosegmentation robust. The fiducial and seeds in the distortion-corrected x-ray images were segmented by our previously developed automatic segmentation algorithm [13], [16], yielding 2D coordinates of the segmented seeds and fiducial features (see Fig. 2b). The pose of each x-ray image was computed by matching the fiducial model to the segmented features [13], [16].

Seed reconstruction

Three-dimensional seed locations were computed from the segmented seeds by our previously developed seed reconstruction algorithm known as APC-REDMAPS [14], [15]. APC-REDMAPS solves the seed reconstruction problem by finding unique correspondences of all the seeds among the segmented images. The reconstruction is formulated as a combinatorial optimization problem with constraints to guarantee to find a known number of implanted seeds while disambiguating overlapping seeds in 2D images. An automatic pose correction (APC) step refines the image poses during the reconstruction using the reconstructed seeds as fiducials. The seed reconstruction and pose correction steps alternate until the reconstruction error becomes less than a threshold. The APC step makes the seed reconstruction process robust to image pose errors by actively correcting them, which in turn enables more accurate seed localization. Once the seed correspondences are found, 3D seed coordinates are obtained by computing the symbolic intersection of the matched backprojected lines (see Fig. 2c).

Fluoroscopy-TRUS registration

The last step of iRUF workflow is fluoroscopy-TRUS registration. Since the seeds are reconstructed as a set of 3D point cloud, we use a points-to-volume registration algorithm that was previously developed in our group [2]. It inputs the reconstructed 3D seed coordinates and TRUS images, and outputs a registered 3D seed coordinates in TRUS coordinate system (see Fig. 2d). It begins with preprocessing TRUS images by adaptive thresholding, morphological image processing, and Gaussian blurring to provide a smoothed candidate seed-only images for guiding the registration optimization. The algorithm then finds an affine transform to align the seed cloud to the smoothed seed-only images by maximizing their overlap.

Post-implant CT/MRI dosimetry

For post-implant dosimetry, CT and MRI scans were performed on Day 1 (one day after the implantation) post-implantation. CT and T2-weighted MR images were rigidly fused, and contours of the prostate, rectum (entire circumference), and urethra (based on indwelling urinary catheter) were drawn on CT-MR fused images. Seeds were initially identified on CT using an automatic segmentation algorithm available in VariSeed, and manually checked and corrected for incorrectly identified or missing seeds. The rectum and urethra were defined in cranial and caudal extent equivalent to prostate length in order to achieve similarity with TRUS-based intraoperative contouring.

Statistical comparison of iRUF, USD, and CT/MRI dosimetry

Prostate and urethral doses were calculated based on iRUF, USD, and CT/MRI approaches for dosimetric comparison. Three parameters for urethral dose (urethral D5, D30, and D50) were chosen based on measures correlating to clinical outcome [20]. Four parameters for prostate (prostatic D90, V100, V150, and V200) were analyzed, as they reflect both target volume coverage as well as dose homogeneity [21]. Although CT/MRI-determined rectal doses were reported, we elected not to compare rectal doses because of differences between intraoperative USD/iRUF and post-implant CT/MR imaging conditions, i.e., the presence of the transrectal probe only on intraoperative US images. Comparative analyses were performed on each dosimetric parameter separately. Since these dosimetric values are not normally distributed, we used Wilcoxon signed rank test rather than a paired Student's *t*-test. To analyze their correlation, intraclass correlation coefficients (ICCs) were computed. The closeness of USD and iRUF dosimetry to CT/MRI dosimetry was further evaluated based on root mean squared differences (RMSD) in dosimetric values between USD/iRUF and CT/MRI.

Results

Eighty patients were prospectively enrolled between January 2011 and August 2014 on this study protocol approved by the institutional review board (IRB). All patients were implanted with Pd-103 to receive a dose of 90 or 125 Gy, prescribed to the periphery of the prostate gland. Among these patients, dosimetry comparison was performed on 66 patients, excluding 14 with incomplete data sets, (12 cases with no post-implant MRI and 2 cases with inconsistent TRUS data).

Scatter plots and quantitative comparison of the dosimetric values as measured by USD, iRUF, and CT/MRI are shown in Figs. 3 and 4, and Table 1. iRUF dosimetric values are closer to those of CT/MRI than USD for 6 out of 7 parameters (except for urethral D5) in terms of mean, median, and mean ratio to CT/MRI. *p*-values computed based on Wilcoxon signed rank test ($\alpha < 0.05$) indicate that iRUF dosimetry shows no significant variation for 3 of 7 dosimetric parameters, vs 2 of 7 parameters for USD dosimetry. Especially, iRUF prostate V100 was close to that of CT/MRI with 0.6% (96.4 vs 97.0%) difference for mean, 0.1% (97.3 vs 97.4%) difference for median, mean ratio to CT/MRI of 1.01, and *p*-value of 0.560 (i.e., no statistically significant difference). iRUF also showed significantly smaller RMSD and higher ICC compared to CT/MRI than USD for all 7 parameters. The overall

ICC between iRUF and CT/MRI dosimetry values for all 7 parameters was 0.42 (0.01 for USD), which is considered as fairly correlated [22]. USD had a tendency to overestimate dose to the prostate when compared to iRUF.

Discussion

Advances in technique as well as physician experience have led to improved dosimetric outcomes for permanent interstitial prostate brachytherapy, but procedural variations such as needle deviation, tissue deformation, and prostatic edema still make the successful execution of the idealized dosimetric plan challenging [3]–[5]. Although the source position can be updated at the time of placement based on TRUS visualization, the current USD approach is susceptible to subsequent tissue or source position changes as well as early edema occurring during the implant [5], [23]–[25]. Prior studies showed that there were correlations between intraoperative USD and post-implant CT dosimetry [26], [27]. However, there could be significant disparities between the two; for example, 38% of patients had >10% disparity, and 11% had >20% disparity of D90 in [26]. Other study analyzed the effect of random source localization errors and found that dose distributions to prostate remained acceptable in meeting minimal the D90 criterion when source errors were considered, but urethral doses increased significantly compared to plans without source placement errors incorporated [28].

Several studies suggest that enhancement in current USD is needed to achieve optimal seed implantation. Potters et al. stated that “future work could incorporate fluoroscopy coupled with ultrasonography to the planning software to improve the registration of the source location” [29]. Zelefsky et al. emphasized the necessity of enhanced image guidance to guarantee optimal dose distribution for all patients [30]. Lee and Zaider compared actual USD with simulated dynamic dosimetry, and predicted that dynamic dosimetry would achieve concurrent increases in prostate dose coverage and conformity yet decreases of maximum rectal and urethral doses [31].

In our study, USD and iRUF dosimetry were compared to Day 1 CT/MRI dosimetry. Although Day 1 CT/MRI dosimetry may not exactly represent the treatment day dosimetry due to prostatic edema, it was chosen as the reference as it provided dosimetry that was measured at the closest feasible time point to the treatment and therefore likely to be most similar to intraoperative results. In this comparison, iRUF was more closely correlated to CT/MRI than USD for all 7 dosimetric parameters examined. The mean ratios of USD and iRUF to CT/MRI values were all greater than 1.0 for all 7 parameters. Given that the prostate dosimetric parameters depend on prostate volume, this may be partly attributable to the well-described phenomenon of prostate volumes being greater when contoured on CT/MRI than those on TRUS (the mean±standard deviation ratio of CT/MRI- vs TRUS-defined prostate volumes was 1.2±0.2 for this cohort). Another potential reason for iRUF dosimetry showing higher doses for prostate dosimetric parameters is the prostatic edema that is present on the post-implant CT/MRI while the intraoperative prostate volume is contoured prior to needle insertions. These also led to relatively high RMSD values for iRUF although they are significantly smaller than USD. However, since both USD and iRUF used the same prostate contour, this alone does not explain the dosimetric differences observed between the two. Rather, iRUF updates seed positions reflecting the effects of edema

developing intraoperatively and reducing the effect of random source localization errors, whereas USD does not take these into account sufficiently. It was shown in prior studies that the degree of edema varies substantially from patient to patient [23], [32], and reductions in dose due to edema could result in >10% reduction in biochemical disease-free survival for patients with moderate to large amounts of edema [33]. Therefore, the ability to intraoperatively assess dose distribution and dynamically adjust for the dosimetric impact of procedural variation including edema would be one of the valuable aspects of iRUF-based dynamic dosimetry.

In this study, we used ICC to measure the correlation, which might be argued since edema might systematically affect dosimetry. In our USD, each seed was marked at the time of deposition and often times later as well when noticeable deviation from the initially marked location was identified. Therefore, edema effect was somewhat reflected in our USD dosimetry, especially for the seeds implanted later, although not fully captured. Seed deviation and resulting dosimetry change caused by edema between USD/iRUF and Day 1 CT/MRI was spatially-varying rather than systematic depending on the order of implantation. Unlike Ishiyama et al. [7] and Westendorp et al. [8] who compared intraoperative CT dosimetry to 1-month CT where differences of edema effect would be greater, we compared to Day 1 CT/MRI in which anatomy change by edema is less significant. Therefore, we believe using ICC to measure correlation is reasonable.

We have no indication that the USD system tested in this study would perform differently from other systems given that USD process in general does not account for the factors (e.g., prostate deformation, seed migration, intraoperative edema, poor needle/seed visualization in TRUS) that may degrade its performance, but acknowledge that this possibility was not tested in this study.

Our study does not allow conclusions to be drawn regarding the magnitude of clinical value of iRUF, which will require a study where iRUF is used intraoperatively, rather than offline. However, these results suggest that dynamic intraoperative dosimetry may improve the practitioner's ability to intraoperatively monitor the implant, and therefore may be expected to improve overall implant quality. Although other studies have demonstrated the benefits of intraoperative dynamic dosimetry, our use of a non-isocentric C-arm and modest additional hardware is notable in that it presents the possibility of performing dynamic dosimetry without added significant new equipment, facilities, or intra-procedural transportation of the patient. Finally, the image processing including segmentation, pose computation, seed reconstruction, and TRUS-fluoroscopy registration takes about 1 minute [13]. When considering C-arm positioning, fiducial setup, image acquisition, and assessment and correction of image processing, the whole iRUF workflow adds approximately 5-10 minutes, which is acceptable for intraoperative use. To prove the utility of iRUF for intraoperative dosimetry assessment and dynamic plan modification, we have incorporated iRUF into an FDA-approved treatment planning system RadVision (Acoustic MedSystems Inc., Savoy, IL). A phase II trial for intraoperative adaptive plan modification using RadVision is in progress.

Conclusions

Intraoperative iRUF approximated post-implant CT/MRI prostate and urethral dosimetry to a greater degree than the current ultrasound-based intraoperative method. iRUF is deployable in combination with a standard mobile C-arm, and demonstrates potential to enable dynamic intraoperative dosimetry. A confirmatory phase II trial utilizing iRUF for intraoperative dynamic plan modification is in progress.

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Fig. 1.

iRUF dosimetry workflow. Three-dimensional locations of implanted seeds are reconstructed (middle upper image) from three x-ray images taken with a mobile C-arm (left image), and are registered to TRUS volume (middle lower image). Dose distribution is computed based on the registered seeds and overlaid to the current TRUS volume with critical structure contours (right image).

Fig. 2. iRUF image processing. (a) Original x-ray. (b) Automatic seed segmentation and fiducial detection. Yellow dots = segmented single seeds; red circles = segmented overlapped (clustered) seeds; green circles = detected fiducial points. (c) 3D reconstructed seed locations (blue dots). (d) TRUS image with registered seeds overlaid with the contours of the prostate (red), PTV (cyan), urethra (blue) and rectum (green).

Fig. 3.

Scatter plots showing individual correlations and differences of prostate D90, V100, and V150 values between iRUF/USD and CT/MRI. Linear regression lines (solid) as well as 45 degree reference line (dotted) for perfect correlation are overlaid. D90 is represented as the percentage dose to the prescribed dose.

Fig. 4.

Scatter plots showing individual correlations and differences of urethral D50, D30, and D5 values between iRUF/USD and CT/MRI. Linear regression lines (solid) as well as 45 degree reference line (dotted) for perfect correlation are overlaid. Values are represented as the percentage dose to the prescribed dose.

Table 1

Comparison of intraoperative USD and iRUF dosimetric values with Day 1 post-implant CT/MRI-based values.

Parameters	Method	Mean±SD (%)	Median (range) (%)	Mean ratio to CT/MRI±SD	RMSD (%)	ICC*	p-value** (vs CT/MRI)
V200	CT/MRI	44.6±10.0	45.9 (18.0-68.7)				
	USD	56.3±10.3	55.3 (33.1-84.0)	1.31±0.33	15.0	0.18	<0.05
	iRUF	47.8±9.6	48.3 (29.6-73.4)	1.11±0.30	9.7	0.52	<0.05
V150	CT/MRI	71.6±10.5	72.4 (45.0-90.4)				
	USD	84.3±7.4	84.5 (62.1-98.7)	1.20±0.18	15.9	-0.04	<0.05
	iRUF	75.5±8.9	76.2 (56.7-93.3)	1.07±0.15	10.1	0.48	<0.05
V100	CT/MRI	96.4±3.0	97.3 (83.7-99.8)				
	USD	99.7±0.5	99.9 (97.9-100.0)	1.03±0.04	4.5	-0.38	<0.05
	iRUF	97.0±2.4	97.4 (87.8-99.8)	1.01±0.04	3.6	0.10	0.560
D90	CT/MRI	120.7±12.7	120.0 (92.0-151.0)				
	USD	140.8±13.5	140.0 (108.8-186.9)	1.18±0.15	25.6	-0.20	<0.05
	iRUF	127.5±14.9	125.0 (91.0-169.0)	1.06±0.11	14.3	0.49	<0.05
UD50	CT/MRI	115.2±20.0	113.6 (44.2-153.0)				
	USD	127.5±12.5	126.0 (97.6-166.2)	1.14±0.26	21.9	0.24	<0.05
	iRUF	124.7±15.0	122.7 (100.0-173.0)	1.11±0.22	18.5	0.49	<0.05
UD30	CT/MRI	103.2±17.7	127.5 (90.0-165.0)				
	USD	134.9±16.3	133.1 (99.2-183.8)	1.05±0.18	21.3	0.23	0.070
	iRUF	134.4±17.7	130.5 (106.0-224.0)	1.04±0.14	18.0	0.49	0.065
UD5	CT/MRI	154.6±33.3	147.2 (100.2-287.0)				
	USD	151.6±35.1	143.7 (104.8-368.8)	1.02±0.37	46.3	0.08	0.277
	iRUF	159.7±41.0	151.0 (113.0-397.0)	1.06±0.29	40.8	0.40	0.308

SD: Standard deviation; RMSD: Root mean squared difference

* Intraclass correlation coefficient: Higher value indicates more correlation between groups

** p-value: Based on Wilcoxon signed rank test. p < 0.05 indicates statistically independent or dissimilar groups