ELSEVIER

BRACHYTHERAPY

Brachytherapy 19 (2020) 38–42

Prostate

MRI-assisted radiosurgery: A quality assurance nomogram for palladium-103 and iodine-125 prostate brachytherapy

Alexander N. Hanania[1,2], Rajat J. Kudchadker[2], Teresa L. Bruno[2], Chad Tang[2], Mitchell S. Anscher[2], Steven J. Frank[2,*]

[1]*Department of Radiation Oncology, Baylor College of Medicine, Houston, TX*
[2]*Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX*

ABSTRACT

PURPOSE: We sought to develop an activity nomogram for magnetic resonance (MR)–planned permanent seed prostate brachytherapy to improve quality assurance through a secondary dosimetric check.

METHODS AND MATERIALS: Patients undergoing MRI-assisted radiosurgery (MARS), whereby MRI is used for preoperative planning and postimplant dosimetry, were reviewed from May 2016 to September 2018. Planned activity (U) was fitted by MR-prostate volume (cc) via simple linear regression. Resulting monotherapy nomograms were compared with institutional nomograms from an ultrasound-planned cohort. Dosimetric coverage and external urinary sphincter (EUS) dose were also assessed for MR-planned patients.

RESULTS: We identified 183 patients treated with MARS: 146 patients received palladium-103 (^{103}Pd; 102 monotherapy and 44 boost), and 37 received iodine-125 (^{125}I) monotherapy. Median prostate volume was 28 cc (interquartile range: 22–35). Lines of best fit for implant activity were $U = 4.344 \times (vol) + 54.13$ (R^2: 95%) for ^{103}Pd monotherapy, $U = 3.202\ (vol) + 39.72$ (R^2: 96%) for ^{103}Pd boost and $U = 0.684\ (vol) + 13.38$ (R^2: 96%) for ^{125}I monotherapy. Compared with ultrasound, MR-planned nomograms had lower activity per volume ($p < 0.05$) for both ^{103}Pd monotherapy (~6%) and ^{125}I monotherapy (~11%), given a median size (30 cc) prostate. Across all MARS implants, postimplant dosimetry revealed a median V100% of 94% (interquartile range: 92–96%). Median EUS V125 was <1 cc for all patients, regardless of isotope.

CONCLUSIONS: We developed a quality assurance nomogram for MR-planned prostate brachytherapy. When compared with ultrasound-planned, MR-planned monotherapy resulted in a lower activity-to-volume ratio while maintaining dosimetric coverage, likely secondary to EUS-sparing and reduced planning target margins.

Keywords: Magnetic resonance (MR); Prostate; Brachytherapy; Nomogram; Palladium; Iodine

Background

The use of MRI in brachytherapy (BT) continues to advance. MR provides a distinct, theoretical advantage when compared with CT and ultrasonography, given the ability to comprehensively visualize the prostate and external urinary sphincter (EUS). Furthermore, the ability to clearly define prostate boundaries despite postimplant edema makes MR an incredibly accurate and valuable tool for evaluating postoperative dosimetry. We have previously described the use of MRI-assisted radiosurgery (MARS) at our institution, in which MR is used over the complete BT workflow, including preoperative planning and postimplant dosimetry (1–3).

Received 26 July 2019; received in revised form 10 September 2019; accepted 10 October 2019.

Financial disclosure: S.F. is a cofounder of C4 Imaging, LLC, for which he reports grants and personal fees. Outside the submitted work, he reports personal fees from Varian, grants from Eli Lilly, grants from Elekta, grants and personal fees from Hitachi, other from Breakthrough Chronic Care, personal fees from Augmenix, and personal fees from National Comprehensive Cancer Center (NCCN). The author(s) received no specific funding for this work. Supported in part by Cancer Center Support (Core) Grant P30CA016672 from the National Cancer Institute, National Institutes of Health, to The University of Texas MD Anderson Cancer Center.

* Corresponding author. Department of Radiation Oncology, University of Texas MD Anderson Cancer Center, 1840 Old Spanish Trail - Unit 1422, Houston, TX 77054. Tel.: +1 713-745-3495; fax: 713-563-6940.

E-mail address: sjfrank@mdanderson.org (S.J. Frank).

1538-4721/$ - see front matter
https://doi.org/10.1016/j.brachy.2019.10.002

Nomograms for calculating planned activity for a given prostate volume have existed since the beginning of permanent seed BT and remain a recommended tool for independent checks of dosimetric calculations (4). Despite standardization of dose prescribed for permanent seed prostate BT, the amount of activity per volume can vary significantly with ultrasound-based planning, potentially resulting in compromised clinical outcomes (5). We hypothesized that MR-planned, low-dose-rate prostate BT with palladium-103 (^{103}Pd) and iodine-125 (^{125}I) results in a decrease in activity-to-volume ratio compared with our historical ultrasound-based planning, given the ability to spare the EUS and reduce planning target volume (PTV) margins.

From our institutional experience, we sought to develop an activity nomogram for MR-planned prostate BT to improve quality assurance through a secondary dosimetric check. Furthermore, we planned to evaluate our Day 0, MR-based dosimetry on patients treated with MARS to assess the dosimetric coverage, heterogeneity, and ability to spare the EUS and to provide meaningful feedback regarding expectations for Day 0 vs. planned implant coverage.

Materials and methods

Patients undergoing MARS prostate BT at our institution from May 2016 to September 2018 were selected for this study, after institutional review board approval. All cases were preoperatively planned with a stranded-seed, modified-uniform (^{103}Pd) and modified-peripheral (^{125}I) loading implant technique with an MIM treatment planning system (MIM Software Inc., Cleveland, OH). A PTV was created as a 2-mm expansion of the prostate on preoperative MR (axial T2-weighted), without expansion posteriorly. In addition, the superior aspect of the EUS was identified at the level of the verumontanum and contoured entirely to the inferior extent defined as the initial muscular ring around the urethra (6). The complete treatment paradigm and procedure for MARS at MD Anderson have been previously described elsewhere (1).

Dose prescribed was 125 Gy for ^{103}Pd monotherapy, 90 Gy for ^{103}Pd boost, and 144 Gy for ^{125}I monotherapy with a seed activity in air kerma strength of 2.457, 1.939, and 0.497 U, respectively. TheraSeed Palladium-103 and AgX100 Iodine-125 BT stranded seeds were used and preloaded with the cobalt dichloride-N-acetylcysteine (C4) contrast agent marker to allow seed localization and postimplant MR dosimetry (7,8). Preplanning target values included V100 > 95%, D90 > prescribed dose, RV100 < 1 cc, and EUS V125 < 1 cc. Planned activity in air kerma strength (U) was fitted by MR prostate volume (cc) via simple linear regression, which has been shown to predict seed and activity requirements well over a prostate range of 20–60 cc (9). R^2 was evaluated for goodness-of-fit. The resulting monotherapy nomograms were compared with historic transrectal ultrasound (TRUS)–based nomograms from our recently published phase II trial (n = 300) by using an F test (10). In addition, we evaluated V100 and D90 between planned and Day 0 dosimetry for patients treated with MARS. A Student's t test for normally distributed data and a Mann–Whitney U test for nonparametric data were used for comparing independent groups of data. Of note, postimplant dosimetry for MARS patients was evaluated on MR as previously described, whereas CT was historically used for the TRUS cohort.

Results

We identified 183 patients treated with MARS prostate BT at our institution; of these, 146 patients received ^{103}Pd (102 monotherapy and 44 boost), and 37 received ^{125}I monotherapy. Median prostate volume was 28 cc (interquartile range [IQR]: 22–35 cc). Median activity planned was 172 U (IQR: 152–197 U), 116 U (IQR: 93–140 U), and 38 U (IQR: 32–43 U) for ^{103}Pd monotherapy, ^{103}Pd boost, and ^{125}I monotherapy, respectively. Postoperative, Day 0, dosimetric characteristics for the three cohorts are presented in Table 1. Lines of best fit for implant activity

Table 1
MRI-assisted radiosurgery treatment details (n = 183 cases)

Treatment variable, median (IQR)	^{103}Pd mono (n = 102)	^{103}Pd boost (n = 44)	^{125}I mono (n = 37)
Prostate volume (cc)	28 (22–33)	23 (17–29)	41 (35–51)
Total activity (U)	172 (152–197)	116 (93–140)	39 (33–48)
Number of seeds	72 (64–84)	60 (48–72)	78 (65–89)
V100 (%)	93 (91–96)	96 (94–98)	95 (92–97)
V150 (%)	63 (58–66)	70 (65–76)	49 (44–54)
V200 (%)	35 (31–39)	42 (38–47)	20 (17–24)
D90 (Gy)	134 (130–143)	106 (102–112)	154 (149–161)
RV100 (cc)	0.02 (0–0.2)	0.02 (0–0.2)	0.02 (0–0.2)
EUS D5 (Gy)	218 (184 274)	181 (161–202)	236 (199–282)
EUS D30 (Gy)	160 (138–187)	137 (126–149)	190 (164–203)
EUS V125 (cc)	0.3 (0.1–0.5)	0.5 (0.3–0.7)	0.3 (0.1–0.7)
EUS V200 (cc)	0.02 (0–0.07)	0.05 (0.03–0.08)	0.01 (0–0.04)

IQR = interquartile range; ^{103}Pd = palladium-103; ^{125}I = iodine-125; EUS = external urinary sphincter.

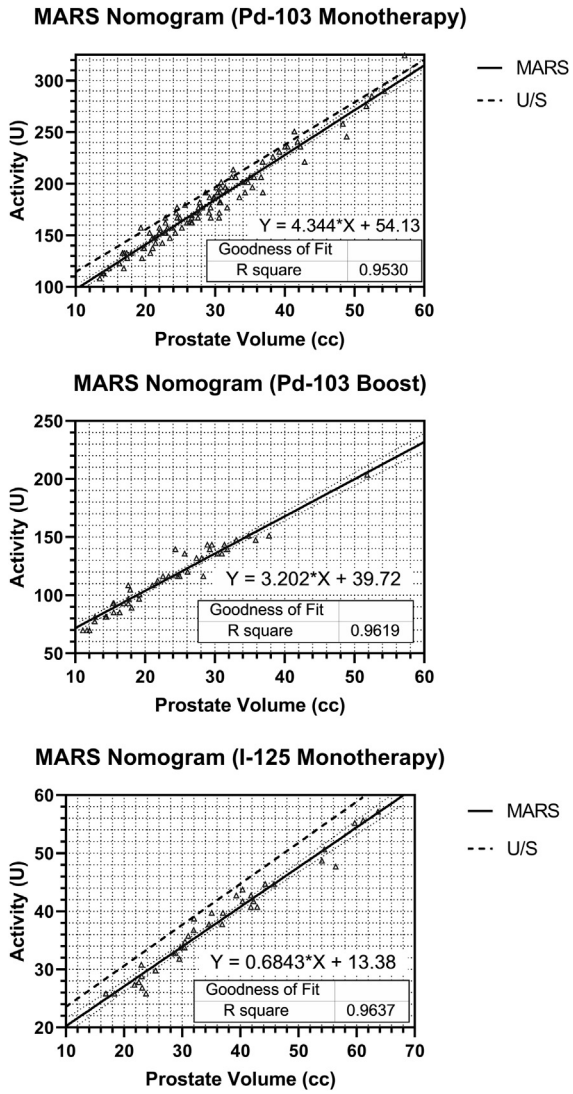

Fig. 1. MRI-assisted radiosurgery (MARS) quality assurance nomograms. Simple linear regression lines (solid) are presented for ^{103}Pd monotherapy (n = 102), ^{103}Pd boost (n = 44), and ^{125}I monotherapy (n = 37) based on patients treated at our institution. Planned activity in air kerma strength (U) is plotted on the y-axis, whereas prostate volume in cubic centimeters is plotted on the x-axis. For patients undergoing monotherapy with either isotope, we present our historic ultrasound-based nomograms (dotted) for comparison, which were significantly higher in terms of activity-to-volume ratio than MARS.

were U = 4.344*(vol) + 54.13 (R^2: 95%) for ^{103}Pd monotherapy, U = 3.202 (Vol) + 39.72 (R^2: 96%) for ^{103}Pd boost, and U = 0.684 (vol) + 13.38 (R^2: 96%) for ^{125}I monotherapy. Compared with TRUS-planned, MR-planned nomograms had lower activity per volume ($p < 0.05$) for both ^{103}Pd monotherapy (~6%) and ^{125}I monotherapy (~11%), given a median size (30 cc) prostate (Fig. 1). Across all MARS implants, postimplant, Day 0 dosimetry revealed a median V100% of 94% (IQR: 92–96%). Furthermore, the median difference between planned and Day 0 coverage (in terms of V100%) for all MARS cases was 5%, whereas the median difference in D90 was

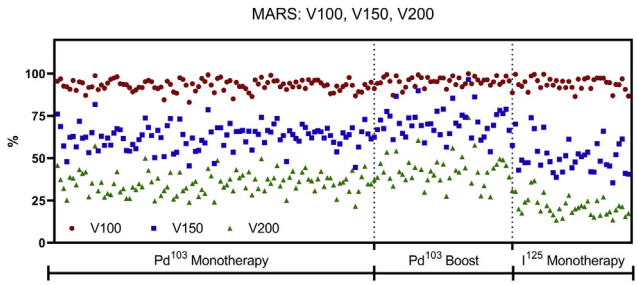

Fig. 2. MARS: dose coverage and heterogeneity (V100, V150, and V200). Dose coverage (V100) as well as heterogeneity (V150 and V200) of all MARS implants are presented for ^{103}Pd monotherapy (n = 102), ^{103}Pd boost (n = 44), and ^{125}I monotherapy (n = 37). MARS implants may demonstrate increased heterogeneity in contrast to ultrasound planned implants, given the active sparing of the external urinary sphincter. This effect seems most pronounced with palladium.

36 Gy for both ^{103}Pd and ^{125}I monotherapy and 19 Gy for ^{103}Pd boost. Dose coverage and heterogeneity across MARS implants, in terms of V100, V150, and V200, are presented (Fig. 2). Median EUS D5 was 218 Gy (184–274) vs. 236 Gy (199–282) for ^{103}Pd and ^{125}I monotherapy, respectively (p = 0.24). Median EUS D30 was significantly less with ^{103}Pd at 160 Gy (138–187) vs. 190 Gy (164–203) for ^{125}I monotherapy ($p < 0.002$; Fig. 3). Median EUS V125 was <1 cc for all patients, regardless of isotope. Median EUS V200 was 0.03 cc (0.007–0.07) for the entire cohort of patients.

Discussion

Three-dimensionally (3D)–planned BT has largely replaced the use of standard look-up nomograms; however, these important tools continue to serve as a secondary, independent, dosimetric check for BT quality assurance (11,12). Ideally, centers performing BT should create institution-specific tools for quality assurance; nomograms are simple to create and use, with detailed, step-by-step instructions for their development available in the literature (13). Benefits of such a secondary check can ensure that planned implants are consistent with institutional standards and decrease plan heterogeneity among differing patients and practitioners. Furthermore, identifying plans that are outside of institutional norms can prevent medical events/mistreatments and reduce seed waste (leading to reduced risk and cost), ultimately improving the value of BT (14). Of note, the implementation of nomograms from external institutions should be done with caution owing to unaccountable interinstitutional variabilities, despite standardized dosing and relatively identical techniques (15). One possible solution for industry to meet this need would be to incorporate independent nomogram checks into the treatment planning system as part of treatment workflow. Such automation would also allow improvements in defining activity-to-volume standards, as the activity nomogram can continue to be refined as the number of completed cases increases.

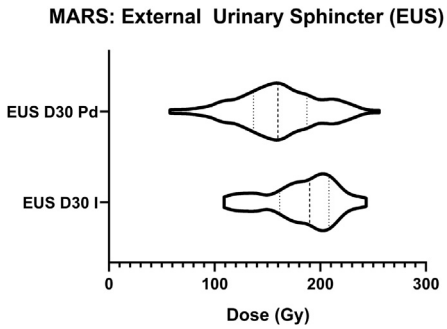

Fig. 3. MARS: external urinary sphincter (EUS) D30. The D30 or minimum dose that 30% of EUS is exposed to is presented for ^{103}Pd vs. ^{125}I monotherapy as violin plots. Visually represented is the wider variance of achievable EUS sparing with palladium. The median is represented by the dashed line, whereas the 25% and 75% quartiles are represented by the dotted lines.

MR provides theoretical advantages for both planning and postoperative dosimetry. In the planning stage, MR allows the brachytherapist to visualize the dominant intraprostatic lesion, allowing dose heterogeneity to advantageously cover the lesion while at the same time, limiting dose to the EUS, potentially reducing rates of urinary bother. Furthermore, when comparing MRI with TRUS, the absolute difference in perceived prostate volume is marginal, with one study by Bowes *et al.* reporting a median 3 cc difference (16), making a comparison of our MR-planned monotherapy nomograms to our historical TRUS-planned nomograms reasonable. In terms of postimplant dosimetry in prostate BT, confident delineation of the organ during postoperative contouring is challenging when using CT alone. Imaging fusion with MR or TRUS has proven to be superior to CT for this task and has been found to provide reliable interobserver agreement (16–18). However, in contrast to TRUS, MR provides clear prostatic imaging even when significant edema is present and allows quantification of dose to the EUS, which is only visible on MR. Furthermore, previous study has shown MR alone to be comparable to MR–CT fusion with the use of MRI markers (2).

Our results suggest that MR-planned permanent seed implants maintain dosimetric coverage while using less overall activity (lower activity-to-volume) comparted with our TRUS-based cohort (pre-TRUS planning and post-CT dosimetry). One reason for this difference is greater confidence in prostate delineation leading to reduced PTV margins (2 and 0 mm posterior) compared with our historical preplanned TRUS cohort. A limitation of this study is being unable to compare our MARS cohort with a cohort undergoing intraoperative TRUS-planning, as this is not done at our institution. During intraoperative TRUS-planning, the treatment is planned at the time of the procedure and with the patient in treatment position. Meanwhile, patients undergoing MARS have an MRI done before their procedure date using a BT protocol and rigid endorectal coil with diameter emulating the TRUS probe. Thus, although the MRI is used for dosimetric planning, it must be carefully fused in reference to the template for the use of intraoperative TRUS during the procedure by using a reproducible method that we have demonstrated to be reliable (1). Template reproducibility can be assured through localization of the prostate base in the ultrasound sagittal plane followed by matching the template to preplanned positioning at the midgland and apex in the ultrasound axial plane. Given these differences, one may argue that the removal of setup error by using an intraoperative technique would likely also prove effective in achieving results similar to those in this study. However, an important contributor to our results is the purposeful avoidance of high dose within the EUS, given that it is well visualized on MR (Fig. 4). Indeed, while reducing PTV margins is one benefit of MARS, the true novelty lies within the ability to selectively distribute heterogeneity. As such, EUS sparing has become

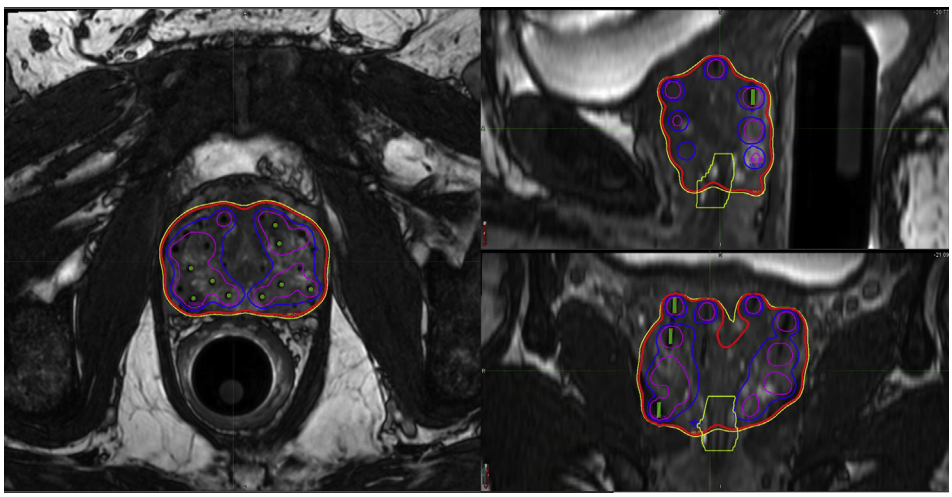

Fig. 4. External urinary sphincter sparing with MR planning. MRI allows us to visualize and account for the EUS during planning. Sparing of the EUS in addition to the reduction of expansion necessary to acquire the planning target volume (PTV) results in implants with reduced activity-to-volume ratio while maintaining appropriate coverage and dose.

the standard at our institution, as we previously found that improvements in the distribution of dose heterogeneity and limiting EUS dose may decrease the incidence of urinary bother, irritation, and function (6). As a consequence of pushing dose away from the EUS, MARS plans may demonstrate increased heterogeneity as shown by the plotted V150 and V200 (Fig. 2), especially with the use of palladium. Furthermore, Day 0 dosimetry suggests improvements in D30 dose to the EUS with palladium-based monotherapy over iodine (Fig. 3). Ultimately, despite increased heterogeneity in these patients, V125 to the EUS never exceeded 1 cc, highlighting the ability of MR-planned BT to selectively distribute dose.

We reported expectations between planned and Day 0 coverage in terms of V100% and D90 with MARS. One major difference compared with TRUS-planned implants evaluated on postimplant CT is the improved accuracy of prostate delineation and reproducible postimplant dosimetry. Unlike postimplant CT, which is complicated by edema (requiring a second CT at $\geq$ 30 days), we have found that differences in dosimetric coverage do not seem to be significant over time for MR-based dosimetry (1,2). Ultimately, coverage (V100 and D90) for Day 0 remained excellent and consistent with high-quality BT. However, given that MR-based implants seem to deliver less activity-to-volume, further research into the clinical implications are necessary. Early quality of life outcomes with MARS have been assessed preliminarily and show a favorable acute toxicity profile, with urinary function returning to baseline within 8 months after treatment (19). Future directions include investigation of whether reduced activity-to-volume implants from MARS result in a decrease of long-term urinary morbidity secondary to EUS sparing while maintaining biochemical and local control.

Conclusions

We developed a quality assurance nomogram for planning MR-based prostate BT at our institution. This clinical tool provides a secondary dosimetric check during the planning process for MR planning with ^{103}Pd monotherapy, ^{103}Pd boost, and ^{125}I monotherapy. Nomograms for MR-planned monotherapy were lower in terms of activity to prostate volume ratio when compared with TRUS-planned, likely secondary to EUS sparing and smaller PTV margins. Despite the lower activity to volume ratio, excellent coverage was maintained for the vast majority of patients treated with MARS evaluated on postimplant MR, which provides unparalleled confidence in identifying the prostate volume during postimplant review. Furthermore, dosimetric analysis on Day 0 suggests improvements in D30 to the EUS with the use of palladium over iodine monotherapy. Longer follow-up is necessary to assess the clinical implications of reduced activity implants and dose reduction to the EUS.

References

[1] Blanchard P, Ménard C, Frank SJ. Clinical use of magnetic resonance imaging across the prostate brachytherapy workflow. *Brachytherapy* 2017;16:734–742.

[2] Martin GV, Pugh TJ, Mahmood U, *et al*. Permanent prostate brachytherapy postimplant magnetic resonance imaging dosimetry using positive contrast magnetic resonance imaging markers. *Brachytherapy* 2017;16:761–769.

[3] Frank SJ, Mourtada F. Bending the slope of the brachytherapy curve: magnetic resonance imaging-assisted radiosurgery for the treatment of prostate cancer. *Brachytherapy* 2017;16:657–658.

[4] Pujades MC, Camacho C, Perez-Calatayud J, *et al*. The use of nomograms in LDR-HDR prostate brachytherapy. *J Contemp Brachytherapy* 2011;3:121–124.

[5] Nath R, Bice WS, Butler WM, *et al*. AAPM recommendations on dose prescription and reporting methods for permanent interstitial brachytherapy for prostate cancer: report of Task Group 137. *Med Phys* 2009;36:5310–5322.

[6] Register SP, Kudchadker RJ, Levy LB, *et al*. An MRI-based dose-response analysis of urinary sphincter dose and urinary morbidity after brachytherapy for prostate cancer in a phase II prospective trial. *Brachytherapy* 2013;12:210–216.

[7] Lim TY, Stafford RJ, Kudchadker RJ, *et al*. MRI characterization of cobalt dichloride-N-acetyl cysteine (C4) contrast agent marker for prostate brachytherapy. *Phys Med Biol* 2014;59:2505–2516.

[8] Sanders JW, Frank SJ, Kudchadker RJ, *et al*. Development and clinical implementation of SeedNet: a sliding-window convolutional neural network for radioactive seed identification in MRI-assisted radiosurgery (MARS). *Magn Reson Med* 2019;81:3888–3900.

[9] Aronowitz JN, Michalski JM, Merrick GS, *et al*. Optimal equations for describing the relationship between prostate volume, number of sources, and total activity in permanent prostate brachytherapy. *Am J Clin Oncol* 2010;33:164–167.

[10] Frank SJ, Pugh TJ, Blanchard P, *et al*. Prospective phase 2 trial of permanent seed implantation prostate brachytherapy for intermediate-risk localized prostate cancer: efficacy, toxicity, and quality of life outcomes. *Int J Radiat Oncol Biol Phys* 2018;100:374–382.

[11] Cohen GN, Amols HI, Zelefsky MJ, *et al*. The Anderson nomograms for permanent interstitial prostate implants: a briefing for practitioners. *Int J Radiat Oncol Biol Phys* 2002;53:504–511.

[12] Raben A, Chen H, Grebler A, *et al*. Prostate seed implantation using 3D-computer assisted intraoperative planning vs. a standard look-up nomogram: improved target conformality with reduction in urethral and rectal wall dose. *Int J Radiat Oncol Biol Phys* 2004;60:1631–1638.

[13] Lafata KJ, Bushe H, Aronowitz JN. A simple technique for the generation of institution-specific nomograms for permanent prostate cancer brachytherapy. *J Contemp Brachytherapy* 2014;6:293–296.

[14] Taylor PK, Riegel AC. Reducing seed waste and increasing value of dynamic intraoperative implantation of Pd-103 seeds in prostate brachytherapy. *J Appl Clin Med Phys* 2018;19:383–388.

[15] Aronowitz JN, Crook JM, Michalski JM, *et al*. Inter-institutional variation of implant activity for permanent prostate brachytherapy. *Brachytherapy* 2008;7:297–300.

[16] Bowes D, Crook JM, Araujo C, *et al*. Ultrasound–CT fusion compared with MR–CT fusion for postimplant dosimetry in permanent prostate brachytherapy. *Brachytherapy* 2013;12:38–43.

[17] Petrik DW, Araujo C, Halperin RM, *et al*. Implications of CT-imaging for postplan quality assessment in prostate brachytherapy. *Int J Radiat Oncol* 2010;78:S356.

[18] Polo A, Cattani F, Vavassori A, *et al*. MR and CT image fusion for postimplant analysis in permanent prostate seed implants. *Int J Radiat Oncol* 2004;60:1572–1579.

[19] Farooqi A, Blanchard P, Bruno T, *et al*. Early quality of life outcomes for MRI-assisted prostate brachytherapy patients. *Brachytherapy* 2017;16:S108.