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Phase II study of intraoperative dosimetry for prostate brachytherapy using registered ultrasound and fluoroscopy

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Abstract

PURPOSE: To assess the performance of a system of intraoperative dosimetry and obtain estimates of dosimetry outcomes achieved when utilizing the system in a Phase II clinical trial.

METHODS AND MATERIALS: Forty-five patients undergoing permanent Pd-103 seed implantation for prostate cancer were prospectively enrolled. Seed implantation was performed and dose was tracked intraoperatively using intraoperative registered ultrasound and fluoroscopy (iRUF). Three-dimensional seed locations were computed from X-rays and registered to ultrasound for intraoperative dosimetry, followed by adaptive plan modification to achieve prostate V100 95% and 95% D90. Time required for iRUF was recorded. Postoperative CT/MRI scans were performed 1 day after the implantation and used as reference for dosimetric analysis. Dosimetric parameters for the prostate and urethra were compared between standard ultrasound-based dosimetry (USD), iRUF, and postoperative CT/MRI.

RESULTS: Mean total time for iRUF was <30 min. A mean of four seeds (0–12) were added per implant to correct cold spots discovered by iRUF. Day 1 CT/MRI prostate V100 was 95% for 44/45 patients; 1 patient had Day 1 V100 93%. No patient had rectal V100 exceeding 1 cc. Compared to CT/MRI, iRUF dosimetry had significantly smaller mean differences and higher correlations for all prostate and urethral dosimetric parameters examined than USD. Both USD and iRUF tended to overestimate dose, but with less bias in iRUF than USD.

CONCLUSIONS: Intraoperative dosimetry utilizing iRUF was associated with acceptable increase in procedure time and enabled very high rates of achieving excellent prostate dose

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Conflict of interest: A US patent (No. 8,233,686) has been filed for the fluoroscopy-based implant reconstruction algorithm.

coverage. iRUF intraoperative dosimetry approximated postoperative CT/MRI dosimetry to a greater degree than USD for the prostate and urethra.

Keywords

Prostate brachytherapy; Intraoperative dosimetry; Fluoroscopy; Ultrasound; Registration

Introduction

Brachytherapy allows for high tumor versus normal tissue dose ratios, but accurate placement of sources within the prostate is critical to its success (1–3). An ideal implant with well-spaced radioactive sources can be difficult to achieve due to multiple factors such as prostate deformations and needle deviation during insertion, prostatic edema, and relaxation of tissues and source movement after needle removal (4, 5). These variations may lead to dosimetric alterations, particularly under dosed regions that are not identified until after the procedure, posing challenges for corrective action and compromising treatment success (6, 7).

To overcome this problem, an approach whereby implanted source positions are updated in real time is needed (8). Although a commonly utilized method relies on visualizing and adjusting each source position at the time of placement (referred herein as “USD”—ultrasound-based dosimetry), frequently sources are not reliably visible on ultrasound, and false signals such as air can mimic the appearance of a seed.

We have previously described a novel system whereby ultrasound and fluoroscopy are quantitatively integrated for intraoperative visualization of seeds (iRUFs) (9). With iRUF, seed positions are calculated from three X-ray images acquired using nonisocentric mobile C-arm and registered to ultrasound. It allows for rapid intraoperative updating of dose distribution and therefore dynamic adjustments can be made to the treatment plan.

We previously reported a study where images were captured and iRUF dosimetry calculated offline (without subsequent intervention) at time of brachytherapy completion (10). Among 80 patients enrolled on this study, we analyzed 66 patients who had complete standard USD, iRUF, and post-operative CT/MRI image/dosimetry data. iRUF dosimetry showed significantly higher correlation with Day 1 (1 day after the treatment) CT/MRI dosimetry for all prostate and urethral dosimetric parameters than USD in terms of intraclass correlation and root mean squared differences. However, it is important to emphasize that because the analysis was all offline, iRUF dosimetry was not utilized to reoptimize the implantation plan or to guide the treatment process.

In contrast, for the present study, the iRUF system was incorporated into an FDA-approved commercial brachy-therapy treatment planning system (TPS), named RadVision (Acoustic MedSystems Inc, Savoy, IL, USA), for functional integration with the treatment planning and intraoperative delivery process. iRUF dosimetry was utilized to intraoperatively reoptimize the implantation plan during the implantation procedure and to guide the treatment process. The goal of this Phase II study was to evaluate the feasibility of using iRUF in the intraoperative setting by assessing additional time added to procedure, as well as

to obtain estimates of the dosimetric results achievable when using the system to guide and modify seed placement. In addition, we sought to confirm correlation of the intraoperative iRUF dosimetry to the standard postoperative CT/MRI dosimetry.

Methods and materials

Patients and treatment

Forty-five patients with localized prostate cancer were prospectively enrolled between October 2014 and September 2016 on this study protocol approved by the institutional review board. All patients were implanted with Pd-103 to dose of either 90 (10 patients) or 125 Gy (35 patients), prescribed to the prostate with 0–3 mm PTV margin. Mean seed activity for 90 Gy implants was 2.0 U, and for 125 Gy implants, it was 2.5 U. The implantation was performed using the standard real-time dosimetry of transrectal ultrasound (TRUS) image guidance (USD), where planning ultrasound images were acquired intraoperatively using a BK Pro-Focus ultrasound scanner (BK Medical, Peabody, MA, USA) and treatment plan was created using RadVision. Seeds were implanted using a hybrid approach with preloaded stranded sources as well as loose seeds (AnchorSeed, Theragenics, Norcross, GA, USA) via Mick applicator (Mick Radio-Nuclear Instruments, Mount Vernon, NY, USA). A physicist interactively updated seed positions in the TPS with input from the physician based on TRUS visualization using a probe mounted on a positionally tracked stepper (EX³ Stepper, CIVCO Medical Solutions, Coralville, IA, USA). Each seed position was confirmed at time of placement by visualization of the seed itself on the TRUS image, and the dose was updated and superimposed on the prostate contour. Infrequently, when source could not be directly visualized, the needle tip was used as surrogate for estimating the seed position. In the midcourse or near the end of the implantation (as desired by the physician), iRUF dosimetry was obtained based on a set of updated transverse TRUS and three X-ray images, and identified cold spots were patched up by adding additional seeds if needed. If significant changes in prostate, urethra, or rectal contours were observed, the physician would revise the contours as needed, and all subsequent intraoperative dosimetric calculations (both USD and iRUF) were based on the revised contours. Before completion of implant and reversal of anesthesia, USD was updated, but the coordinates of an added seed were modified from the planned coordinates only if it could obviously be matched to its location on the plan, as well as clearly visible on TRUS. iRUF final dosimetry was also captured before completion of implant, after any remedial seeds had been added; this iRUF final dosimetry was utilized for comparison to postoperative CT/MRI.

Intraoperative iRUF dosimetry

iRUF computes implanted seed locations from three X-ray images and fuses the reconstructed seed locations to TRUS images, thus allowing us to monitor the dose and dynamically modify the plan intraoperatively. Transverse TRUS images were automatically acquired at 1 mm intervals as the physician retracted the TRUS probe from the base to apex of the prostate to image the prostate. Three X-ray images were taken within a 20° cone around the anterior-posterior axis without changing the positioning of the patient using an OEC 9800 mobile C-arm (GE Healthcare, Milwaukee, WI, USA) to image the seeds. A tracking fiducial was placed above the patient's pelvic area using a flexible arm that is

attached to the template and imaged along with seeds in the same X-ray images for C-arm pose tracking. The C-arm was calibrated to compute the intrinsic imaging parameters (i.e., focal spot, source to detector distance, distortion map) using a calibration phantom before the procedure started (9). The obtained X-ray images were automatically segmented to produce 2-D seed locations and corresponding image poses (9). The segmentations were inspected and corrected for any erroneous segmentation by a physicist. Three-dimensional seed positions were reconstructed by APC-REDMAPS algorithm (11) that finds correspondence between identified seeds in three X-ray images while iteratively correcting X-ray image pose errors. The reconstructed seed positions were then registered to the TRUS images by a points-to-volume registration algorithm (12). We refer readers to our prior publications (9–12) for the details of these image processing algorithms. RadVision allowed us to toggle between the seed positions identified by USD and iRUF so that we could compare both dose distributions and detect cold spots (see Fig. 1). The implantation plan was immediately modified after the iRUF dosimetry assessment to patch up the detected cold spots with additional seeds.

Postoperative CT/MRI dosimetry

For postoperative dosimetry, CT and MRI scans were performed 1 day after the implantation (Day 1). Note that the AAPM recommends that in addition to intraoperative dosimetry, Day 0 and/or Day 16 CT/MRI are performed for Pd-103 (13). Seeds were identified on CT using an automatic segmentation algorithm available in VariSeed 9.0 (Varian, Palo Alto, CA, USA) followed by manual verification and correction for incorrectly identified or missing seeds. Postoperative dosimetry was also calculated using VariSeed. The prostate, rectum, and urethra were contoured on T2-weighted MR images that were rigidly fused to CT. To achieve similarity with TRUS-based contouring, the rectum and urethra were defined in cranial and caudal extent equivalent to prostate length in MR images.

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

To evaluate the clinical performance of iRUF, we assessed the agreement of USD and iRUF dosimetry measured at the end of the treatment to Day 1 CT/MRI dosimetry. Two parameters for the prostate (V100 and D90) and a parameter for the urethra (D30) were assessed. The prostate V100 was normalized to the prostate volume, and the prostate D90 and urethral D30 were normalized to the prescribed dose. Because of significant differences in imaging condition between the intraoperative USD/iRUF (with TRUS probe) and postoperative CT/MRI (without TRUS probe), we did not compare rectal dosimetric parameters. Scatterplots and Bland-Altman plots are shown for each parameter comparing iRUF and USD to CT/MRI. Differences are summarized as mean absolute differences (MADs). Overall agreement was assessed using concordance correlation coefficients (CCCs) (14).

Results

Mean total additional procedure time for iRUF was 29.8 min (14–45 min overall, with ~12 min for each iRUF session), and the median total anesthesia time was 145 min (interquartile range of 15 min). The measured iRUF time includes imaging and dosimetry computation,

dose assessment, and adaptive plan modification. A preliminary rule with consideration for early suspension of accrual was based on predicted iRUF time exceeding 30 min (75% certainty in >50% of patients), but with leeway for the physician to make determination based on totality of clinical performance. Although initial 4 cases had iRUF time 35–44 min, decision was made to proceed with accrual with expectation that additional experience would lead to improvements in time efficiency and also based on observation of positive CT/MRI dosimetric outcomes. Overall, amongst 45 patients, 20 (44%) had iRUF total time >30 min (Table 1).

With regard to dosimetric outcomes, Day 1 CT/MRI prostate V100 was 95% for 44 of 45 patients enrolled (1 patient had V100 of 93%) with median of 98.3% and interquartile range (IQR) of 3.13%. The prostate D90 was 100% for all 45 patients with median of 122.1% and IQR of 16.96%. The urethral D30 had median of 124.7% and IQR of 18.09%. No patient had rectal V100 exceeding 1 cc (median 0.03 cc; IQR 0.18 cc). Based on cold spots identified solely on iRUF, a mean of four seeds were added per patient (range 0–12), and the majority of patients required additional seeds based on intraoperative iRUF (44 of 45 patients). Table 1 summarizes the numbers of total implanted seeds and additionally implanted seeds after iRUF; Fig. 2 shows locations of seeds added based on iRUF intraoperative dosimetry. Approximately 1/3 of seeds added were in the anterior base, similar to what others have reported with intraoperative dosimetry systems (15), whereas the other two-thirds were in varying locations.

Table 2 summarizes the differences (MAD) and similarities (concordance correlation coefficients [CCC] with 95% confidence intervals) of USD or iRUF dosimetric parameters to those of CT/MRI. MADs were smaller and CCC was positive and higher for iRUF than USD for all parameters. For prostate V100 in both iRUF and USD, the concordance is very low and the confidence intervals contain zero; however, there is an extremely small range over which this parameter is measured because all values are greater than 92% and capped at 100%. Because of the 100% cap, there is proportional difference variability, apparent in the Bland-Altman plot by the cone shape with decreasing variability as the average nears 100%. When differences between iRUF and CT/MRI prostate V100 are expressed as percentage of average volume, most are within $\pm 5\%$. Prostate D90 concordance by CCC was 0.42 for iRUF with 95% confidence interval excluding zero, whereas for USD concordance, it was 0.13 with 95% confidence interval including zero. For urethral D30, the concordance for iRUF and USD was 0.43 and 0.33, respectively.

Scatter and Bland-Altman plots comparing iRUF and USD dosimetry to CT/MRI for the prostate and urethra are shown in Figs. 3 and 4. USD and iRUF tended to overestimate all three parameters than CT/MRI, with less bias in iRUF than USD. This can be seen in the Bland-Altman plots where the horizontal thick blue lines are above the horizontal zero level (i.e., no difference). For USD, the bias is significantly high for all parameters except for prostate V100, which is marginal. For iRUF, the location differential is not significant for prostate V100 and urethral D30, whereas bias for prostate D90 is slightly higher. USD dosimetry values showed much higher bias than those of iRUF for all three parameters investigated. Although there were significant scale differentials for prostate V100, D90, and

urethral D30 for both USD and iRUF, they were greater in USD than those in iRUF for all parameters.

Discussion

Although prior studies indicated some correlation between intraoperative USD and postoperative CT or CT/MRI dosimetry, there exists significant disparity between them (10, 16–18), suggesting that current USD approach needs improvement to achieve optimal implant distribution (19–22). Recently, Taussky *et al.* reported that intraoperative USD was predictive of Day 30 dosimetry but with low predictive power due to intraprostatic seed migration and other intraoperative factors that are unpredictable in USD, and biochemical recurrence-free rate was not dependent on any intraoperative USD dosimetry parameters (22). A few groups combined intraoperative CT with TRUS and performed intraoperative adaptive plan modification similarly as our approach, demonstrating improved prostate dose coverage and correlation with Day 30 (15, 23, 24) and Day 0 (15) dosimetry. However, these approaches require a specific CT system, for example, O-arm or C-arm cone-beam CT that is not commonly available in many hospitals. More importantly, the patient pose is significantly different between TRUS and CT scans, that is, lithotomy versus supine (without leg support), which causes significant prostate position and shape change, making CT-TRUS registration less accurate and adaptive remedial seed planning challenging.

Our prior study demonstrated that our novel iRUF system approximated postoperative CT/MRI prostate and urethral dosimetry to a greater degree than USD, but since dosimetry was analyzed offline rather than intraoperatively, we were unable to show potential impacts of utilizing iRUF on the actual prostatic doses achieved (10).

In the present study, iRUF has been incorporated into a brachytherapy TPS and utilized for intraoperative dynamic plan modification. To our knowledge, this represents the largest prospective study of intraoperative dosimetry for permanent brachytherapy. Unlike our prior study where only end-of-treatment USD and iRUF (with no additional seed implantation) were compared, the implantation plan was modified and additional seeds were added to patch up the identified cold spots based on iRUF dosimetry in this study, yielding excellent prostatic coverage and normal structure sparing due to its improved correlation with CT/MRI dosimetry. These results strongly suggest that iRUF provides the capability to intraoperatively monitor and improve overall treatment quality. Further study is underway to assess and compare clinical outcomes between patients treated with or without iRUF.

Unlike Ishiyama *et al.* (24) and Westendorp *et al.* (23) where intraoperative CT dosimetry was compared to 1-month postoperative CT, USD and iRUF dosimetry were compared to Day 1 CT/MRI dosimetry in this study, as Day 1 CT/MRI provided dosimetry that was measured at the closest feasible time point to the treatment and therefore likely to be most similar to intraoperative readings. In this comparison, iRUF showed lower mean absolute differences and higher correlations to CT/MRI than USD for all three dosimetric parameters examined. Considering the fact that the USD used in this study benefited from iRUF, that is, additionally implanted seeds after iRUF were included in the USD (although seed positions

were marked under TRUS only), actual improvement in final dosimetry when using iRUF versus sole USD is expected to be greater than the presented results.

We performed 2–3 iRUF sessions for each case. Repeated iRUF sessions were performed to verify that the additionally implanted seeds successfully patched up the identified cold spots. On average, these iRUF sessions added less than 30 min including the seed localization, dose computation, assessment, and adaptive plan modification to the standard USD-based implantation, which we considered as clinically acceptable. Although there are sparse data suggesting potential increased risk accrued extending time under anesthesia (25), such analyses are confounded by greater anesthesia time usually being associated with more complicated surgical procedures. No patient in this study experienced postoperative complications preventing same-day anesthesia recovery and discharge. If utilized in routine practice, we expect the time added by iRUF to be partially or completely offset by the ability to avoid the need for TRUS-based seed localization, whereas for purposes of comparison within this trial we had to track seeds using both methods.

A strength of our iRUF system is the use of mobile C-arm with minor additional hardware, while other intraoperative dosimetry approaches may require substantial workflow modification, potentially costly imaging equipment, or facilities not readily available in many centers. We also believe this system is well suited for application in a focal brachytherapy paradigm (26, 27) and are currently developing a method for targeting via integration of deformable (diagnostic) molecular image registration to be tested in a clinical trial.

Conclusions

iRUF dosimetry was demonstrated to be feasible with acceptable time added to intraoperative procedure and was associated with outstanding dosimetric outcomes. We confirmed that iRUF approximated CT/MRI prostate and urethral dosimetry to a greater degree than the current USD. iRUF was implemented in an FDA-approved TPS and deployed in combination with a standard mobile C-arm and demonstrated its clinical utility for intraoperative dosimetry and plan modification.

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Fig. 1.

Example of an iRUF-identified area of underdosing. After placement of all seeds in treatment plan, a region of posterior midapical prostate appears covered by prescription isodose line when viewed with USD (left), but inadequately covered when assessed using iRUF (right). Seeds were subsequently added to the plan to improve coverage. Red: prostate, orange: PTV, magenta: urethra, brown: rectum, green: V100, blue: V150, light blue squares: identified seeds. (The prostate contour is larger than PTV because it was revised at the time of iRUF dosimetry, whereas PTV remains as defined at the time of initial intraoperative planning). iRUF = intraoperative registered ultrasound and fluoroscopy; USD = ultrasound-based dosimetry. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Fig. 2.

Distribution of seeds (percentage rounded to ones' place) added based on iRUF intraoperative dosimetry. A total of 184 seeds for 45 patients were added based on iRUF feedback. Added seed locations based on the prostate divided into estimated thirds of the prostate in base-to-apex, anterior-posterior, and right-to-left directions. iRUF = intraoperative registered ultrasound and fluoroscopy.

Fig. 3. Scatter and Bland-Altman plots showing individual correlations and differences of prostate V100 (top two rows) and D90 (bottom two rows) values between iRUF/USD and CT/MRI. Each dosimetric parameter shows untransformed data with linear regression lines (solid) as well as the 45°-reference line (dotted) representing perfect correlation. iRUF = intraoperative registered ultrasound and fluoroscopy; USD = ultrasound-based dosimetry.

Fig. 4. Scatter (top row) and Bland-Altman (bottom row) plots showing individual correlations and differences of urethral D30 values between iRUF/USD and CT/MRI. Linear regression lines (solid) as well as 45°-reference line (dotted) for perfect correlation are overlaid. iRUF = intraoperative registered ultrasound and fluoroscopy; USD = ultrasound-based dosimetry.

Table 1

Numbers of total implanted and additionally implanted seeds after iRUF, number of iRUF sessions, and iRUF time added to procedure

Patients	Num. total implanted seeds	Num. added seeds with iRUF	Num. iRUF sessions	iRUF time (min)	Patients	Num. total implanted seeds	Num. added seeds with iRUF	Num. iRUF sessions	iRUF time (min)
1	99	6	3	35	24	80	3	2	31
2	113	4	3	35	25	105	3	2	31
3	108	3	3	44	26	95	4	2	32
4	111	5	3	41	27	104	2	2	26
5	104	2	3	33	28	100	4	2	20
6	94	6	3	30	29	48	4	3	42
7	63	4	3	28	30	67	6	2	35
8	91	5	3	29	31	65	3	2	24
9	122	12	3	36	32	77	4	2	36
10	80	4	3	32	33	66	4	2	26
11	92	3	3	35	34	65	6	2	15
12	91	6	3	32	35	72	2	2	33
13	65	3	3	30	36	61	3	2	30
14	81	2	2	21	37	85	3	2	21
15	82	2	2	25	38	79	7	3	45
16	89	4	2	28	39	92	4	3	41
17	99	3	2	15.5	40	92	3	2	27
18	68	2	3	26	41	84	5	2	25
19	80	10	3	28	42	76	5	2	34
20	94	3	3	22	43	96	5	3	40
21	92	0	2	14	44	79	6	3	27
22	94	2	2	25	45	72	4	3	31
23	70	3	2	24	Average	85.4	4	2.5	29.8

iRUF = intraoperative registered ultrasound and fluoroscopy.

Table 2

Comparison of intraoperative USD and iRUF dosimetric values with Day 1 CT/MRI-based values. Overall agreement was assessed using CCC

Parameter	Method	Mean ± SD	Mean ± SD absolute difference	CCC	CI ^a
V100	CT/MR	0.98 ± 0.02			
	iRUF	0.98 ± 0.01	0.01 ± 0.01	0.13	-0.15, 0.39
	USD	0.98 ± 0.01	0.02 ± 0.02	-0.13	-0.38, 0.14
D90	CT/MR	1.22 ± 0.10			
	iRUF	1.26 ± 0.09	0.08 ± 0.07	0.42	0.18, 0.61
	USD	1.34 ± 0.11	0.14 ± 0.10	0.13	-0.05, 0.3
UD30	CT/MR	1.26 ± 0.14			
	iRUF	1.29 ± 0.12	0.10 ± 0.09	0.43	0.17, 0.64
	USD	1.37 ± 0.13	0.14 ± 0.10	0.33	0.13, 0.51

CCC = concordance correlation coefficients; iRUF = intraoperative registered ultrasound and fluoroscopy; SD = standard deviation; UD30 = urethral D30; USD 5 ultrasound-based dosimetry; V100 and D90 5 prostate V100 and D90.

^a 95% confidence interval based on CCC.