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REVIEW ARTICLE

Biomarkers in the setting of benign prostatic hyperplasia-induced lower urinary tract symptoms: what an interventional radiologist needs to know

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ABSTRACT:

With increasing evidence to support prostate artery embolization (PAE) in the treatment of benign prostatic hyperplasia (BPH)-induced lower urinary tract symptoms (LUTS), Interventional Radiologists have begun to play an important role in the management of these patients. One area of knowledge needed when developing a PAE practice is knowledge of prostate-specific antigen (PSA) and other biomarkers utilized to detect prostate cancer in this population and what role they should play in the work up and follow-up of patients presenting with presumed BPH-induced LUTS. Furthermore, understanding how to evaluate presumed BPH-induced LUTS and stratify the risk of prostate cancer is an important skill to develop. The goal of this review is to provide Interventional Radiologists who have begun or aim to begin a PAE practice with the information they need to know regarding PSA levels and prostate cancer risk stratification for this patient population.

INTRODUCTION

Lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH) is a highly prevalent pathology affecting a large percentage of males greater than 60 years old.^{1,2} LUTS include increased nocturia, frequent urination of small amounts, involuntary urge to urinate, dysuria, delayed start, prolonged time, weak stream and incomplete emptying of the bladder.^{1,2} Pharmacotherapy and lifestyle modifications are utilized as first-line therapy for BPH-induced LUTS. Unfortunately, many patients progress and require further intervention, necessitating the need for procedural or surgical intervention.³

When patients have medically refractive BPH-induced LUTS, transurethral resection of the prostate (TURP) is considered the gold standard therapy; however, over the last decade, there has been a progressive drive to develop several minimally invasive treatment options for patients with medically refractive BPH-induced LUTS. Among these, prostate artery embolization (PAE) has shown consistently encouraging results.⁴⁻⁷ The positive results of PAE in the treatment of this disease has led to Interventional Radiologist participating in the management of a new disease area.

One of the main challenges of treating the BPH-induced LUTS population is the large array of tests such as prostate-specific antigen (PSA) which are designed to screen for or diagnose prostate cancer as this entity shares similar patient demographics and occasionally similar clinical presentation to BPH-induced LUTS. When treating BPH, most of the value of these tests resides in their sensitivity, as cancer should be ruled out, prior to making treatment choices. However, specificity is of great interest as well, given biopsies are uncomfortable for patients and carry a small complication rate. The Interventional Radiologist who would like to build or already has an established PAE practice should understand the value of each test and be comfortable with the work-up. The aim of this paper is to review these relevant markers for the practicing Interventional Radiologist interested in PAE.

PROSTATE-SPECIFIC ANTIGEN (PSA)

PSA is a glycoprotein that is produced by the prostate epithelial cells and is secreted in the semen for purposes of liquefaction.⁸ PSA also diffuses into the blood in small quantities that can be measured.⁹ PSA is frequently obtained in patients in their fifth or sixth decades of life and in combination with the digital rectal exam (DRE) has been

a mainstay of preventive medicine since the late 1980s. It is still the most widely and sometimes the only used marker to screen for prostate cancer. However, PSA is a non-specific marker that can be elevated in benign conditions such as BPH and prostatitis, after certain activities such as ejaculation or bike riding, and after some medical procedures or interventions such as DRE. Age and race are also important variables affecting the levels of PSA with an interval of normal values widening proportionally to the patient's age.¹⁰ It is also important to understand that certain medications may decrease PSA in the presence of cancer, namely, 5- α reductase inhibitors (like finasteride and dutasteride), dietary supplements, aspirin, statins and thiazide diuretics, while others such as testosterone may elevate PSA.

PSA in the asymptomatic general population

Since PSA was introduced as a screening method, more prostate cancer diagnoses have been made and the mortality rates have decreased.¹¹ However, it is not clear that PSA screening is responsible for these outcomes and the validity of PSA as a screening method remains controversial. PSA has been reported to have a sensitivity of as high as 86% and a specificity of 33% when using a cutoff of 4.0 ng ml⁻¹; however, these values vary greatly depending on the study.¹² This means that the majority of patients who undergo prostate biopsy based on serum PSA levels deal with the cost, psychological stress, and a small chance of complication despite having benign disease.^{13,14} It is also important to understand that even if a diagnosis of prostate cancer is made, it is frequently considered "clinically insignificant" if the Gleason score is less than 7 (9). These factors perhaps explain why no mortality benefit was shown in a large randomized-controlled trial comparing patients who underwent PSA and DRE screening annually and those who did not.¹⁵ Following these results, the United States Preventative Services Task Force (USPSTF) recommended only screening 55–69-year-old males on a case-by-case basis, and recommended against routine screening in patients older than 70.^{9,16,17} However, societies such as the European association of Urology (EAU) and American Urologic Association (AUA) have been more favorable towards the use of PSA screening.¹⁸ Regardless, in general practice, the PSA is frequently obtained and if elevated, a prostate biopsy and at times a multiparametric MRI ensues as work-up for the diagnosis of prostate cancer.

PSA and BPH-induced LUTS

There is some controversy in the literature about measuring PSA for BPH-induced LUTS. The EAU guidelines recommend PSA to be included in the work-up of BPH-induced LUTS if the diagnosis of cancer would affect treatment¹⁹ while the AUA guidelines recommend it for all presenting patients.²⁰ However, in day-to-day practice, most providers obtain a PSA as part of the work-up of BPH.²¹ Similarly, in the literature reporting safety and efficacy of PAE, PSA is consistently measured and followed after treatment. One often cited indication for PSA measurement is to rule out aggressive cancers given the age overlap between patients suffering from BPH and those at risk for prostate cancer. Increased PSA levels are also associated with LUTS symptomatology: urinary retention and therefore need for intervention may be associated with higher levels of PSA.²² Furthermore,

increased baseline PSA in patients with no symptoms or mild symptoms may correlate with increased risk for developing LUTS.²³ Finally, as expected, there is a positive relationship between the prostate volume and PSA level, although prostate size is known to poorly correlate with LUTS.²⁴

PSA is also commonly measured during follow-up of patients who have undergone PAE. The ischemic damage to the gland causes PSA to spill into the blood stream and variation in its levels can be appreciated. Some authors have found that smaller particles, which penetrate more distally in the arterial arcade of the gland, may produce a greater ischemic effect and degree of PSA increase immediately after PAE.²⁵ Petrillo *et al* reported a positive correlation between the particle size and the rise in PSA, which they attributed to ischemic effect.²⁶ However, PSA decrease overtime has not necessarily correlated with clinical improvement in terms of International Prostate System Score (IPSS) and quality of life (QoL).²⁷ While a single study has indicated substantial increase in PSA at 24 h may be associated with improved IPSS outcomes,²⁸ Nonetheless, PSA measurement is a common component of PAE studies, despite the lack of clear evidence that links non-responders to lower or absent PSA variation pre- and post-procedure. The data are limited by variability in the reported time points at which a drop in PSA post-treatment can be appreciated.^{25,29} Furthermore, it would not be unexpected for the PSA to recover partially, especially in the long-term follow-up,³⁰ possibly as a subclinical expression of BPH recurrence.

PSA velocity

PSA velocity is seldomly used to differentiate cancer from BPH, and its diagnostic utility is debated.³¹ The main concept behind PSA velocity is that PSA rises faster in patients with prostate cancer compared to those with BPH, potentially predicting cancer several years before the diagnosis would otherwise be made. To calculate the PSA velocity, at least three PSA measurements at least 1 year apart from each other are required. Carter *et al* showed an increase of 0.75 ng ml⁻¹ per year was significantly more common in patients with prostate cancer compared to those with BPH. Furthermore, they found that the rate of change of PSA could distinguish patients with BPH from those with cancer with a sensitivity of 72% and a specificity of 90% at any value of PSA.³² PSA velocity has several limitations including its variability with time and age; also, despite the efforts to standardize the method used to calculate a PSA value, there is significant variability between available assays that makes comparison difficult. Finally, it requires multiple time points with at least 1 year in between, so is not possible to calculate for patients without this historic data when presenting for presumed BPH-induced LUTS. However, it is cost-effective, in that no further testing is needed besides that which has already been performed.

Free PSA (fPSA), Complexed PSA (cPSA), and Percent [-2]proPSA

There are two main types of PSA measured in the blood; the difference resides in whether or not the molecule is bound to other circulatory proteins; free PSA (fPSA) represents the portion of the total PSA which is not bound to other circulatory

Figure 1. Author recommended decision tree on which patients to screen with PSA before PAE. PSA = prostate specific antigen

proteins.^{33,34} The fPSA is a smaller fraction of PSA in males with prostate cancer as compared to those with BPH.³⁵ It seems to be particularly useful for patients with a PSA between 4 ng ml⁻¹ and 10 ng ml⁻¹ and is often ordered in adjunct to PSA. If fPSA is greater than 25%, males are much more likely to have a benign process, allowing these patients to avoid undergoing prostate biopsy and the complications that are associated with the procedure.^{36,37} In fact, several studies found a sensitivity of 95% and a specificity of 20% if a fPSA cutoff of 25% was utilized.^{36,38} A different study demonstrated 92% sensitivity and 23% specificity using a cutoff of 20%.³⁹ The cost-effectiveness of this widely available test was performed by a Spanish group, they found that in a cohort of patients with a PSA between 4 and 10 ng ml⁻¹, it provided significant savings by allowing some patients to avoid biopsy.⁴⁰

Complexed PSA (cPSA) measures a fraction of the PSA that is not free, in particular the proportion attached to a serum protein (alpha1-antichymotrypsin).^{41,42} Isoform [-2]proPSA is produced by the prostate parenchyma and is transformed into PSA by a luminal enzyme. While neither fPSA or cPSA is widely used in clinical practice, one study found that cPSA lead to the greatest cost savings when being compared to PSA and fPSA.⁴³

PSA density (PSAD)

As may be gleaned from the name PSA density (PSAD) is calculated by dividing the serum PSA in ng/mL by the volume of the prostate gland in mL.^{44,45} Its specificity and sensitivity have been reported to be 85 and 75% when using a cutoff of 0.1 and it seems to function especially well in patients with a PSA above 4 ng ml⁻¹ and PSA velocity above 0.75 ng ml⁻¹ per year.⁴⁶ A similar study found that if a PSAD cutoff of 0.208 was utilized, then the specificity was 97% and sensitivity was 84%.⁴⁷ While another demonstrated a cutoff value of 0.218 provided a sensitivity of greater than 90%.⁴⁸ Furthermore, PSAD has been found to provide cost savings when compared to the use of PSA alone or PSA and DRE to direct prostate biopsy decisions.⁴⁹

Because prostate cancer is found primarily, but not exclusively, in the peripheral zone and BPH is primarily driven by hyperplasia in the transition zone, the transition zone PSAD (TZPSAD) and peripheral zone PSAD (PZPSAD) have also been suggested to help differentiate the causes of elevated PSA.^{44,45,50} The TZPSAD is calculated by dividing the serum PSA by the volume of the transition zone and the PZPSAD is calculated by dividing the serum PSA by the volume of the peripheral zone. These values have been utilized to create nomograms which have been found to be more predictive of clinically significant prostate cancers, than PSA alone.^{44,45} A recent study, which utilized prostate magnetic resonance imaging (MRI), found that TZPSAD was more effective than PSAD alone in predicting clinically significant prostate cancer.⁵¹ This study found that a cutoff of 0.15 ng/mL² for PSAD and 0.22 ng/mL² for TZPSAD ideally differentiated clinically significant prostate cancers from those who were not clinically significant.⁵¹ Given the use of cross-sectional imaging prior to PAE, PSAD can be an effective tool for risk stratifying patients with elevated PSA.

OTHER SERUM/URINE MARKERS AND RISK STRATIFICATION TOOLS AND ALGORITHMS FOR PROSTATE CANCER

As discussed above, PSA is not a perfect marker in terms of a prostate cancer screening tool.^{9,33} However, the use of PSA remains prevalent within the healthcare system, and during work-up and treatment of BPH patients. It may be difficult for Interventional Radiologists to know what to do in the setting of an abnormal PSA, and therefore we introduce some other optional markers and algorithms for Interventional Radiologists to be familiar with which may help guide their decision-making.

Serum markers

Prostate health index (PHI)

PHI uses a calculation to evaluate the PSA, fPSA, and another isoform of PSA [-2]proPSA and is calculated by mathematical formula $([-2]proPSA/fPSA) \times \sqrt{PSA}$.⁵²⁻⁵⁴ The use of PHI in a group of patients with PSA between 4 and 10 ng ml⁻¹ resulted in a sensitivity of 95% with a specificity of 27% in one study, better than PSA or fPSA alone.⁵³ Furthermore, some authors have suggested that PHI can be useful in predicting those patients who will have clinically significant prostate cancers (Gleason score ≥ 7).⁵⁴ PHI has also been shown to provide cost savings when used to direct which patients require biopsy, as compared to PSA alone.⁵⁵

4kscore® test

This multivariate model incorporates four protein serum markers (PSA, fPSA, intact PSA, and human kallikrein 2[hK2]) as well as age and DRE.⁵⁶ One study, of patients with a PSA >3 ng ml⁻¹ demonstrated a sensitivity of 83% and specificity of 75%, when using a 20% risk of prostate cancer as the threshold.⁵⁶ This would result in avoiding 60% of biopsies while only missing 17% of all cancers and 3% of high-grade or "clinically significant" cancers.⁵⁶ Similar to the other reviewed biomarkers, the 4K score has been found to provide cost savings as compared to the use of PSA alone by reducing biopsies, however, at least in one

Figure 2. Author recommended decision tree on management of screening PSA levels in patients presenting to IR clinic during PAE consultation. PSA = prostate specific antigen, MRI = Magnetic resonance imaging, CTA = computed tomography angiography, PAE = prostate artery embolization, PSAD = PSA density

simulation the savings from the 4K score were not as great as with SelectMDx (discussed below).⁵⁷

Urinary markers

Because prostatic excretions mix with the urine when the ejaculatory duct joins the urethra, and cancer cells are expelled in this fashion as well, urine is a viable method of prostate cancer detection.⁹

Prostate cancer antigen 3 (PCA3)

PCA3 is also known as differential display code 3 (DD3) is a non-coding ribonucleic acid (RNA) which is overexpressed in prostate cancer cells.⁵⁸ In clinical practice, it is typically presented as a PCA3 score which is calculated by dividing the PCA3 by the PSA and multiplying by 1,000.^{59,60} It has been clinically approved by the FDA since 2012 and has primarily been utilized to help determine which patients should undergo repeat biopsy after an initial biopsy revealed benign disease in the setting of an elevated PSA.^{59,60} However, some studies have found that if it was included in the screening portion of prostate cancer detection it could potentially reduce the number of biopsies by 55% while only causing $\leq 2\%$ of clinically significant cancers to be missed.⁶¹ The ideal cutoff for the score is still under debate with values of 20, 35, and 50 having been recommended by various authors.⁹

ExoDX prostate intelligiscore

ExoDX is commercially available and works by detecting three genes (ERG, PCA3, and SAM Pointed Domain ETS Transcription Factor (SPDEF)) in the urinary exosomes.^{62,63} This has been found to outperform PSA and a sensitivity of 75% and specificity of 54% has been demonstrated.⁶² Because SPDEF may correlate

with aggressive cancers, it has also been found to be of benefit when looking for only clinically significant cancers, having a sensitivity of 95% and specificity of 50% in this cohort.⁶² Some have suggested that utilization of this technique could reduce the number of biopsies by 27%.⁶³ ExoDX was found to provide cost savings as compared to PSA in one simulation, and these savings were greater than PHI and the 4K score provided.⁵⁷

SelectMDx

SelectMDx is another commercially available tool which works based on messenger RNA detection of homeobox C6 (HOXC6) and Distal-less homeobox 1 (DLX1) in urine.⁶⁴ This tool appears to excel at detecting clinically significant cancers with one study showing a sensitivity of 91%, specificity of 36%, and negative predictive value (NPV) of 93% in this setting.⁶⁵ When evaluated in four European countries, SelectMDx was found to result in healthcare savings as compared to standard of care PSA and biopsy.⁶⁶

Other urinary proteins

Various other proteins including TMPRSS2-ERG and second chromosome locus associated with prostate 1 (SchLAP1) have been implicated in the pathogenesis of prostate cancer and evaluated for their value as screening or prognostic tools.^{67–69} However, they are not currently frequently utilized and thus not likely to be of significant use to most Interventional Radiologists.

OTHER USEFUL TOOLS

Family history

A family history of prostate cancer has clearly been shown to increase an individual's risk of developing the disease. One study found that if males had a father or brother diagnosed with prostate cancer they are two to three times more likely of being diagnosed and nearly nine times more likely if they have both a father and a brother with prostate cancer.^{70,71} Whether or not having a family history of prostate cancer predisposes males to aggressive forms of the disease is less clear. Brandt et al found that males with a brother or father who died of prostate cancer were twice as likely to succumb to the disease as those who did not.⁷² However, in a recent structured review, Telang et al did not find any evidence to suggest that family history of the disease was an important factor in determining who was and was not appropriate for active surveillance.⁷³

There are a number of genes that are linked to prostate cancer including BRCA1, BRCA2, ATM, CHECK2, PALB2, MLH1, MSH2, MSH6, and PMS2(74). These can be tested by drawing blood or using a saliva swab. Given the high incidence for tumors associated with these genes, genetic testing counseling is recommended in patients with a family history of prostate cancer, high-risk or very-high-risk localized prostate cancer, regional or metastatic prostate cancer regardless of family history, Ashkenazi Jewish ancestry or intraductal cancer demonstrated on biopsy.⁷⁴

Digital rectal examination (DRE)

Although of historic importance, DRE is not routinely performed in current practice for screening purposes. Sensitivity and specificity of the exam was reported to be barely above randomness with a positive predictive value (PPV) of

41%.⁷⁵ In general, when recommended, screening should be done with the PSA with or without DRE.^{76,77} The shortcomings of this exam are attributable to the subjectivity, experience of the operators and the fact that T1 tumors are, by definition, not palpable. However, DRE in conjunction with the patient history could be a useful inexpensive tool to diagnose prostatitis. Given that in general Interventional Radiologists do not receive formal training in DRE the overall recommendation is to refer the exam to an expert when it cannot be avoided. This is one more reason to build a collegial environment with an urologist, especially in the beginning, is of high value and conducive to providing the best possible care to patients.

Multiparametric MRI (mpMRI)

A complete review of the available imaging is beyond the scope of this paper, however as it interlaces closely with the serum marker interpretation and because this technology is slowly becoming part of the work-up it's included here. However, its use as a triage test has been debated and is still controversial.⁷⁸ As discussed above, a work-up based only on serologic markers is subject to significant limitations. The core of mpMRI relies on standard T1, T2, diffusion-weighted (DWI) and apparent diffusion coefficient (ADC) maps, in addition to dynamic contrast enhancement sequences and can be associated with several experimental sequences.⁷⁹ The positive predictive value is up to 98%.⁸⁰

The main limitations include its costs, the variability between MRI equipment, the use of surface versus endorectal coils, the size and grade of the lesion and the experience of the reader.

Risk calculators

A recent systematic review identified greater than 125 described risk calculators for prostate cancer.^{81,82} However, only a few of these have been validated outside of the initial studies.⁶³ When comparing different risk calculators head-to-head, a recent publication found that incorporation of prostate volume increased the prediction of clinically significant prostate cancers.⁸³ This study compared ERSPC RPCRC, Finne, Chun, ProstataClass, Karakiewicz, Sunnybrook, and PCPT 2.0 (HG) risk calculators and failed to show significant differences among them when evaluating for the presence of all prostate cancers.⁸³ However, the ERSPC RPCRC did perform the best in the setting of predicting clinically significant prostate cancers; by utilizing a biopsy cutoff of 4%, 32% of biopsies could be avoided, while maintaining 95% sensitivity for detecting clinically significant prostate cancers.⁸³

Importance to interventional radiologist

PAE continues to establish itself as a viable treatment option for BPH-induced LUTS.⁴⁻⁷ Due to the possibility of prostate cancer occurring in patients with BPH-induced LUTS, it is clinically relevant to Interventional Radiologists treating this population to be aware of the screening tools for this disease and how to advise patients. It is important to understand the USPTF

guidelines published in 2017 that recommended against routine screening for prostate cancer in males older than 70 with PSA and recommended screening younger males 55–69 with PSA on a case by-case basis.^{9,16,17} The Interventionalist should be aware that the AUA differ slightly in their recommendations and they suggest routine screening in the 55–69 age group after informed discussion.⁹ However, these guidelines are for patients without symptoms of BPH and the AUA continues to recommend PSA be utilized in the work-up of males presenting with BPH-induced LUTS²⁰ while the EAU only recommends the addition of PSA to the work-up of BPH-induced LUTS if it would be of clinical impact.¹⁹

In practice, most patients referred for consideration of PAE will likely have a PSA and many will be elevated, leaving the Interventionalist with a diagnostic challenge. The differential diagnosis often narrows down to BPH versus prostate cancer, however, other conditions should be excluded by collecting a thorough history and when necessary a physical examination. While the easiest answer in these situations is to simply refer for biopsy if the PSA is ≥ 4 ng ml⁻¹, this will expose the majority of these patients to an uncomfortable test which may not provide clinically useful information. In these settings, the authors would suggest considering one of the markers or algorithms discussed above to help risk stratify the patient and allow to reduce the amount of biopsy when they are not necessary. The algorithm used by the authors to decide whether or not to get a PSA is presented in Figure 1, while Figure 2 describes our suggested algorithm for how to interpret or handle a PSA.

Additionally, the authors would like to point out that knowledge of these basic tests is important to the interventionalist for another reason as well, namely interaction with Urologist. If the Interventional Radiologist wishes to provide good clinical care to the BPH-induced LUTS patient cohort, it is important that they have an understanding of these tests, as discussed above, but this knowledge also allows their Urology colleagues to recognize that they are well informed and therefore able to provide full clinical care to patients. However, as stated several times, this knowledge should not be gained in an attempt to remove Urologist from the work-up and treatment of these patients, as they continue to have valuable input to provide.

CONCLUSIONS

Being able to interpret PSA levels require knowledge and experience. PSA is a sensitive screening test but not specific to prostate cancer. Quite often Interventional Radiologists will face a situation of having a patient with PSA in the gray zone of 4–10 ng ml⁻¹. Using additional serum or urine biomarkers, prostate cancer risk calculators, cross-sectional imaging (CT or MRI), and/or algorithms will empower Interventional Radiologist to stratify patients with elevated PSA and reduce the number of patients that require biopsy. It is always appropriate to establish a collegial relationship with the urologist, especially at the beginning.

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