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Prostate Zonal Volumetry as a Predictor of Clinical Outcomes for Prostate Artery Embolization

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Abstract

Purpose To determine prostate baseline zonal volumetry and correlate these findings with clinical outcomes for patients who underwent prostate artery embolization (PAE) for lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH).

Materials and Methods This is a retrospective study that included patients treated by PAE from 2010 to 2014. Baseline and 6-month follow-up evaluations included prostate MRI with whole prostate (WP) and central gland (CG) volume measurements—as well as prostate zonal volumetry index (ZVi) calculation, defined as the CG/WP volumes relation—the International Prostate Symptom Score (IPSS), and the Quality of life (QoL) index. Baseline WP, CG, and ZVi were statistical compared to IPSS and QoL values at 6 months.

Results A total of 93 consecutive patients were included, with mean age of 63.4 years (range, 51–86). Clinical failure, defined as IPSS > 7 or QoL > 2, was seen in four cases (4.3%). Mean reductions in prostate volumes after PAE were of 30.6% and 31.2% for WP and CG, respectively ($p < 0.0001$). Clinical parameters had mean decrease from 21 to 3.3 points for IPSS, and from 4.7 to 1.2 points for QoL ($p < 0.0001$). Baseline WP, CG, and ZVi correlated to the degree of clinical improvement ($p < 0.05$ for all). The baseline ZVi cut-off calculated for better clinical outcomes was > 0.45, with 85% sensitivity and 75% specificity.

Conclusions Baseline CG and WP volumes as well as ZVi presented strong correlation with clinical outcomes in patients undergoing PAE, and its assessment should be considered in pre-treatment evaluation whenever possible. Both patients and medical team should be aware of the possibility of less favorable outcomes when ZVi < 0.45.

Keywords Benign prostatic hyperplasia · Prostate artery embolization · Imaging · Embolization · Interventional radiology

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Introduction

The prostate, unlike many other organs that atrophy with age, usually increases in volume due more frequently to benign prostatic hyperplasia (BPH) nodules situated in the central gland [1, 2]. BPH is the most common benign neoplasia in men, causing lower urinary tract symptoms (LUTS) in approximately 50% of men in their 80s [3]. LUTS secondary to BPH, such as urinary hesitancy, intermittency, urgency, incomplete bladder emptying, weak stream, and nocturia, can have a significant impact in patients' quality of life (QoL) [4].

International guidelines define pharmacological as the first-line treatment for symptomatic BPH, and surgery is reserved for complicated cases or ineffective/untolerated drug treatment [4, 5]. Recently, prostate artery embolization (PAE) has been adopted for the treatment of LUTS related to BPH (Fig. 1) and emerged as an important alternative for both medical and surgical treatments. Previous studies have established PAE as a safe and effective procedure, associated with reduction in symptoms and improvement of functional and clinical outcomes, as well as decrease of prostate volume [6–12]. However, detailed knowledge regarding the influence of prostate zonal volumetry in clinical outcomes after PAE remains unclear and would be useful to design treatment strategy and define the best candidate for the procedure.

The purpose of this study is to correlate aspects of prostate volumetry to clinical outcomes for patients who underwent PAE to treat LUTS secondary to BPH.

Materials and Methods

This is a single-center retrospective study that included 93 patients with moderate or severe LUTS (IPSS > 7 or with indwelling catheter due to urinary retention) secondary to BPH treated by PAE from 2010 to 2014. The institutional review board approved the study, and all patients provided informed consent for the procedure.

All of them had LUTS refractory or intolerant to pharmacological treatment (α-1-adrenergic receptor antagonist and/or 5-α-reductase inhibitor). Patients with histologic diagnosis of prostate cancer, bladder disorders, or creatinine level > 2.0 mg/dL were excluded. All patients with a serum prostate-specific antigen (PSA) level > 4.0 ng/mL or with an abnormal digital rectal examination underwent transrectal ultrasound-guided prostate biopsy to exclude the presence of prostate malignancy.

Baseline and 6-month follow-up evaluations included prostate-specific antigen (PSA) testing, the International Prostate Symptom Score (IPSS), and the Quality of life (QoL) index assessment and pelvic MRI. Whole prostate (WP), central gland (CG), and peripheral zone volumes, as well as the prostate zonal volumetry index (ZVi), which was defined as the CG/WP volumes relation, were statistically compared to clinical outcomes as assessed by IPSS and QoL at 6 months. These same variables were also correlated to clinical failure, which was defined by IPSS > 7 or QoL > 2. Finally, a ZVi cut-off for better clinical outcomes was statistically determined.

MRI data Acquisition

MRI examinations of the prostate were performed at baseline (1 to 3 months before PAE) and 6 months after the procedure, on a 1.5-T (Signa HDxt, GE Healthcare) or a 3-T (Achieava, Philips Healthcare) superconducting unit with phased-array torso coils. Examination protocol included thin-section high-spatial-resolution axial and sagittal T2-weighted fast spin-echo images and dynamic contrast-enhanced (DCE) T1-weighted axial images. The contrast agent (gadoterate dimeglumine, Dotarem, and Guerbet) was injected as a bolus at a dose of 0.1 mmol/kg at a rate of 2.0 mL/s followed by 20 mL of saline flush.

Prostate Volume Measurements

The WP and CG dimensions were measured on the T2-weighted sequences. The transverse diameters were measured in the axial plane, and the craniocaudal and anteroposterior diameters were obtained from the sagittal views (Fig. 2). WP and CG volumes were calculated using the formula for volume estimation of a prolate ellipsoid (transverse diameter x craniocaudal diameter x anteroposterior diameter $\times \pi/6$) [13, 14]. The volume of the peripheral zone was calculated by subtracting the CG volume from the WP volume ($Vpz = Vwp - Vcg$). The volume reductions were calculated by percentage. The ZVi was calculated as follows:

$$\text{ZVi} = \frac{\text{Baseline CG volume}}{\text{Baseline WP volume}}$$

Two different radiologists, with 7 and 5 years of experience, evaluated each MRI examination, and disparate measurements were resolved by consensus.

Clinical Evaluation

Patients' clinical symptoms were assessed via the IPSS questionnaire and the IPSS-QoL item, for which responses range from "6, Terrible" to "0, Delighted." The total PSA levels were part of the clinical evaluation. Pre-procedure evaluation was performed within 1 month before PAE and post-PAE follow-up evaluation on consultation during the first week, 3 and 6 months thereafter. The degree of

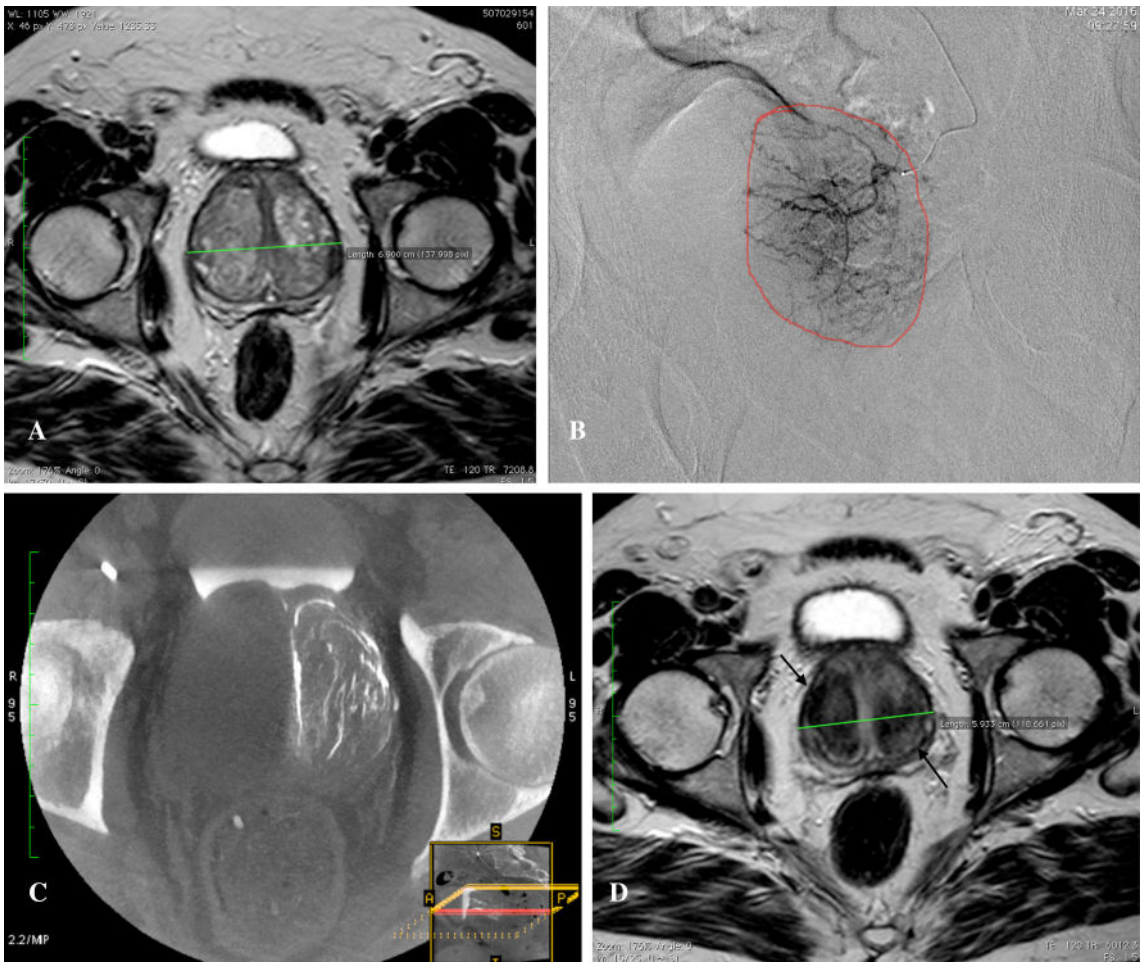

Fig. 1 **A** Pre-PAE axial T2-weighted MRI demonstrating enlargement of the prostate due to BPH nodules in the central gland. **B** Pre-embolization DSA of the left central gland branch showing typical hypervascular aspect (*highlighted area*). **C** Pre-embolization cone-beam CT confirming the DSA findings, showing enhancement of the left central gland. **D** Follow-up MRI demonstrating volumetric reduction of the prostate after PAE, as well as infarction of BPH nodules in the central gland (*arrows*)

clinical improvement was calculated subtracting the baseline value of IPSS or QoL from the follow-up value. Thus, in case of clinical improvement, the change has a negative value.

Clinical failure was defined as IPSS > 7 or QoL > 2 during follow-up, or impossibility of removal of indwelling catheter in patients with pre-PAE urinary retention.

Embolization Procedure

The PAE procedures were performed in the interventional radiology suite Innova DSA (GE Healthcare, Chalfont St. Giles, Buckinghamshire, UK) or FD20 digital subtraction angiography unit (Philips, Best, The Netherlands) with nonionic contrast medium (320 mgI/mL iodixanol [Visipaque; GE Healthcare, Cork, Ireland]). All patients underwent PAE according to previously described methods, with the aim of embolization of every feeding branch to the prostate, bilaterally [15, 16]. Procedures were performed under local anesthesia through a unilateral femoral artery puncture approach, and patients were discharged from 2 to 6 h after PAE. Selective catheterization of the right and left inferior vesical arteries was performed using a 2.0F microcatheter (Progreat®, Terumo, Tokyo, Japan), and angiography was performed to ensure that the tip of the microcatheter was positioned distally to bladder, rectal, or seminal vesicle branches. Embolization was performed with 300–500 μm tris-acryl Embosphere Microspheres (Biosphere Medical, Roissy, France) until complete stasis.

Statistical Analysis

Statistical analysis was conducted using 2014 R Core Team software. Baseline and follow-up values for prostate zonal volumes were compared using paired t tests. The comparisons for WP, CG, PZ, and ZVi and post-procedure IPSS and QoL were performed using the Wilcoxon signed-

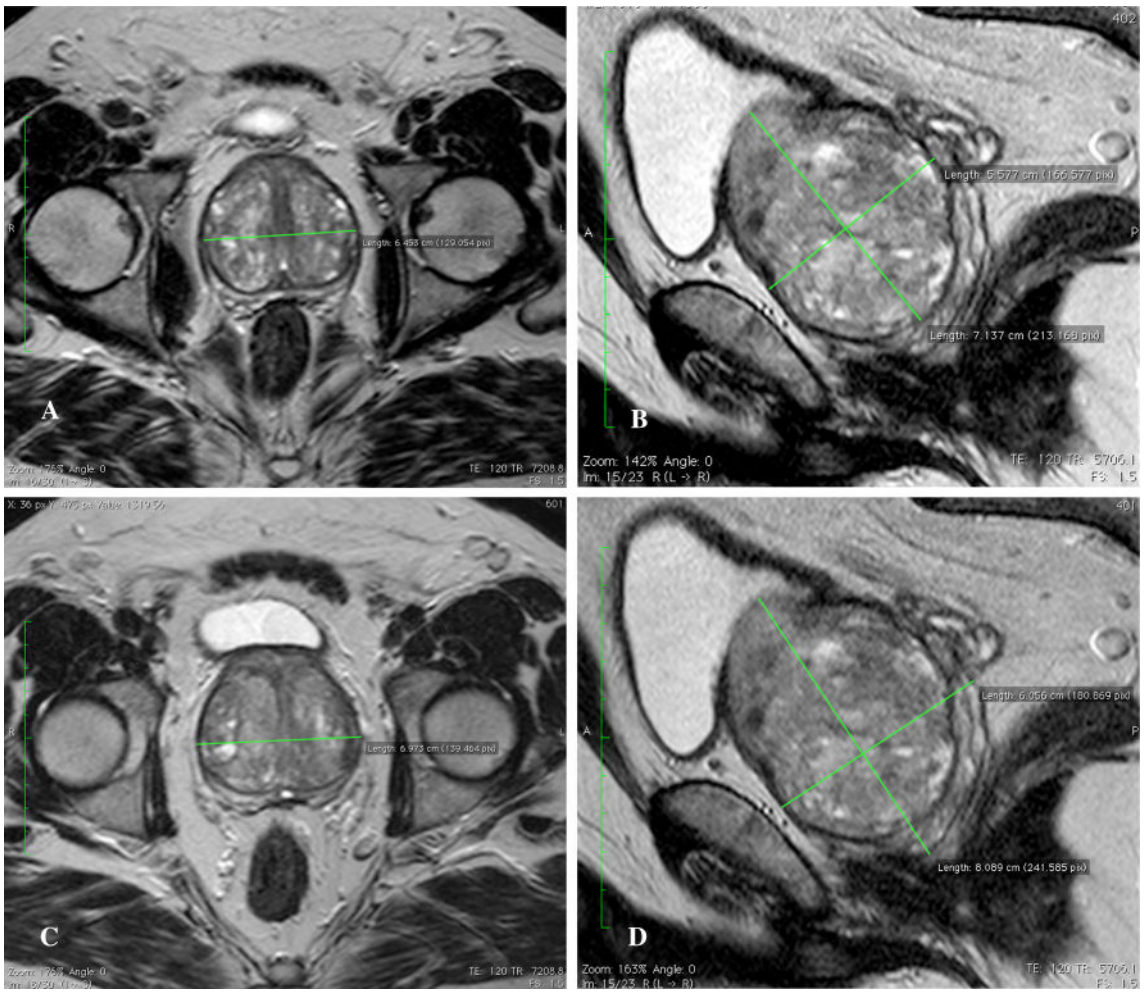

Fig. 2 T2-weighted pelvic MRI in axial and sagittal views exemplifying CG (**A**, **B**) and WP (**C**, **D**) transverse, craniocaudal, and anterior–posterior measurements. In this case, patient presented with a favorable ZVi of = 0.748

rank test. The relationships between prostate zonal volumes and clinical variants were assessed by Spearman's rank correlation. The significance level for all statistical tests was defined as two-sided p value ≤ 0.05.

Results

A total of 93 consecutive patients were treated, with mean age of 63.4 years (range, 51-86), and bilateral embolization was achieved in 100% of the cases. Clinical failure, defined as IPSS > 7 or QoL > 2 during follow-up period, was seen in four cases in this cohort (4.3%). At 6-month follow-up, mean PSA was statistically significantly lower than at baseline ($p < 0.0001$).

Reduction in prostate volumes after PAE was found to be significant ($p < 0.0001$), with mean decrease of 30.6, 31.2, and 29.4% for WP, CG, and peripheral zone, respectively (Table 1). Clinical parameters had a significantly mean decrease from 21 to 3.3 points for IPSS, and from 4.7 to 1.2 points for QoL, comparing 6-month follow-up and baseline results ($p < 0.0001$). This represents an 84.2% IPSS reduction and a 74.4% QoL decrease.

Comparing baseline volumes to outcomes, higher pre-PAE WP was significantly correlated to the degree of clinical improvement as assessed by QoL ($p < 0.05$, Fig. 3A), as well as pre-PAE CG volume, that correlated to the degree of improvement as assessed by IPSS ($p < 0.05$) and QoL ($p < 0.05$, Fig. 3B). In a similar way, the ZVi also correlated to the degree of clinical improvement as assessed by IPSS ($p < 0.05$) and QoL ($p < 0.05$, Fig. 3C). The baseline ZVi cut-off calculated for better clinical outcomes was >0.45, with 85% sensitivity and 75% specificity, $p < 0.05$ (Fig. 4).

No statistical correlation was observed between baseline WP, CG, or ZVi and clinical failure (IPSS > 7 or QoL > 2).

Volume reduction of the WP and CG presented with a direct statistical relation to outcomes—the higher was the reduction, the better was the clinical improvement as assessed by IPSS and QoL ($p < 0.05$ for both).

No peripheral zone baseline volume and peripheral zone volume reduction correlated to clinical outcomes in this series.

Discussion

Although PAE had been settled as a safe and effective alternative for treatment of LUTS due to BPH [6–12], questions still remain concerning clinical and radiological predictors of outcomes. Indeed, identifying the best candidate for PAE seems to be one of the major questions yet to be answered and would certainly affect the efficacy of the method and help to state the real role of PAE for patients with enlarged prostates.

As previously described, PAE seems to work mainly in the hypervascular portion of the prostate, which is the central gland, in an analogue fashion as seen in other hypervascular tumors such as uterine fibroids. Frenk et al. [14] recently addressed this issue and concluded that the infarction of the hypervascular BPH nodules ultimately leads to prostate volume reduction and consequent clinical improvement. Thus, it is logical to consider that the greater is the baseline enlargement of central gland (due to BPH nodules), the better would be the overall clinical response after PAE.

In this study, such characteristic was explored by assessing the baseline CG volume and the ZVi, which translates experimentally the referred *rationale*—the higher are these values, the larger is the BPH component. Indeed, as expected, higher baseline CG and ZVi correlated to better clinical outcomes at 6-month follow-up (period of maximum prostate volume reduction), as assessed by IPSS and QoL questionnaires ($p < 0.05$ for both), traducing the greater component of treatable disease in this group of patients. Otherwise, prostates with lower baseline ZVi were related with lower LUTS improvement, although some amelioration still occurred. This could be explained by the fact that some BPH component does exist even in low ZVi prostates, component which can be effectively addressed by embolization. Some authors also defend the theory that PAE also works in the stromal component of central gland, altering the muscular tonus mediated by alpha-adrenergic receptors, a mechanism not directly related to shrinkage of BPH nodules and volumetric reduction itself [17].

A few investigations have previously correlated baseline WP volume to clinical outcomes, with divergent findings.

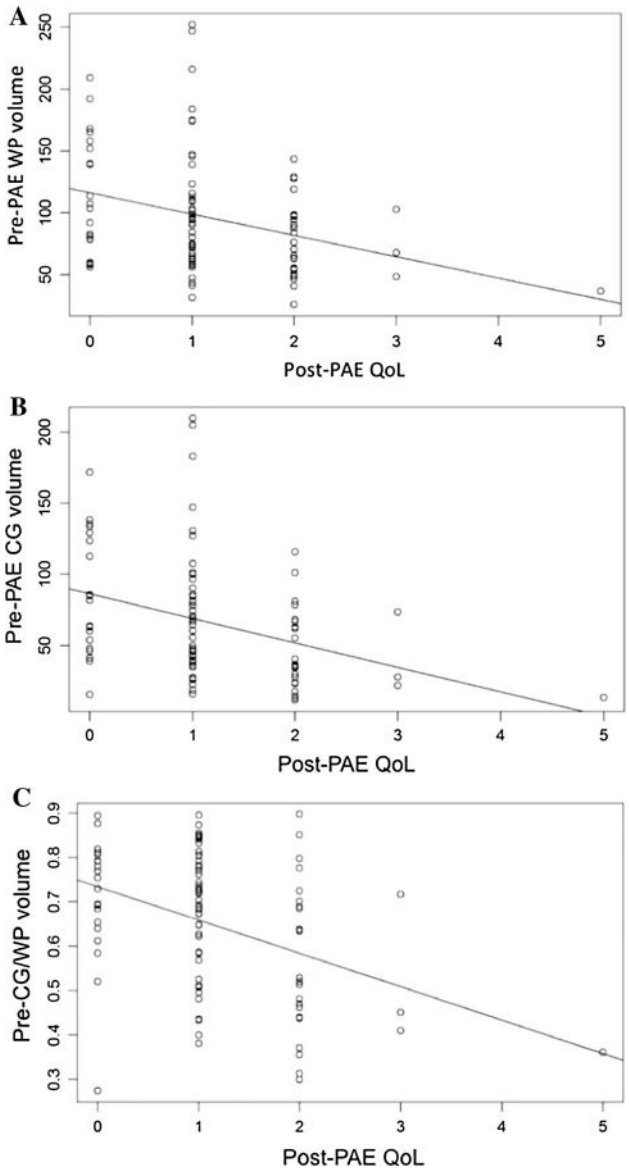

Fig. 3 Correlation between baseline **A** WP, **B** CG, and **C** ZVi and clinical outcomes after PAE as assessed by QoL ($p < 0.001$ for all). Prostate volumes in cm^3

Table 1 Prostate zonal volumetry before and after PAE

Region	Volume before PAE (mean ± SD)	Volume after PAE (mean ± SD)	*p* value
Whole prostate (WP)	96.2 ± 46.8	66.7 ± 29.7	<0.0001
Central gland (CG)	66.3 ± 42.8	45.6 ± 27.7	<0.0001
Peripheral zone (PZ)	29.9 ± 14.1	21.1 ± 8.2	<0.0001

Volumes in cm^3

SD standard deviation

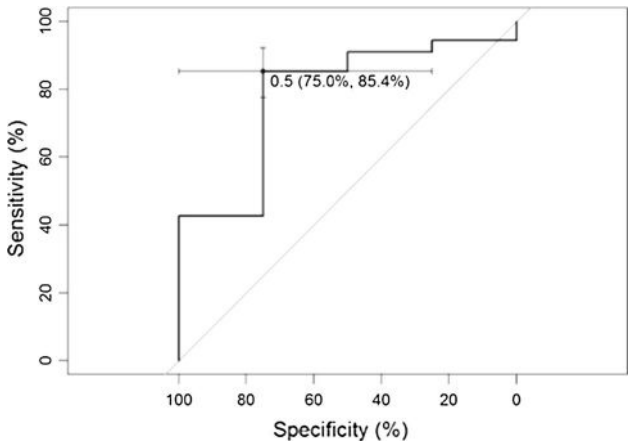

Fig. 4 Baseline ZVi cut-off calculated for clinical outcomes. Better results were achieved when ZVi > 0.45 (85% sensitivity, 75% specificity, $p < 0.05$)

Assis et al. [12] and Wang et al. [18]—single-arm studies—demonstrated encouraging outcomes in larger prostates (> 80–90 g), even better than historically described results for 'any volume' prostates. However, this conclusion could be somewhat biased by the non-controlled nature of the studies. Bagla et al. [19], on the other hand, demonstrated that clinical results were similar between patients with prostates <50 cm^3, 50–80 cm^3, and >80 cm^3 ($p > 0.05$ for IPSS, QoL, and IIEF), concluding that PAE outcomes in smaller prostates (total volume) were not inferior to that observed in larger ones. In the present study, both larger baseline WP and CG volumes were associated with more favorable outcomes after PAE.

Nevertheless, no study aimed to investigate baseline CG or ZVi as an outcome predictor for PAE so far—indeed, this relation can be more accurately correlated to outcomes than total volume itself, as total volume increase is not necessarily a consequence of BPH. This idea was corroborated in this study, once baseline CG and ZVi seemed to be a better predictors then WP, as these parameters predicted outcomes as assessed by both QoL and IPSS values, while WP volume correlated only to QoL. Finally, a baseline ZVi > 0.45 correlated to better outcomes after PAE (sensibility = 85%, specificity = 75%, $p < 0.05$).

Data obtained showed that not only baseline zonal volumes were important predictors of outcomes, but also the degree of its reduction that indeed seems to play a major role in clinical improvement after PAE. In this study, higher absolute reductions of both WP and CG volume themselves also leaded to better outcomes ($p < 0.05$). Differently, no baseline or post-PAE volumes of peripheral zone, as well as its reduction, correlated to LUTS improvement, as intuitively expected. Peripheral zone component is mostly not implicated to BPH obstruction mechanism, and it also seems to be less affected by PAE due to its inherent hypovascularity.

Despite the significant difference in LUTS improvement (assessed by IPSS and QoL), no correlation between baseline WP, CG, and ZVi, and *clinical failure* (IPSS > 7 or QoL > 2) was demonstrated, probably due to small sample and relatively short follow-up period, leading to the low overall incidence of clinical failure in the whole casuistic. Longer follow-up period is warranted to clarify this specific issue and would possible demonstrate a higher incidence of failure and/or long-term recurrence in patients with less favorable baseline volumetry.

Findings described in this investigation would probably have important consequences in patients' selection for PAE. First of all, although the prostate volumetry could be estimated by ultrasound (US), it is probably more accurately assessed by pelvic MRI. Moreover, MRI also characterizes better the necrosis of BPH nodules caused by PAE and detects more precisely possible complications or associated diseases, such as suspect lesions for neoplasia. However, it is important to consider the costs involved in such pre-procedure evaluation, as referring every patient to pelvic MRI could not be economical viable in all situations. Furthermore, other treatment options—such as TURP, laser enucleation, or transvesical prostatectomy—could be considered to those patients with unfavorable baseline volumetry findings. Ultimately, both Interventional Radiologists and Urologists should look carefully for other causes of LUTS in patients with low ZVi, since the prevalence of such causes could be higher in this specific universe of patients.

Although this study demonstrated new predictors of outcomes in patients undergoing PAE, as well as introduced the ZVi concept and defined a specific threshold for it, it also has its limitations—most importantly the retrospective nature of the study, as well as the relative short follow-up period and small sample size. With larger sample size and longer follow-up period, it is possible that CG and ZVi also correlate to clinical failure and medium/long-term recurrence. Such study is desirable to consolidate these new concepts, as well as to remove possible bias related to the retrospective nature of this investigation. Moreover, prostates measurements were achieved by the ellipse formula estimative, and no direct volumetric assessment was performed, which can lead to some degree of imprecision. Finally, although this study has included patients with prostates of any volume, a considerable number of them presented with clinically large glands (>80–100 cm^3), resulting in a mean baseline volume of 96.2 cm^3. Thus, it is not absolutely clear whether the findings are reproducible in all subgroups of patients, such as those with small prostates.

In conclusion, baseline CG and WP volumes as well as ZVi presented strong correlation to clinical outcomes in patients undergoing PAE, and its assessment should be considered in pre-treatment evaluation whenever possible. Both patients and medical team should be aware of the possibility of less favorable outcomes when ZVi < 0.45. Finally, studies including larger cohorts and longer follow-up periods are still warranted to corroborate such findings.

Compliance with Ethical Standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

References

1. Berry SJ, Coffey DS, Walsh PC, Ewing LL. The development of human benign prostatic hyperplasia with age. J Urol. 1984;132:474–9.
2. Anderson JB, Roehrborn CG, Schalken JA, Emberton M. The progression of benign prostatic hyperplasia: examining the evidence and determining the risk. Eur Urol. 2001;39:390–9.
3. Emberton M, Andriole GL, de la Rosette J, Djavan B, Hoefner K, Vela Navarrete R, et al. Benign prostatic hyperplasia: a progressive disease of aging men. Urology. 2003;61:267–73.
4. Oelke M, Bachmann A, Descazeaud A, Emberton M, Gravas S, Michel MC, et al. EAU guidelines on the treatment and follow-up of non-neurogenic male lower urinary tract symptoms including benign prostatic obstruction. Eur Urol. 2013;64:118–40.
5. McVary KT, Roehrborn CG, Avins AL, Barry MJ, Bruskewitz RC, Donnell RF, et al. Update on AUA Guideline on the Management of Benign Prostatic Hyperplasia. J Urol. 2011;185:1793–803.
6. Antunes AA, Carnevale FC, da Motta-Leal-Filho JM, Yoshinaga EM, Cerri LM, Baroni RH, et al. Clinical, laboratorial and urodynamic findings of prostatic artery embolization for the treatment of urinary retention related to benign prostatic hyperplasia. A prospective singe-center pilot study. Cardiovasc Intervent Radiol. 2013;36:978–86.
7. Carnevale FC, Antunes AA, da Motta-Leal-Filho JM, de Oliveira Cerri LM, Baroni RH, Marcelino AS, et al. Prostatic artery embolization as a primary treatment for benign prostatic hyperplasia: preliminary results in two patients. Cardiovasc Intervent Radiol. 2010;33:355–61.
8. Carnevale FC, da Motta-Leal-Filho JM, Antunes AA, Baroni RH, Marcelino AS, Cerri LM, et al. Quality of life and clinical symptom improvement support prostatic artery embolization for patients with acute urinary retention caused by benign prostatic hyperplasia. J Vasc Interv Radiol. 2013;24:535–42.
9. Bilhim T, Pisco JM, Rio Tinto H, Fernandes L, Pinheiro LC, Furtado A, et al. Prostatic arterial embolization to treat benign prostatic hyperplasia. J Vasc Interv Radiol. 2012;23:1403–15.
10. Bagla S, Martin CP, van Breda A, Sheridan MJ, Sterling KM, Papadouris D, et al. Early results from a United States trial of prostatic artery embolization in the treatment of benign prostatic hyperplasia. J Vasc Interv Radiol. 2014;25:47–52.
11. Pisco JM, Rio Tinto H, Campos Pinheiro L, Bilhim T, Duarte M, Fernandes L, et al. Embolisation of prostatic arteries as treatment of moderate to severe lower urinary symptoms (LUTS) secondary to benign hyperplasia: results of short- and mid-term follow-up. Eur Radiol. 2013;23:2561–72.
12. de Assis AM, Moreira AM, de Paula Rodrigues VC, Yoshinaga EM, Antunes AA, Harward SH, et al. Prostatic artery embolization for treatment of benign prostatic hyperplasia in patients with prostate >90 g: a prospective single-center study. J Vasc Interv Radiol. 2015;26:87–93.
13. Sosna J, Rofsky NM, Gaston SM, DeWolf WC, Lenkinski RE. Determinations of prostate volume at 3-tesla using an external phased array coil. Acad Radiol. 2003;10:846–53.
14. Frenk NE, Baroni RH, Carnevale FC, Gonçalves OM, Antunes AA, Srougi M, Cerri GG. MRI findings after prostatic artery embolization for treatment of benign hyperplasia. Am J Roentgenol. 2014;203:813–21.
15. Carnevale FC, Antunes AA. Prostatic artery embolization for enlarged prostates due to benign prostatic hyperplasia. How I do it. Cardiovasc Intervent Radiol. 2014;37:1602–5.
16. Carnevale FC, Moreira AM. The "PErFecTED technique": proximal embolization first, then embolize distal for benign prostatic hyperplasia. Cardiovasc Intervent Radiol. 2014;37:1602–5.
17. Sun F, Crisostomo V, Baéz-Díaz C, Sanchez FM. Prostatic artery embolization (PAE) for symptomatic benign prostatic hyperplasia (BPH): part 1, pathological background and clinical implications. Cardiovasc Intervent Radiol. 2016;39:1–7.
18. Wang MQ, Guo LP, Zhang GD, Yuan K, Li K, Duan F, et al. Prostatic arterial embolization for the treatment of lower urinary tract symptoms due to large (> 80 mL) benign prostatic hyperplasia: results of midterm follow-up from Chinese population. BMC Urol. 2015;15:33.
19. Bagla S, Smirniotopoulos JB, Orlando JC, van Breda A, Vadlamudi V. Comparative analysis of prostate volume as a predictor of outcome in prostate artery embolization. J Vasc Interv Radiol. 2015;26:1832–8.