Journal of Oncology Research
Research Article

Comparison of ^{125}I and ^{103}Pd Isotopes in Escalating Dose to Intraprostatic Lesions for Low Dose Rate Prostate Brachytherapy: Dosimetry and Acute Toxicity

Muenkel J[1], Traughber BJ[1], Xu ZZ[1], Ellis RJ[2], Ponsky L[3] and Podder TK[1*]

[*1]Department of Radiation Oncology, University Hospitals Seidman Cancer Center, Case Western Reserve University School of Medicine, 11100 Euclid Avenue, Cleveland, Ohio 44106, USA

[2]Department of Radiation Oncology, Penn State Cancer Institute, Penn State College of Medicine, Hershey, PA 17033

[3]Department of Urology, University Hospitals Seidman Cancer Center, Case Western Reserve University School of Medicine ,11100 Euclid Avenue, Cleveland, Ohio 44106, USA

Received: 31 August, 2019**; Accepted:** 18 September, 2019**; Published:** 25 September, 2019

***Corresponding Author:** Tarun K Podder, University Hospitals Seidman Cancer, Center Case Western Reserve University School of Medicine, 11100 Euclid Avenue, Cleveland, Ohio 44106, USA. E-mail: Tarun.Podder@UHhospitals.org

Copyright: © 2019 Muenkel J, Traughber BJ, Xu ZZ, et al. (2019) Comparison of ^{125}I and ^{103}Pd Isotopes in Escalating Dose to Intraprostatic Lesions for Low Dose Rate Prostate Brachytherapy: Dosimetry and Acute Toxicity. J Oncol Res: 3(1): 01-14.

Abstract

Aim:

This study aims to investigate the dosimetric coverage and acute toxicity for patients with dose escalation to dominant intraprostatic lesions (DIL) while performing LDR brachytherapy with ^{125}I and ^{103}Pd.

Methods:

In our institute, one hundred eighty-nine consecutive patients underwent LDR prostate seed implant (PSI) brachytherapy for stage T1c-T3b prostate cancer. These patients had an average Gleason score of 7 and an average PSA of 8.67ng/ml. At least one DIL was found in 113 (59.8%) patients and dose was escalated to 150% of the prescription. All patients were treated with either ^{125}I or ^{103}Pd with or without an external beam radiation therapy (EBRT) boost. Dosimetric parameters from the post-operative plan, including prostate $V_{100\%}$, DIL $V_{150\%}$, rectum D_{2cc}, and urethra $D_{10\%}$, were evaluated for patients with and without DIL. Acute rectal and urinary toxicities were determined from the one to three month follow-up visit

Results:

The only significant dosimetric difference was found for the urethra $D_{10\%}$ with an average of 134.7% ± 25.2% versus 144.4% ± 28.4% for the DIL and no DIL patients. Compared to patients treated with ^{103}Pd, those treated with ^{125}I had lower prostate $V_{150\%}$ and $V_{200\%}$, but had higher rectum D_{2cc} and urethra $V_{100\%}$ with comparable DIL coverage. DIL patients treated with PSI as monotherapy experienced less nocturia and more patients reported no toxicities compared to the no DIL group.

Conclusions:

This study reveals that dose escalation to DILs using ^{103}Pd is possible without overdosing normal structures and without increasing any acute rectal and urinary toxicities and the results are comparable with ^{125}I implants.

Keywords: Dose Escalation; Prostate; mpMRI; Dominant Intraprostatic Lesion; Dose Paining

Introduction

Prostate cancer is the most commonly diagnosed cancer and second leading cause of cancer related death in men in the United States. In 2019, it is estimated that 174,650 men will be diagnosed with prostate cancer (PCa) with 18.1% mortality rate (1). Among several treatment options available, the external beam radiation therapy (EBRT) with or without brachytherapy has been well established as standard of care and have been shown to be effective in long term follow-up (2-6). Multiple studies have shown that dose escalation to the dominant lesion within the prostate has improved disease control and some even suggested that the dose escalation may be essential in order to overcome the tolerance of the more radio-resistant cancer cells (7-9). Some studies have also shown an increase in quality of life for patients treated with brachytherapy over EBRT alone or surgery (10,11). Based on the efficacy of brachytherapy with dose-escalation, the American Brachytherapy Society (ABS), Groupe Européen de Curitherapie (and the European Society for Radiotherapy and Oncology (GEC-ESTRO) have incorporated it in their recommendations (4,12).

Over the years, improved imaging techniques have enhanced the ability to better identify the dominant intraprostatic lesions (DIL). In a previous study, our research group used SPECT/CT capromab pendetide to identify the DIL and other studies have used multiparametric magnetic resonance imaging (mpMRI) for DIL identification (8, 13-15). Gaudet et al. evaluated the toxicities for patients with DIL who received intraprostatic boost using ^{125}I. They found no significant difference in the late and acute urinary and rectal toxicities between patients who received standard plans and intraprostatic boost plans for monotherapy (16). Tissaveringhe et al. published a phase II study on the comparison of treating DIL using HDR and LDR monotherapy with ^{125}I isotope (17,18). They concluded that HDR monotherapy was comparable to LDR monotherapy in terms of DIL D90 coverage. In addition, HDR monotherapy was able to further reduce the doses to the critical structures such as urethra. Both these studies used ^{125}I isotope for LDR monotherapy. No study was found in literature which investigated different isotope (e.g. ^{103}Pd, which has shorter

half-life and sharp dose fall-off) or LDR boost following EBRT.

In this current study we have investigated the effect of ^{103}Pd isotope in regard to the dosimetric coverage and toxicities for patients with dose escalation to the DIL for LDR monotherapy as well as LDR boost and compared all those parameters with a group of prostate patients treated with ^{125}I isotope.

Materials and Methods

This study was performed under the IRB approved protocol number CHRV 0080. Between January 2016 and October 2018, 189 consecutive patients underwent LDR prostate seed implant (PSI) brachytherapy for stage T1c-T3b prostate cancer. These patients had an average Gleason score of 7 with a range of 6 to 10 and a pretreatment PSA of 8.67ng/ml, with a range of 2.74 ng/ml to 64.82ng/ml (Table 1). Each patient underwent an mpMRI using 3-Tesla (3-T) magnetic strength to determine the presence of a DIL. The mpMRI utilized three main imaging sequences: T2 weighted (T2W), diffusion weighted image (DWI), and dynamic contrast-enhancement image (DCEI), which were used for diagnosing and reporting the results based on the prostate imaging reporting and data system (19). The T2W image provides anatomic detail of the prostate which is typically used to discern normal tissue from abnormal tissue within the prostate as seen in Figure 1A . Not all cancerous tissues are easily visible on the T2W image, and conversely there may be benign growths that maybe prominent in the image. These limitations make it necessary to have functional image sequences for an adequate diagnosis. In this context, the DWI provides information about the diffusion of water molecules through the tissue. Normal prostate tissue has higher diffusion rates than prostate cancer tissue.

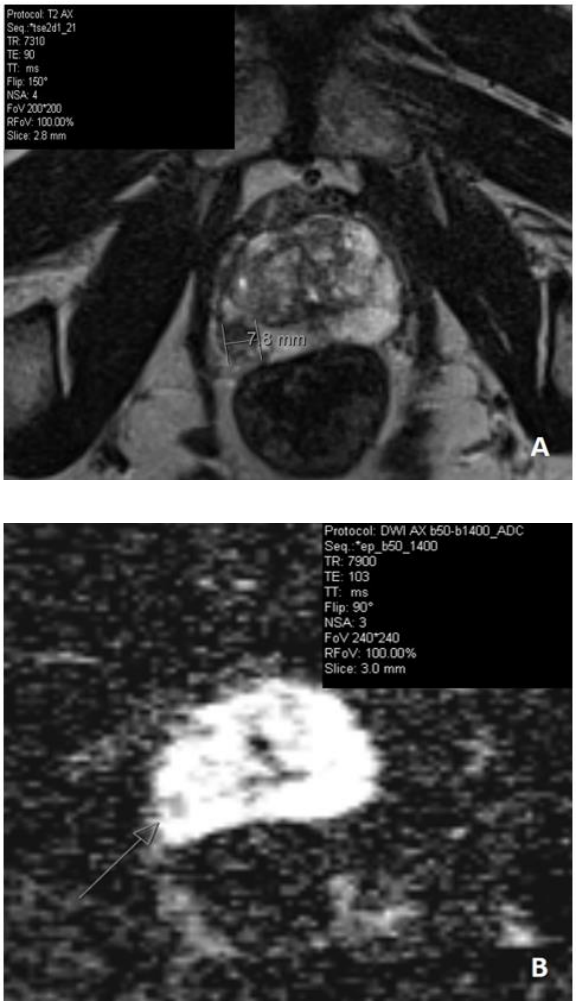
Table (1) Prostate cancer patient characteristics.

Variable	Monotherapy		Boost	
	DIL (n/N)	No DIL	DIL	No DIL
Age (year)				
≤65	(11/80)	(15/55)	(8/33)	(4/21)
>65	(69/80)	(40/55)	(25/33)	(17/21)
PSA (ng/ml)				
≤4	(1/80)	(5/55)	(2/21)	(0/21)
10-Apr	(72/80)	(46/55)	(8/21)	(13/21)
>10	(7/80)	(4/55)	(11/21)	(8/21)
Gleason score				
6-7	(80/80)	(55/55)	(12/33)	(10/21)
8-10	(0/80)	(0/55)	(21/33)	(11/21)
Stage				
T1c	(77/80)	(54/55)	(28/33)	(17/21)
T2a	(3/80)	(0/55)	(2/33)	(1/21)
T3b, T3c	(0/80)	(1/55)	(3/33)	(3/21)
Volumes (cc)	39.5±12.1	41.6±15.1	30.7±11.3	32.8±14.1
Total Seeds	83±14	87±18	73±15	81±19
Total Needles	24±3	25±4	21±4	23±5

It is particularly helpful in detecting tumors in the peripheral region of the prostate gland. Additionally, DCEI uses a gadolinium contrast agent with a T1W image sequence to visualize abnormal blood flow within the tumor due to angiogenesis, which is seen in Figure 1B. An optional fourth imaging sequence is magnetic resonance spectroscopic imaging (MRSI), which is used to determine the biochemical concentration of biomarkers associated with cancer. Most cancers have an elevated ratio of choline plus creatine over citrate than normal tissue, which can help distinguish between prostate cancer and a benign growth (8,15).

Out of the 189 patients, 113 (59.8%) patients had at least one DIL, identified with mpMRI, which was dose escalated to 150% of the prescription. Ten percent were PIRADS 3, 47% were PIRADS 4 and 43% were PIRADS 5. 72.5% of the DILs were found to be in the peripheral zone of the prostate. There were 12 patients in group I, 81 patients in group IIA, 15 patients in group IIB, and 5 patients in group III. 80 of the patients received brachytherapy as a monotherapy and 33 received it as a boost after EBRT. Of the 113 patients, 29 (25.7%) received ADT. The other 76 (40.2%) patients did not have an identified DIL. This patient group comprised of 8 patients in group I, 57 patients in group IIA, 9 patients in group IIB, and 2 patients in group III. 55 of the patients received LDR brachytherapy as a monotherapy and 21 received it as a boost after EBRT. Of the 76 no DIL patients, 20 (26.3%) received ADT. All patients were treated with either ^{125}I or ^{103}Pd to a prescription dose of 145Gy (0.51U / 0.40mCi per seed) or 125Gy (2.33U / 1.8mCi per seed), respectively for LDR monotherapy or as a LDR boost of 110Gy (0.46U/0.36mCi per seed) or 100Gy (1.81U/1.40mCi per seed) following 45Gy of EBRT.

Figure (1) An example of a DIL characterized as a PIRADS 4 for a patient with a Gleason score of 6,PSA of 9.9ng/ml, and volume of 1.42cc on the mpMRI; T2W (A) and DCEI (B) sequences.



Our institutional choice for isotope favors ^{103}Pd especially in boost and high risk cases. ^{125}I is used for either large glands, typically over 50cc's to limit the total number of needles placed, or for use in some low risk patients opting for treatment. More recently the use of ^{125}I has been expanded in intermediate risk if prescribed as monotherapy as well to add more robust coverage beyond the capsule to help cover for possible extracapsular disease at the discretion of the prescribing brachytherapist;

in particular for patients with dominate PIRADS 4 Gleason 7 (4+3) who decline external beam boost.

With the results from RTOG 0232 showing similar outcomes without the use of external beam radiation, monotherapy use in this subset has grown to well over 50% compared to our historical 50/50 split in this category (20). Typical stratification factors for boost use have been PSA $\geq$15 ng/mL, Gleason score $\geq$ 8 , or bulky intermediate risk disease with $\geq$ 50% positive cores, or findings on MRI planning suggestive of risk for extracapsular disease. In this study, 80 (70.8%) patients with a DIL received brachytherapy as a monotherapy, with 56 receiving ^{125}I and 24 receiving ^{103}Pd, and 55 (72.4%) patients without a DIL received brachytherapy as a boost, with 39 receiving ^{125}I and 16 receiving ^{103}Pd. Of the patients receiving ^{125}I, there were 10 patients in group I, 85 patients in group IIA, 6 patients in group IIB, and 2 patients in group III, and of the patients receiving ^{103}Pd, there were 10 patients in group I, 53 patients in group IIA, 18 patients in group IIB, and 5 patients in group III. The patients who received ^{125}I were given ADT significantly less than the patients who received ^{103}Pd, 12.6% versus 41.8%, respectively.

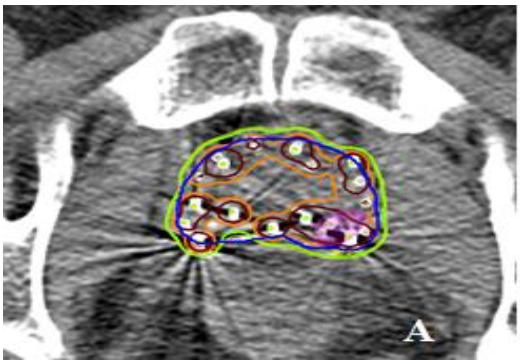
A couple of weeks before the implant, a pre-operative was created in MIM Symphony (MIMvista Corporation, Cleveland, OH) using the T2W MRI. The prescription dose covered at least 99% of the prostate volume, the prostate $V_{150\%}$ was kept ≤60% of the prescription, and the prostate V_{200}% was ≤25% of prescription. At least 95% of the urethra was targeted to receive the prescription dose with ≤5% of the contour receiving 150% of the prescription. The rectum D_{2cc} was targeted to receive less than 95% and D_{1cc}<100% of the prescription dose. For the patients with a DIL, the DIL volume was dose escalated to 150% of the prescription with at least 95% DIL coverage. Irrespective of the location (peripheral or central) of DIL, it was covered with 150% of prescribed dose. As a result, the prostate V_{150} is shifted from the standard modified peripheral load to accommodate coverage of the diagnostic molecular target volumes and pathologically known disease locations while trying to maintain the prostate V_{150} and V_{200} in our institutional standards. Escalation of the prostate V_{150} and V_{200} to 75% and 35% of prescribed dose, or urethral dose exceeding a V_{150} of > 5% of the urethra are accepted as needed to provide coverage, but strived to be avoided. Small glands or the use of ^{103}Pd may often require relaxing these initial baseline goals for 99% 40-60% and <25% for prostate V_{100}, V_{150}, and $V_{200,}$ respectively. Consequently, some portions of the DIL does then often get ≥200% of the Rx dose. We use the post implant V_{150} coverage as a measure of implant quality for dose escalation to the DIL.

On the day of the seed implant, the patient was positioned on the OR table and put under general anesthesia before placing the transrectal ultrasound (TRUS) probe in the rectum for acquiring images for intra-operative dosimetric planning or plan modification. The captured TRUS images were co-registered to the MRI-based preplan. The plan was modified based on the ultrasound image, when required. The individual seeds were then implanted using Mick applicator (Mick Radio-Nuclear Instruments, Inc., NY) and real-time dosimetry was updated based on needle and seed position during the implantation. After the procedure was completed, the patient was transported to the radiation oncology department for a post-operative CT scan and post-operative dosimetric evaluation (Figure

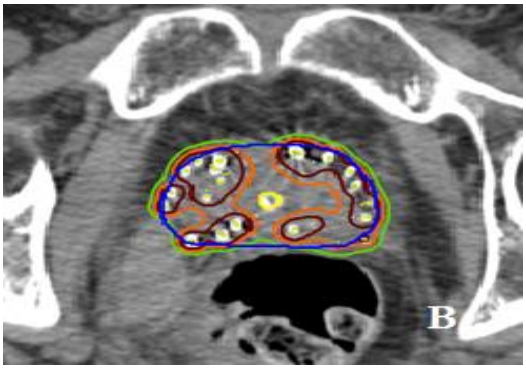
2). The foley catheter remained in place for the CT scan to aid in contouring of the urethra and determining the dose. The CT was fused to the MRI in order to transfer the DIL contour to the planning CT and all of the implanted seeds were identified for dosimetric computation.

Figure (2) (A) Post-operative plan for a patient with a DIL (pink). (B) Post-operative plan for a patient without a DIL. Prostate is outlined in blue, the green isodose line corresponds to 100%, orange is 150%, and brown is 200%.

(A) Post-operative plan for a patient with a DIL(pink).



(B) Post-operative plan for a patient without a DIL.



Various dosimetric parameters from the post-operative plan, including prostate D_{90}, $V_{100\%}$, DIL $V_{150\%}$, rectum D_{2cc}, and urethra $D_{10\%}$ were evaluated. The dosimetric parameters were compared for patients with a DIL versus patients without a DIL, implants with ^{125}I versus ^{103}Pd, and the dosimetric coverage from our previous study by Ellis et al (7). The acute toxicity data collected from patients' one to three month follow-up (FU) visit included frequency, urgency, nocturia, and dysuria. The grade of the toxicity was determined by the concerned radiation oncologist upon discussion with the patient during FU visit, as per RTOG's Cooperative Group Common Toxicity Criteria. The incidence of toxicities was also evaluated between the DIL versus no DIL patients and the ^{125}I versus ^{103}Pd implants. P-value <0.05 based on a paired t-test was considered statistically significant.

Results

The post-operative dosimetry for the 113 patients with a DIL and the 76 patients without a DIL is shown in (Table 2). This was generally completed on day after the procedure, and only repeated if significant edema was detected that reduced anticipated coverage, thus the numbers listed in the following tables would be expected to possibly be higher if routinely completed at 2 to 4 weeks postoperatively. The DIL patients' average urethra $D_{10\%}$ was 134.7% ± 25.2% of the prescription while the patients without a DIL had an average urethra $D_{10\%}$ of 144.4% ± 28.4%. The volume of the prostate in DIL patient group was slightly smaller (36.9cc *vs*. 39.1cc). However, the required number of seeds and number of needles for per unit volume of the prostate were very similar for the patients with a DIL and without a DIL (Table 2).

The DILs had an average volume of 1.78±1.61cc, median of 1.3cc, and three of the patients had two DILs. A majority of the DILs was in the peripheral zone of the prostate. The DILs located in the peripheral zone were

easier to cover with higher dose as compared to those in the central zone; size of the DIL did not affect the dosimetric coverage. For all the DILs, over 80% of the volumes were covered with over 150% of the prescribed dose (Table 3). To escalate the dose to DIL, the concentration of seeds and needles in and around the DIL volume was higher.

Table (2) Post-operative dosimetric parameter for patients with and without a DIL treated with ^{125}I versus ^{103}Pd isotope.

Parameter	^{125}I			^{103}Pd		
	DIL(N=62)	No DIL(N=41)		DIL(N=51)	No DIL(N=35)	
	Mean ±SD	Mean ±SD	p-value	Mean ±SD	Mean ±SD	p-value
Prostate Volume (cc)	41.5 ± 12.7	45.2 ± 16.5	0.235	31.4 ± 9.7	32.1 ± 9.8	0.743
Prostate $D_{90\%}$ (% Rx)	108.8 ± 7.8	108.2 ± 8.5	0.728	106.8 ± 9.6	109.6 ± 8.7	0.159
Prostate $V_{100\%}$ (% vol)	94.0 ± 4.0	93.9 ± 4.1	0.907	92.7 ± 4.5	93.9 ± 3.5	0.166
Prostate $V_{150\%}$ (% vol)	51.2 ± 10.8	50.0 ± 11.0	0.574	59.2 ± 8.8	60.2 ± 9.3	0.601
Prostate $V_{200\%}$ (% vol)	24.3 ± 7.5	24.2 ± 12.1	0.967	34.3 ± 7.4	34.8 ± 7.7	0.731
Rectum D_{2cc} (% Rx)	51.5 ± 15.2	50.9 ± 15.4	0.842	36.3 ± 21.5	39.7 ± 17.9	0.424
Urethra $V_{100\%}$ (% Rx)	84.5 ± 15.0	78.9 ± 24.1	0.184	66.6 ± 28.8	75.4 ± 20.1	0.099
Urethra $V_{150\%}$ (% vol)	7.5 ± 15.9	8.3 ± 15.9	0.809	9.5 ± 18.3	11.8 ± 13.1	0.498
Urethra $D_{10\%}$ (% Rx)	133.9 ± 17.7	139.3 ± 27.1	0.268	135.5 ± 32.2	150.3 ± 29.1	0.029*

Analyzing all patients treated with ^{125}I found no significant dosimetric differences between DIL and no DIL patient groups. For the patients treated with ^{103}Pd, the only significant difference between the DIL and no DIL patients was the urethra $D_{10\%}$, which averaged 135.5% ± 32.2% and 150.3% ± 29.1% (Table 2), respectively.

Table 2 presented the post-operative dosimetric parameters for the patients with a DIL treated with ^{125}I versus ^{103}Pd. As expected, the patients treated with ^{125}I had lower prostate $V_{150\%}$ and $V_{200\%}$ than ^{103}Pd patients, due to the difference of inherent dosimetric characteristics of these two isotopes. Similar trend has also been observed by other groups including Niehaus et al (19). Although within the recommended limit (i.e. 100% of the prescription dose), the rectum D_{2cc} for ^{125}I treatments was found to be higher than those for ^{103}Pd. The urethra $V_{100\%}$ was also better for ^{125}I at 84.5% ±

18.8% versus 66.6% ± 28.8% for ^{103}Pd. Similar outcomes were found for ^{125}I versus ^{103}Pd for the no DIL patients. The prostate $V_{150\%}$ and $V_{200\%}$ were higher for ^{103}Pd, and the rectum D_{2cc} was still considerably higher for ^{125}I versus ^{103}Pd.

The pre-operative and post-operative coverage of the DIL with both isotopes (^{125}I and ^{103}Pd) were presented in Table 3. The coverage of V_{100} of DIL in both pre-operative and post-operative plans were larger than 99%. The coverage of V_{150} of DIL in post-operative was slightly better for ^{125}I compared to the one for ^{103}Pd ($p>0.05$). Although significant difference in V_{200} of DIL was found between two isotopes for pre-operative plan, there was no difference in post-operative dosimetry.

Table (3) Pre-Operative and Post-operative dosimetric coverage of DIL volume with ^{125}I and ^{103}Pd.

Parameter	Pre-Operative			Post-Operative		
	^{125}I	^{103}Pd	p-value	^{125}I	^{103}Pd	p-value
DIL $V_{100\%}$ (% vol)	99.8±2.9	99.9±0.2	0.83	99.8±0.6	99.2±2.5	0.89
DIL $V_{150\%}$ (% vol)	96.0±10.6	97.2±4.4	0.88	84.5±18.7	82.1±16.5	0.82
DIL $V_{200\%}$ (% vol)	63.8±17.3	72.1±13.5	0.05	51.0±24.1	51.8±23.2	0.13

Table (4) Reported urinary and rectal toxicity cases for patients treated with ^{125}I and ^{103}Pd.

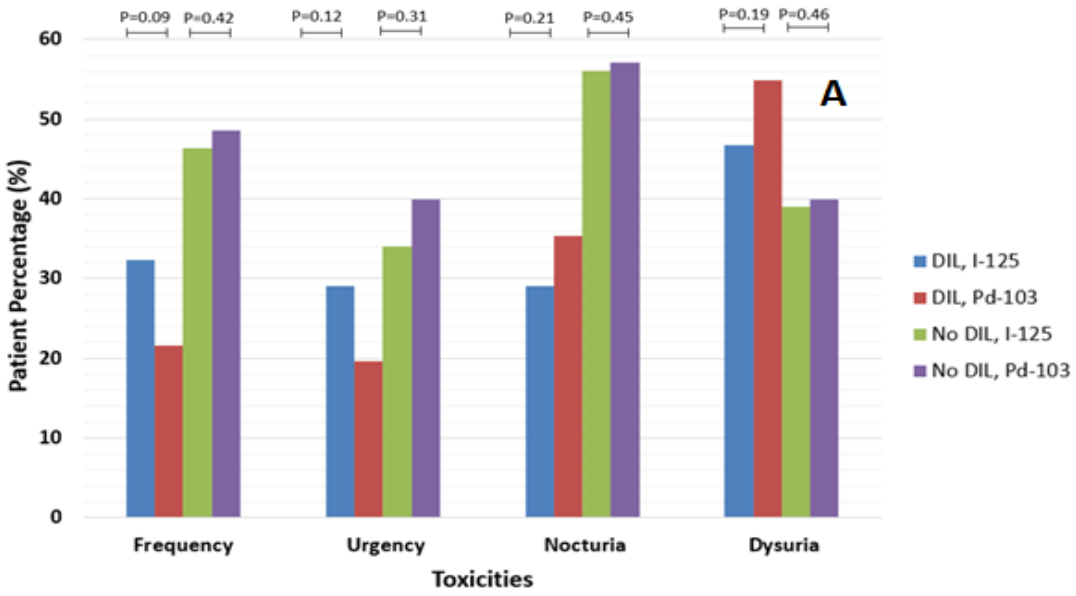
Sources Patients Evaluated	DIL			No DIL		
	I-125	Pd-103		I-125	Pd-103	
	62	51	p-value	41	35	p-value
Frequency	20	11	0.10	19	17	0.42
Urgency	18	10	0.13	14	14	0.3
Nocturia	18	18	0.26	23	20	0.46
Dysuria	29	28	0.20	16	14	0.47
Incontinence	4	3	0.45	3	2	0.39
Hematuria	10	7	0.36	3	2	0.29
Blood in Ejaculate	1	3	0.11	1	2	0.24
Weak Stream	1	0	0.14	3	2	0.18
Loose Stool	0	1	0.18	1	0	0.39
Diarrhea	1	1	0.44	0	1	0.14
Rectal Bleeding	1	0	0.45	0	0	0.19
No Toxicity Reported	14	12	0.27	3	2	0.41

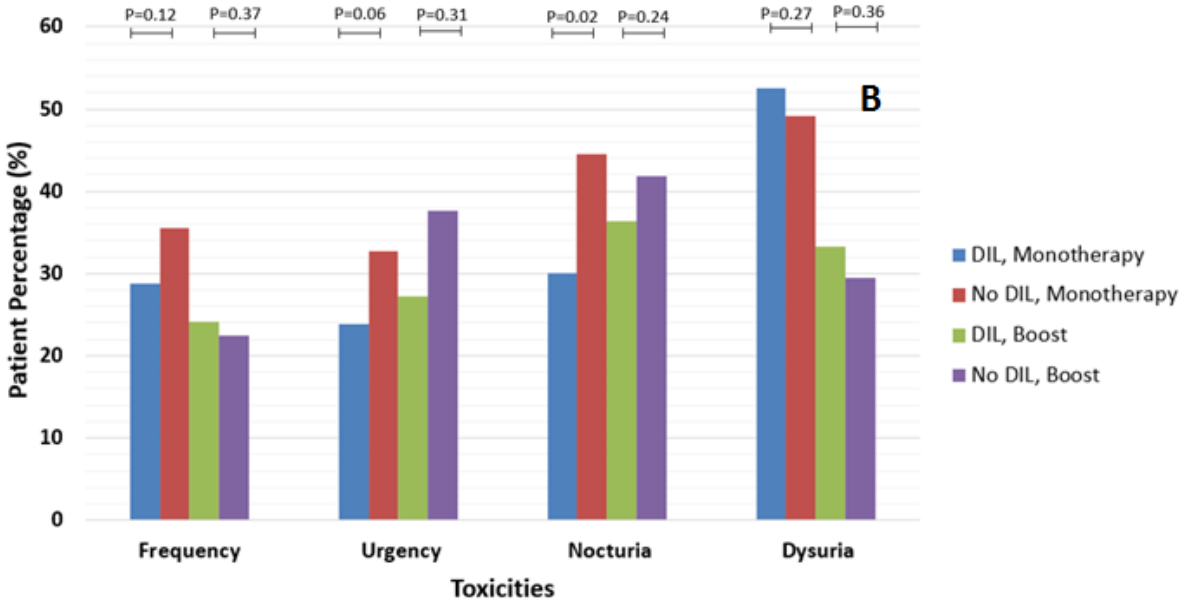
Table 4 presented the incidence of various urinary and rectal acute toxicities for the DIL and no DIL patients. The DIL patients had less occurrence of frequency (27.4% *vs*. 47.4%), urgency (24.7% *vs*. 38.6%), nocturia (31.8% *vs*. 56.6%), incontinence (6.2% *vs*. 6.6%), blood in ejaculation (3.5% *vs*. 3.9%), and weak stream (0.9% *vs*. 6.6%). In addition,

DIL patients had higher percentage of no toxicities reported (23.0% *vs*. 6.6%). There was only one case of rectal bleeding, three cases of persistent diarrhea, and two cases of post procedure catheter use. These patients had no significant difference for any of the analyzed dosimetric parameters.

Figure 3A illustrated the four most common toxicities for the DIL and no DIL patients treated with either ^{125}I or ^{103}Pd. Compared to the no DIL group, the DIL group demonstrated less frequency, urgency, and nocturia. Among patients treated with ^{103}Pd, the DIL group were found to have significantly less urination frequency ($p < 0.05$) as compared to the no DIL group (Figure 3A). As shown in Figure 3B, patients had DIL treated with PSI as monotherapy demonstrated a significant increase in nocturia rate ($p < 0.05$).

Figure (3) (A) Incidence of urinary toxicities for patients with and without DIL treated with ^{125}I and ^{103}Pd. (B) Incidence of urinary toxicities for patients with and without DIL treated with PSI as monotherapy and boost.





Discussion

Dose escalation of the mpMRI identified DIL has similar post-implant dosimetry outcomes compared to no DIL patients treated with LDR boost and LDR monotherapy using ^{125}I and ^{103}Pd isotopes. This agreed with the results reported by Gaudet et al. using ^{125}I (16). In addition, our study demonstrated significant difference in urethra $D_{10\%}$ of patients treated with ^{103}Pd and lower urinary toxicity in DIL patients. There is no significant difference between the prostate $V_{150\%}$ for patients with and without a DIL. The 150% prescription coverage of the DIL was due to lining up the 150% with the DIL rather than adding more 150% prescription to cover the DIL. Especially with a majority of the DILs on the periphery, where traditionally a majority of the seeds would be placed, obtaining the desired coverage does not require a drastic change in dosimetry compared to patients without a DIL. Whether or not there is a clinical benefit to dose escalating the DIL is still unknown, but covering it does not appear to significantly increase acute toxicities. These patients will continue to be followed to analyze long term survival and toxicities.

It is to be noted that not all mpMRI detected DILs lesions are in fact cancerous. Anderson et al. analyzed the correlation of mpMRI identified DILs with biopsy proven prostate cancer (21). They retrospectively analyzed 57 patients who had received an mpMRI and targeted biopsy. Thirty patients were found to have PIRADS 1 to PIRADS 3 lesions and the other 27 patients had PIRADS 4 or PIRADS 5 lesions on imaging. After analyzing the biopsy results, each patient fell into one of three categories: match (MRI lesion and positive biopsy correlate), miss (MRI lesion and positive biopsy are incompatible), and partial miss (MRI lesion and positive biopsy correlate in one

hemigland, but not the other side). For the PIRADS 1 to PIRADS 3 patients, 33% of the cases matched, 10% missed, and 57% were a partial miss compared to 67% matched, 4% missed, and 30% partial miss for PIRADS 4 and PIRADS 5 lesions. This results in an MRI specificity and sensitivity of 0.525 and 0.700 for PIRADS 1 to PIRADS 3 lesions and 0.825 and 0.786, respectively for PIRADS 4 and PIRADS 5 lesions. The PIRADS 4 and PIRADS 5 mpMRI identified lesions had a higher correlation with a positive biopsy (19). The previous study published by Ellis et al. had 239 patients with T1c to T3b prostate cancer with an average Gleason score of 6 and PSA of 9ng/ml (7). The only difference in prescriptions between the previous study and current is the ^{125}I monotherapy prescription dose was 144Gy, while current study used 145Gy. To identify and delineate of the DIL, Ellis et al. used SPECT/CT with capromab pendetide, instead of mpMRI that is used in the current study. In both studies, all the PSI were performed by the same physician group in the same clinic. The coverage to the prostate and DIL obtained for the current study is significantly better than the previous study, with the DIL $V_{150\%}$ increased from 72.2 ± 24.4% to 83.4 ± 17.8%, the prostate $V_{100\%}$ increasing from 93.4 ± 4.3% to 88.1 ± 8.2%, and prostate $D_{90\%}$ increased from 107.9 ± 8.7% to 100.3 ± 16.1% (p-value<0.001). This shows improvement over time using the current MRI preplanned technique over our previous method with ultrasound and cognitive fusion for the functional study. By switching to MRI based planning and fusing these volumes to the live ultrasound at the time of intraoperative planning, as well as using real-time planning to account for needle deviation and seed "slippage" or motion, we have shown an improvement in our post-operative dosimetric planning target coverage. Relying on the DIL $V_{200\%}$ post-operative coverage may be too highly influenced by the sharp penumbra and steep dose fall off at such a high dose. This is similar to the fact that prostate $D_{90\%}$ is superior to $V_{100\%}$ in reporting implant quality.

The urethra $D_{10\%}$ of the DIL group treated with ^{103}Pd was significantly lower than those of the no DIL group (Table 2). The location of most of the DILs was in the periphery towards the lateral posterior portion of the prostate. With the dose escalation occurring away from the urethra, it is expected that the urethra $D_{10\%}$ would not be higher for the DIL compared to the no DIL patients. Stratifying by the isotope resulted in no difference in the urethra $D_{10\%}$ for ^{125}I, but a significant difference observed for ^{103}Pd between the DIL and no DIL patients. Compared to the dose distribution of ^{125}I, ^{103}Pd has a steeper dose falloff, which results in having to place seeds closer together to obtain the desired minimum coverage, but by doing so increased the high dose volume as shown in Table 2. Having the DIL away from the urethra with an increased number of seeds compared to a more homogeneous seed distribution used to cover the prostate without a DIL seems to be the reason for the decreased urethra $D_{10\%}$. This may also explain the significantly less frequency the ^{103}Pd DIL patients reported compared to the ^{103}Pd no DIL patients. The increased rectum D_{2cc} and urethra V_{100} for patients treated with ^{125}I are attributed to the less steep dose gradient.

Prostate cancer can be treated with either LDR or HDR brachytherapy. For decades LDR brachytherapy has been the standard of care for treating prostate cancer.

However, with the assistance of real-time ultrasound based planning, HDR has started to become widely accepted. Tissanverasinghe et al. compared dose escalation to DILs using LDR and HDR brachytherapy in a Phase II randomized trial of 60 patients (17). They included 31 patients who received LDR brachytherapy with the DIL dose escalated to 150% and 29 patients received HDR brachytherapy with the DIL dose escalated to 125%. For patients with peripheral DILs (74% of lesions), the ratios of DIL $D_{90\%}$ and desired peripheral dose (i.e. 150% of prescription dose for LDR and 125% of prescription dose for HDR) were comparable for LDR and HDR. However, the ratios for the central (6% of lesions) and anterior (20% of lesions) DILs were significantly higher for HDR brachytherapy. Therefore, they suggest that HDR brachytherapy dose escalation may be better when the DIL is closer to critical organs.

Comparing to patients who received a boost after EBRT patients, those who received PSI as a monotherapy demonstrated similar incidence of toxicities except patients treated with monotherapy experienced a higher rate of dysuria. The reason for this difference is still not very clear. One contributing factor for the boost patients reporting lower rates of dysuria could be that the dysuria was reported during the external beam treatment and they had received certain complication management. By the time the PSI was completed and acute toxicities were being surveyed, the dysuria was already under control or not bothering.

In general, the DIL group exhibited lower acute toxicity. This may be due to the lower urethral dose in DIL group (especially, V_{150} and D_{10} for both isotopes), which warrants further long-term study. Especially, patients who had DIL treated with ^{103}Pd were found to have less urination frequency, which might be related to the reduced dose to urethra (V_{100}, V_{150} and D_{10} of urethra; see Table 2). However, all the other toxicities were not found to be statistically significant. The ability to dose escalation to DIL may result in an improvement in disease free survival and overall survival. But for prostate this will require very long term follow-up, which is beyond the scope of this study. One weakness of this study is small sample size and short patient follow-up period for late toxicity analysis. We will incorporate more patients in the future study as well as long-term tumor control data.

Conclusions

The current study demonstrated the ability to dose escalated to lesions without overdosing normal structures and causing increased acute toxicity using the ^{103}Pd isotope, which has higher BED and sharper dose fall-off than the ^{125}I isotope. When using ^{103}Pd isotope, patients had reported less urinary toxicities as compared to ^{125}I isotope.

Conflict Of Interest

Authors have no conflict of interest to report.

References

1. Siegel RL, Miller KD, Jemal A (2019) Cancer statistics. CA Cancer J Clin; 69(1): 7-34.
2. Sylvester JE, Grimm PD, Wong J, et al. (2011) Fifteen-year biochemical relapse-free survival, cause specific survival, and overall survival following ^{125}I prostate

brachytherapy in clinically localized prostate cancer: Seattle experience. Int J Rad Oncol Biol Phys; 81(2): 376-381.

3. Kittel JA, Reddy CA, Smith KL, et al. (2015) Long-term efficacy and toxicity of low-dose-rate ^{125}I prostate brachytherapy monotherapy in low, intermediate, and high risk prostate cancer. Int J Rad Oncol Biol Phys; 92(4): 884-893.
4. Davis BJ, Horwitz EM, Lee WR, et al. (2012) American Brachytherapy Society consensus guidelines for transrectal ultrasound-guided permanent prostate brachytherapy. Brachytherapy; 11(1): 6-19.
5. Routman DM, Funk RK, Stish BJ, et al. (2019) Permanent prostate brachytherapy monotherapy with I-125for low- and intermediate-risk prostate cancer: Outcomes in 974 patients. Brachytherapy; 18(1): 1-7.
6. Glaser SM, Dohopolski MJ, Balasubramani GK, et al. (2017) Brachytherapy boost for prostate cancer: Trends in care and survival outcomes.
   Brachytherapy; 16(2): 330-341.
7. Ellis RJ, Zhou H, Kim E, et al. (2007) Biochemical disease-free survival rates following definitive low-dose-rate prostate brachytherapy with dose escalation to biological target volumes identified with SPECT/CT capromab pendetide. Brachytherapy; 6(1): 16-25.
8. Nicolae AM, Venugopal N, Ravi A (2016) Trends in targeted prostate brachytherapy: from multiparametric MRI to nanomolecules radiosensitizers. Cancer Nanotechnol; 7(6): 1-17.
9. Gomez-Iturriaga A, Casquero F, Urresola A, et al. (2016) Dose escalation to dominant intraprostatic lesions with MRI-transrectal ultrasound fusion High-Dose-Rate prostate brachytherapy. Prospective phase II trial. Radiother Oncolo; 119(1): 9 1-96.
10. Hayes HJ, Ollendorf DA, Pearson SD, et al. (2010) Active surveillance compared with initial treatment for med with low-risk prostate cancer: A decision analysis JAMA; 304(21): 2373-2380.
11. Steuten LMG, Revel VP. Comparative cost/QALY of guideline-recommended prostate cancer treatments: a UK cost perspective. 2nd ESTRO Forum. PD-0371:S145.2013.
12. Hoskin PJ, Colombo A, Henry A, et al. (2013) GEC/ESTRO recommendations on high dose rate afterloading brachytherapy for localized prostate cancer: An update. Radiol Oncol; 107(3): 325-332.
13. Pullini S, Signor MA, Pancot M, et al. (2016) Impact of multiparametric magnetic resonance imaging on risk group assessment of patients with prostate cancer addressed to external beam radiation therapy. Eur J Radiol; 85(4): 764-770.
14. Ghai S, Haider M (2015) Multiparametric-MRI in diagnosis of prostate cancer. Indian J Urol; 31(3): 194-201.
15. Panebianco V, Barchetti F, Sciarra A, et al. (2013) Multiparametric magnetic resonance imaging vs. standard care in men being evaluated for prostate cancer: a randomized study. Urol Oncol; 33(1):e1-17.
16. Weinreb JC, Barentsz JO, Choyke PL et al. (2016) PIRADS prostate imaging – reporting and data system: 2015, version 2. Eur Urol; 69(1): 16-40.

17. Gaudet M, Vigneault E, Aubin S, et al. (2010) Dose escalation to the dominant intraprostatic lesion defined by sextant biopsy in permanent prostate I-125 implant: A prospective comparative toxicity analysis. Int J Radiat Oncol Biol Phys; 77(1): 153-159
18. Tissaverasinghe S, Crook J, Bachand F, et al. (2019) Dose to the dominant intraprostatic lesion using HDR vs. LDR monotherapy: A phase II randomized trial. Brachytherapy; 18(3): 299-305.
19. Prestidge BR, Winter K, Sanda MG. et al. (2016) Initial Report of NRG Oncology/RTOG0232: A phase III study comparing combined external beam radiation and transperoneal interstitial permanent brachytherapy with brachytherapy alone for select patients with intermediate risk prostatic carcinoma. Int J Rad Oncol Biol Phys; 96(2): S4.
20. Niehaus A, Merrick GS, Butler WM, et al. (2006) The influence of isotope and prostate volume on urinary morbidity after prostate brachytherapy. Int J Rad Oncol Biol Phys; 64(1): 136-143.
21. Anderson ES, Margolis DJA, Mesko S, et al. (2014) Multiparametric MRI identifies and stratifies prostate cancer lesions: Implications for targeting intraprostatic targets. Brachytherapy; 13(3):292-298.