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Clinical Investigation

A Proof-of-Concept Study on the Use of Prostate Artery Embolization Before Definitive Radiation Therapy in Prostate Cancer

Jeffrey Peacock, MD,[a,1] Dhiraj Sikaria, MD,[b,1] Laura Maun-Garcia, AA,[a] Khosrow Javedan, PhD,[a] Kosj Yamoah, MD, PhD,[a] and Nainesh Parikh, MD[c,*]

[a]*Radiation Oncology, Moffitt Cancer Center, Tampa, Florida;* [b]*Morsani College of Medicine, Tampa, Florida; and* [c]*Interventional Radiology, Moffitt Cancer Center, Tampa, Florida*

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Abstract

Purpose: Prostatic artery embolization (PAE) is an effective therapy for alleviating lower urinary tract symptoms (LUTS) in patients with benign prostatic hyperplasia; however, is not well studied in patients with concurrent prostate cancer (PCa). We demonstrate a proof of concept for PAE before definitive radiation therapy (RT) in patients with PCa.

Methods and Materials: From December 2017 to July 2019, 9 patients with PCa underwent PAE for the indication of LUTS from benign prostatic hyperplasia with concurrent PCa. Five received radiation and all follow-ups at our institution and were therefore included in the analysis. Median follow-up was 18 months from the time of PAE. Side effects during radiation were quantified using the Common Terminology Criteria for Adverse Events scoring system. Pre- and post-PAE plans were compared in the 5 patients by performing an isovolumetric expansion of the post-PAE plan (treated plan) equivalent to the measured volume reduction after PAE. Patient 1 (PT-01) and PT-02 had prostate RT alone whereas PT-03, PT-04, and PT-05 had prostate with elective nodal coverage RT. Mean doses to organs at risk were compared between the 2 plans.

Results: The mean International Prostate Symptom Score reduction after PAE was 13.8 (5.0-30.0; $P = .02$). The mean prostatic volume reduction after PAE was 23.1% (7.2%-47.7%). There were no Common Terminology Criteria for Adverse Events grade 3 (severe) or higher during radiation. Post-PAE plans in PT-01 and PT-02 had on average 23.2%, 39.8%, and 22.9% decrease in mean dose across the bladder, rectum, and penile bulb, respectively, compared with the pre-PAE plans. There were no appreciable differences in dosimetry in PT03, PT-04, and PT-05 who had nodal coverage. There was no biochemical failure in any of the patients.

Conclusions: We demonstrate a proof of concept that PAE is a clinically significant adjunctive therapy for alleviating LUTS and achieving significant volume reduction before RT, resulting in decreased radiation-related toxicity from RT for PCa.

Introduction

Lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH) are a significant cause of morbidity and health care expenditure. The gold standard for moderate-severe LUTS from BPH is transurethral resection of the prostate (TURP). However, TURP is

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* Corresponding author: Nainesh Parikh, MD; E-mail: Nainesh.Parikh@moffitt.org

[1] J.P. and D.S. contributed equally to this study and manuscript

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associated with several postoperative complications, including sphincter injury, infection, retrograde ejaculation, bladder neck stenosis, and erectile dysfunction.[1,2]

Prostatic artery embolization (PAE) has recently been well-studied as a minimally invasive alternative to TURP, particularly for patients with "massive" glands (ie, glands $>$ 80 gm).[3-5] PAE has been shown to be associated with shorter hospital stays and lower cost when compared directly to TURP, with equivalent clinical outcomes.[6-9] Additionally, PAE has been associated with significant prostate volume reduction of up to 40% with decreases in prostate-specific antigen of up to 50%.[6] Thus, PAE is a safe and effective treatment alternative for patients with moderate-severe LUTS from BPH,[10] and may in fact be preferred.

The benefit of PAE before definitive radiation therapy (RT) in men with localized prostate cancer has not been published until this analysis. Radiation is considered standard of care for prostate cancer, but can result in exacerbation of LUTS during treatment, with acute and chronic toxicity ranging from 10% to 25%.[11] We investigated to determine if PAE may decrease symptoms before radiation and to determine the effect of post-PAE volume reduction on reduction of radiation dose to organs at risk (OAR). Finally, we suggest the concept that PAE before RT may lead to decreased acute toxicity during radiation.

Methods and Materials

Patient characteristics

This is an institutional review board—approved retrospective study that evaluated 9 patients with the diagnosis of prostate cancer who received PAE for the indication of moderate-severe LUTS from BPH in the setting of prostate cancer from December 2017 to July 2019. Four patients were excluded because they did not have their entire RT treatment session and entire 6-month clinical follow-up at our institution, leaving 5 patients for analysis. Median age was 71 years (48-76 years), and all patients were considered to have high-risk prostate cancer before PAE. Median follow-up was 18 months from the time of PAE. The mean pre-PAE prostate volume size was 95.8 cc (33.6-231.0 cc). The mean pre-PAE International Prostate Symptom Score (IPSS) score was 17.4 (7.0-35.0). Patient (PT)-01 and PT-02 received prostate radiation alone. PT-03, PT-04, and PT-05 had radiation to the pelvis for elective nodal coverage in addition to the prostate. Radiation followed the PAE procedure with a median time of approximately 4.5 months (2.0-14.5 months).

Prostate artery embolization procedure

PAE was performed by a single interventional radiologist. Femoral or radial access was obtained. Each prostatic artery (see Fig 1) was accessed with a 2.4 French microcatheter. Embolization was performed using 300 to 500 micron embospheres (Merritt Medical, Inc, Salt Lake City, UT). All patients were admitted for overnight observation postprocedure and were given a standard 7-day postprocedural cocktail of prophylactic medications.

Assessment of treatment related effects

The Society of Interventional Radiology grading scale was used to assess complications from PAE. IPSS score was used to assess clinical response to PAE at 3 months after the procedure and Common Terminology Criteria for Adverse Events was used to assess gastrointestinal/genitourinary (GU) toxicity during radiation treatment. Changes in IPSS were compared using a two-tailed Student t test.

Radiation treatment planning

Pre-PAE prostate volumes were contoured on T1/T2 magnetic resonance image sequences that were acquired before PAE by a radiation oncologist on the Pinnacle treatment planning software (Philips Inc, Amsterdam, Netherlands). Post-PAE prostate volumes were determined at the time of computed tomography simulation for RT.

To identify the dosimetric differences between the pre- and post-PAE volumes, the 5 patients had plans created using the pre-PAE prostate volumes. The pre-PAE planning target volume (PTV) was simulated by creating an isovolumetric expansion equal to the change in prostate volume before PAE and at the time of computed tomography simulation (see Fig 2). Five pre-PAE plans were created by a dosimetrist specializing in prostate cancer radiation treatment plans blinded to the intent of the research. The pre-PAE PTVs were compared with the treatment plans (post-PAE PTV) that the patient received during treatment. In the event of nodal volume coverage, only the prostate PTV contours were expanded and elective nodal volumes were the same for the pre- and post-PTV plans. All the plans used intensity modulated RT. The details of the radiation can be found in Table 1. The organs at risk were assessed by mean dose to the rectum, bladder, and penile bulb.

Results

Patient characteristics are described in Table 1. The average IPSS score pre-PAE was 17.4 compared with the post-PAE score of 3.6 ($P = .02$). The average volume reduction from the PAE was 23.1% (7.2%-47.7%).

The indication for PAE was for symptomatic improvement of LUTS before definitive RT in all cases. There was no Society of Interventional Radiology grade C

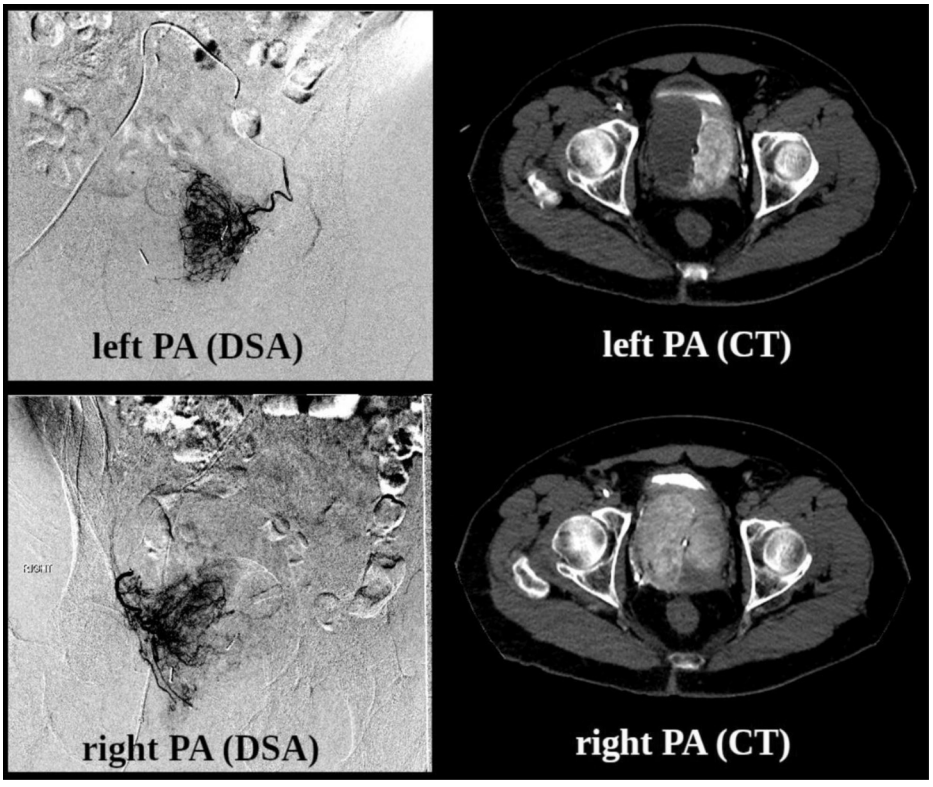

Figure 1 Super selective digital subtraction angiography (first column) and computed tomography (CT) angiographic (second column) acquisitions of the left (first row) and right (second row) prostatic artery.

(requiring therapy or hospitalization >48 hours) or higher side effects of the procedure. There were no Common Terminology Criteria for Adverse Events grade 3 (severe or medically significant) or higher side effects during radiation treatment. No patients had biochemical failure, with a median follow-up of 18 months.

Dosimetric differences between pre- and post-PAE plans were compared in PT-01 and PT-02 (Fig 3). These patients had prostate RT alone. Raw values and percent difference in estimated dosage for the 2 patients are given in Table 2. The PTV covered by the 100% prescription isodose line in PT-01 and PT-02 was slightly higher in the post-PAE plan compared with the pre- PAE plan (98.5% vs 94.6% and 99.5% vs 98.2%, respectively). Despite maintaining adequate coverage, there was significant reduction to dose to organs at risk in the post-PAE plans compared to the pre-PAE plans. Post-PAE plans in PT-01 and PT-02 had on average 23.2%, 39.8%, and 22.9% decrease in mean dose across the bladder, rectum, and penile bulb, respectively, compared with the pre-PAE plans. There were no appreciable dosimetric differences in PT-03, PT-04, and PT-05, who had elective nodal coverage for their high-risk prostate cancer.

Discussion

This study suggests the proof of concept that PAE in men who have LUTS from BPH before definitive RT for

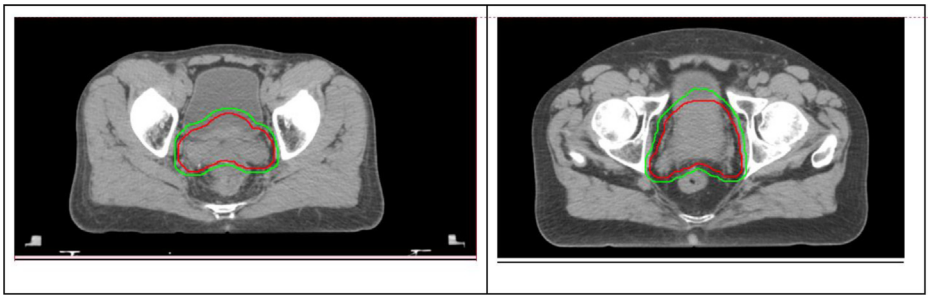

Figure 2 Patient (PT)-01 (left) and PT-02 (right) with isovolumetric expansions to represent pre-prostatic artery embolization (PAE) volumes (green) and post-PAE volumes (red). (A color version of this figure is available at https://doi.org/10.1016/j.adro.2020.11.004.)

Table 1 Patient and treatment characteristics

	Age	Date of PAE	Pre-vol cm^3	Post- vol cm^3	Delta	Pre-IPSS	Post-IPSS	Androgen deprivation therapy	Gleason	Pre-PSA	Post-PSA	Prostate RT	Pelvic RT	Delta month
PT-01	48	9/2017	231	165	28.6%	7	2	Y	3 + 3	37.70	7.25	3 Gy × 20	N/A	10
PT-02	71	12/2018	153	80	47.7%	35	5	Y	4 + 3	13.17	3.18	2 Gy × 39	N/A	3
PT-03	73	01/19	126	105	16.7%	18	6	Y	4 + 4	6.40	0.44	2 Gy × 39	2 Gy × 22	14.5
PT-04	76	1/2018	34	31	7.2%	13	4	Y	4 + 5	0.49	0.04	1.8 Gy × 45	1.8 Gy × 25	2
PT-05	68	3/2018	116	98	15.5%	14	1	Y	4 + 3 tertiary 5	2.09	1.69	15 Gy brachy boost + 1.8 Gy × 25	1.8 Gy × 25	4.5

Abbreviations: IPSS = International Prostate Symptom Score; PAE = prostatic artery embolization; PSA = prostate-specific antigen; PT = patient; RT = radiation therapy.

prostate cancer reduces the rate of GU toxicity. We suggest that this is due to improved urinary symptoms before RT and reduced organ exposure from volume reduction after PAE. All patients in this study experienced significant improvement in LUTS at 3 months after PAE, which is consistent with previously published results.[6-9] Moreover, no patient experienced grade 3 or higher toxicity during radiation treatment.

Although this study suggests that acute GU toxicity in men who have LUTS from BPH is significantly improved by having PAE before RT, the additional benefit of prostate volume reduction also has an effect on treatment planning. We demonstrate in 2 cases where PAE resulted in a significant reduction in organs at risk dose. Numerous randomized studies have shown that reducing dose to organs at risk reduces toxicity in prostate radiation. By reducing the volume of the prostate, PAE can be a useful adjunctive therapy by allowing for adequate coverage while simultaneously resulting in decreased short- and long-term GU/gastrointestinal toxicity.

It is important to consider that the 3 patients who had nodal volume coverage did not see any appreciable differences in organs at risk dosing when treating to the pre- and post-PAE PTV volumes because the entire pelvis is treated followed by a cone down to the prostate. The changes in pre-PAE PTV only affected the cone down volume. We therefore conclude that most of the dosimetric benefit will be seen in patients who are treated to the prostate alone.

All patients analyzed showed clinical improvement after PAE based on significant IPSS improvement. Furthermore, the results show that the benefits of PAE as a minimally invasive method for control of LUTS can be extended to the prostate cancer population without adverse results.

Limitations

The major limitation of the study is the small number of patients included in the analysis. For this reason, we present this as a proof-of-concept, with the understanding that far more in-depth, prospective analysis must be performed. Other limitations include lack of consistent dosimetry plans across the 5 patients included in the analysis and an inherent statistical limitation induced by comparing theoretical treatment plans with actual treatment plans.

Conclusions

We demonstrate a proof of concept study showing that PAE is a clinically effective adjunctive therapy for improving LUTS and achieving significant volume reduction before definitive radiation in patients with prostate cancer. This leads to decreased dose to organs at

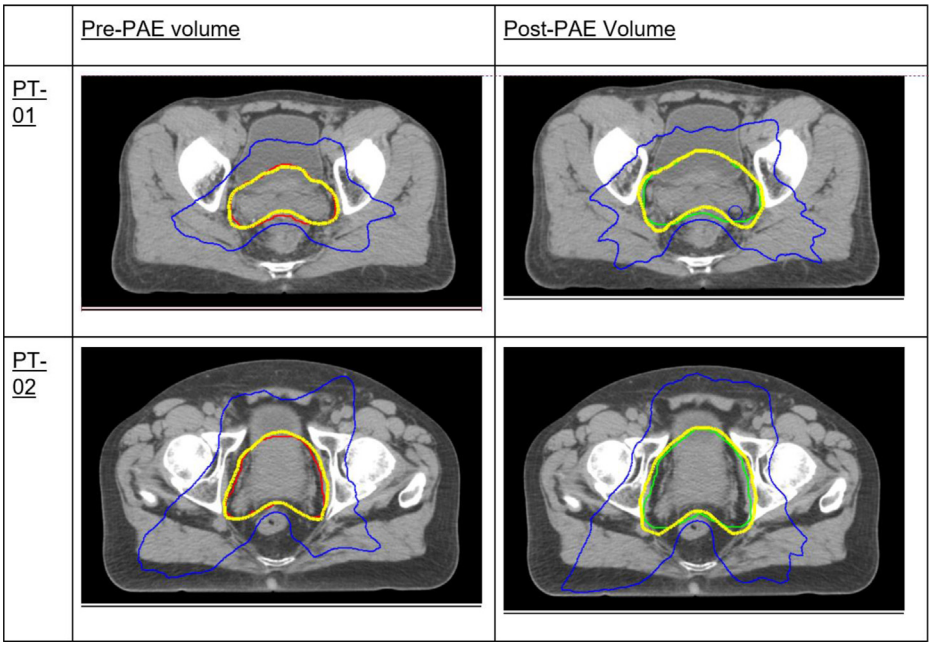

Figure 3 Top row is patient (PT)-01 treated to 60 Gy in 30 fractions. Bottom row is PT-02 treated to 78 Gy in 39 fractions. Two plans were created using the pre-prostatic artery embolization (PAE) volume (green) and post-PAE volume (red) planning target volumes (PTVs). The yellow represents the prescription dose isodose line, and the blue represents the 50% prescription isodose line. (A color version of this figure is available at https://doi.org/10.1016/j.adro.2020.11.004.)

Table 2 The coverage and mean dose to OAR using pre- and post-PAE volumes from 2 separate plans

PT-01	Pre-PAE	Post-PAE	% difference
Volume cm^3	231.0	165.0	−28.6%
PTV coverage %	94.6%	98.5%	
Bladder dose	2267.1 cGy	1914.2 cGy	−15.6%
Penile bulb dose	2569.5 cGy	2110.4 cGy	−17.8%
Rectum dose	3205.6 cGy	2667.7 cGy	−16.8%
PT-02			
Volume cc	153.0	80.0	−47.7%
PTV coverage %	98.2%	99.5%	
Bladder dose	2787.2 cGy	1926.6 cGy	−30.9%
Penile bulb dose	4355.2 cGy	3142.0 cGy	−27.9%
Rectum dose	3554.8 cGy	1399.3 cGy	−60.6%

Abbreviations: OAR = organs at risk; PAE = prostatic artery embolization; PT = patient; PTV = planning target volume.

risk, which may result in a clinically significant decrease in radiation-induced toxicity.

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