Screening and Detection of Prostate Cancer—Review of Literature and Current Perspective

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Abstract Screening of prostatic cancer is a matter of debate among uro-oncologist. With many new screening modalities like prostatic health index (PHI), 4K testing the role of screening has increased as one is able to stratify patients with serum prostate specific antigen level in a grey zone of 4–10 ng/ml and normal digital rectal examination into various risk groups, thus avoiding unnecessary biopsy which was the pitfalls of routine screening practice. PHI is better at predicting malignancy while 4K is better at predicting high-grade disease. This in combination with multiparametric MRI especially with prostate imaging reporting and data system score has made screening less difficult and more meaningful for a practising uro-oncologist.

Keywords Screening · Prostate cancer · Newer screening modalities · PIRADS

Introduction

Among urologic cancers, the screening and detection of prostate cancer have always been a contentious issue. It has been a matter of debate among the medical professionals regarding

the actual benefit versus the cost effectiveness of screening this disease. Moreover, a few recent introductions in the diagnostic testing of prostate cancer may have the potential to alter current guidelines. As the medical community is divided on this issue, in this article we have reviewed the available investigations and given a current perspective on it.

Methods

Literature search done using PUBMED and Google scholar using terms “newer advances in prostate screening”, “transcriptomics in prostate cancer”, “proteomics in prostate cancer” and “metabolomics in prostate cancer” was used. Articles primarily after 2010 and other important studies prior to it were selected and reviewed here.

Traditional Screening Methods, What Is New?

Digital Rectal Examination

It has been a part of standard screening and is currently recommended by most professional societies that a health care giver should at least do digital rectal examination (DRE). DRE (sensitivity, specificity, PPV—81, 40 and 42%) can independently detect patients at risk of prostate cancer, and if detected by DRE, one should consider the possibility of clinically significant disease irrespective of serum prostate specific antigen (Sr. PSA) [1]. Cancer detection rates when Sr. PSA is between 2.5 and 4 ng/ml are 20% [2]. Also, patients with abnormal DRE tend to have more disease burden and aggressive disease [3].

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Prostate-Specific Antigen

Since its description as a screening test in 1991 by Catolona [4], Sr. PSA and its derivative's use in screening have long been debated.

Currently, a Sr. PSA cut value of 4 ng/ml seems to be followed widely. However, the chances of having cancer below this value are around 15% [5]. The chances of cancer with a PSA value of 4 to 10 are 22–25% and above 10 are 50–67% [4, 6].

Various authors have suggested using total PSA and its various modifications like free:total PSA ratio (F/T ratio), PSA density (PSAD), PSA velocity (PSAV) and complex PSA (cPSA) in improving the prostatic cancer detection. Patients who had initial PSA <4 ng/ml an increase in PSA level over time are associated with increased risk of prostate cancer but were not associated with more aggressive tumours. Among all derivatives, complex PSA between 2.6 and 4 has better sensitivity and specificity compared to all other PSA subtypes [7, 8].

Free to Total Ratio

PSA in serum is in two forms, free and complexed forms to serum proteins like alpha1 antichymotripsin, alpha2 macroglobulin and alpha1 protease inhibitor. The free component is about 5–35% of total PSA [9–11]. It has been found that the PSA produced by cancer cells escape degradation and hence occur in complexed form in serum; thus, when Sr. PSA is between 4 and 10 ng/ml and free to total PSA ratio (F/T ratio) is less than 25%, one should strongly suspect malignancy of prostate, thus avoiding up to 20% of unnecessary prostate biopsies [12].

PSA Density

The ratio of Sr. PSA and the volume of the prostate gland are called the PSA density [13]. A cut-off value of 0.15 or greater is used when Sr. PSA is between 4 and 10 ng/ml to guide a clinician in performing a prostate biopsy [14, 15]. Use of other derivatives like PSA transitional zone density (more sensitive and specific than PSAD) [16] and complexed PSAD has been described [17]. It has a greater role in determining aggressive nature of the tumour [18, 19]. It is also useful in distinguishing benign prostatic hyperplasia (BPH) from prostate cancer [20]. Though intra-observer variability exists in measuring prostate volume, it does not affect the measurement of PSAD [21].

PSA Velocity

It is the rate of change of Sr. PSA which is corrected for elapsed time between measurements. A value of more than 0.75 µg/l/year is useful in stratifying patient who would

require a biopsy especially when the Sr. PSA is within the grey zone of 4–10 ng/ml [22]. However, it has a greater role in follow-up of patients in active surveillance as well as in patients who have undergone radical prostatectomy or radiotherapy [23–25].

Prostate Cancer Antigen 3

Prostate cancer antigen 3 (PCA3) is a gene that expresses a non-coding RNA. PCA3 is only expressed in human prostate tissue, and the gene is highly over expressed in prostate cancer. Because of its restricted expression profile, the PCA3 RNA is useful as a tumour marker. Urinary PCA3 has been evaluated as a diagnostic tool for prostatic cancer. In a meta-analysis involving 13 trials, the sensitivity and specificity of urinary PCA3 were reported as 62 and 75%, respectively [26]. Its use has been validated in various countries in different races [27–29]. PCA3 is useful in predicting a positive biopsy when Sr. PSA is between 4 and 10 ng/ml and more useful in combination with PSAD [28, 29].

There is a controversy on the cut-off value of urinary PCA3. Some studies have established urinary PCA3 at 35 as a cut-off [29–31]. At cut-off of 35, PCA3 as a second-line biomarker had potential to avoid 65.7 and 50.1% biopsies at first round and at median FU of 10.1 months, respectively, missing only 3.2% of high-grade prostate cancer [27]. At cut-off value of 20, urine PCA3 is predicted to have better sensitivity (95.4%) and negative predictive value (97.5%) for this test [32]. At cut-off 35 PCA3 in urine avoided more biopsies but missed 28% of prostate cancer [33]. Nevertheless, the clinical practice till date has been to use the cut-off at 35. The use of PCA3 has been advised against in BRCA mutation carriers as many patients have elevated PCA3 in the absence of prostatic cancer [34].

Prostatic Health Index

Prostatic health index is calculated using the following formula: $([-2] \text{ proPSA/free PSA}) \times \sqrt{\text{PSA}}$ where the various forms of PSA are used. Its usefulness in various clinical studies is affirmative. At various cut-offs of Sr. PSA, prostatic health index (PHI) had a better AUC when compared to other forms of Sr. PSA (Fig. 1) [35, 36]. In comparison with Sr. PSA (AUC, 0.525) and its other derivatives (%fPSA (AUC, 0.648), fPSA (AUC, 0.615), p2PSA (AUC, 0.557)), PHI was found to have an AUC of 0.703 and it directly correlates with Gleason scores ($p = 0.013$) and has an AUC of 0.724 for Gleason score (GS) $\geq 4 + 3$ disease, thus having a greater predictive accuracy [35]. It not only increases the rate of prostatic cancer detection but also improves in predicting high-grade and clinically aggressive prostatic tumours [35, 37–39]. When cut-off of 25.5 is used for PHI in patients with Sr. PSA between 2.5 and 10 ng/ml, 17.2% biopsies could have

Fig. 1 Receiver operating curves for prostatic health index [35]

been avoided, only 3.8% cancers with a GS of 7 would have been missed and about 26% of unnecessary biopsy can be avoided [40]. Catalona et al. suggested a physician could recommend biopsy for a patient with a PHI ≥ 55.0 (risk = 52.1%) and surveillance for certain groups with a PHI < 25.0 (risk = 11.0%) [41]. Also, studies have shown that PHI has better correlation with the Gleason score in comparison with PCA3 or TMPRSS2:ERG [41]

OPKO 4K Test

OPKO 4K test involves the measurement of four kallikreins namely tPSA, fPSA, iPSA and hk2 (total PSA, free PSA, intact PSA and human kallikrein 2) in serum and used in nomogram with DRE, prior biopsies and age to get a probability score for prostate cancer. It was used in serum from ERSCP patients who underwent prostatectomies and seemed to predict aggressive disease [42]. OPKO 4K test has an AUC of 0.84 for prediction of aggressive prostatic cancer—pT3–T4, extracapsular extension, tumour volume $> 0.5 \text{ cm}^3$ or any Gleason grade ≥ 4 [42]. Parekh et al. predicted a possible reduction of 30–58% in the number of biopsies and a delay in diagnosis in only 1.3–4.7% of Gleason ≥ 7 prostate cancer

cases using 4K test with a cut-off of 7.5%; however, it depends on the threshold used for biopsy [43].

In a study done on Stockholm county subjects, a comparison between PHI, 4K test and Sr. PSA was done. The 4K tests had AUCs of 69.0 while predicting prostate cancer of any grade and 71.8 while predicting prostate cancer of Gleason score ≥ 7 . Meanwhile, PHI had an AUC of 70.4 for any prostate cancer and 71.1 for high-grade prostate cancer of GS > 7 . Both had higher AUCs in comparison with Sr. PSA value and age ($p < 0.0001$ for both). However, this difference in AUC between 4K test and PHI was not significant. The limitation of this study though is that no DRE information is available [44].

In summary, it is clear that when Sr. PSA is used for screening of prostate cancer, one can wait till the value is less than 4 ng/ml. The real problem arises when the value is in the “grey zone” between 4 and 10 ng/ml when till now, various derivatives like PSAD, complex PSA and PSAV have been used as discussed earlier. But with an emerging test like 4K and PHI which have better predictive accuracy than those, a significant number of unwanted biopsies can be avoided. It appears from the emerging evidence that PHI is better in just predicting the risk of having prostate cancer, while 4K Score test is better in predicting the risk of having high-risk prostate cancer. These tests in combination may provide a better idea of long-term

risk of aggressive prostate cancer in men especially in patients of low-grade tumours on active surveillance.

Radiology—What Is New?

Multiparametric MRI and PIRADS Score

Multiparametric MRI in prostatic cancer is used in both detecting and staging of prostatic cancer. It includes a combination of high-resolution T2-weighted images (T2WI) to assess anatomy and diffusion-weighted imaging (DWI) and MR spectroscopic imaging (MRSI) which is highly specific in characterising lesions [45, 46]. Dynamic contrast-enhanced MRI (DCE-MRI) has a high sensitivity in cancer detection [47–49].

DCE-MRI, DWI and T2WI are accurate in detecting tumours $>0.5 \text{ cm}^3$ volume [49, 50], while MRSI and T2WI are useful in both excluding and detecting high-grade cancers $>0.5 \text{ cm}^3$ (sensitivity 93%, NPV 98%) [51, 52]. Various “acquisition protocols” are used in multiparametric MRI, which include detection protocols, staging protocols, and node and bone protocols.

Multiparametric MRI can be helpful in the management of the following:

Low risk patients:

- For stratifying patients towards active surveillance by detecting adverse prognostic features such as tumour volume and higher grade tumours, particularly in the anterior and apical lesions.
- Confirming the absence of significant intra-prostatic disease.
- Multiparametric MRI can be used to facilitate nerve sparing surgery.
- Focussed radiotherapy.

In intermediate risk group:

- To detect minimal extracapsular disease.

In high risk patients:-

- MRI to detect skeletal or nodal metastases is recommended [53].

In TRUS biopsy is negative but persistently high serum PSA:

Multiparametric MRI using the “detection protocol” can be applied before further TRUS-guided biopsy for superior results [54–57].

MRI Fusion Technology

Fusion technology using multiparametric MRI and real time ultrasound helps in identifying more clinically significant

cancers than the conventional biopsy. Fusion biopsy is 2–3 times more sensitive and allows us to both target suspicious lesions and also during follow-up in active surveillance [30, 58]. Recent advances include MRI–MRI fusion technology and cognitive fusion technology [30].

PIRADS

PIRADS stands for prostate imaging reporting and data systems was proposed by the European Society of Urogenital Radiology (ESUR) in the year 2012 [53]. Multiparametric MRI lesions are scored for better risk stratification of prostatic cancer. In this scoring system, every parameter T2WI (peripheral zone (PZ) and transition zone (TZ) different descriptions), DWI, DCE-MRI and MRSI is scored on a five-point scale. Then, an overall score given to each lesion can predict a clinically significant lesion. A score is given according to each variable. The problems with PIRADS scoring system is that there is no consensus on how to come to a final score based on the individual criteria under each imaging modality.

PIRADS version 2.0 has been proposed which instead of giving a 15-point score gives, a 5-point score is taking dominant sequence into consideration using different modalities. In the peripheral zone, the dominant sequence is diffusion-weighted MRI, whereas in the transition zone, the dominant sequence is T2-weighted MRI. MR spectroscopy has been removed. DCE types have been reduced to positive and negative and only play a role in score 3 lesions in the peripheral zone wherein a positive DCE-MRI could increase the score from 3 to 4 for that lesion [59]. This is still under investigation.

PIRADS 2.0 Score Parameters [59]

T2-Weighted Imaging

Peripheral zone

1. Uniform high signal intensity (SI)
2. Linear or wedge-shaped hypo intensity or diffuse mild hypo intensity, usually indistinct margin
3. Heterogeneous signal intensity or non-circumscribed, rounded and moderate hypo intensity; includes others that do not qualify as 2, 4 or 5
4. Circumscribed, homogenous moderately hypo intense focus or mass confined to prostate and $<1.5 \text{ cm}$ in the greatest dimension
5. Same as 4 but $\geq 1.5 \text{ cm}$ in the greatest dimension or definite extra prostatic extension/invasive behaviour

Transition zone

1. Homogenous intermediate signal intensity

2. Circumscribed hypo intense or heterogeneous encapsulated nodule(s) (BPH)
3. Heterogeneous signal intensity with obscured margins. Includes others that do not qualify as 2, 4 or 5
4. Lenticular or non-circumscribed, homogenous moderately hypo intense and <1.5 cm in the greatest dimension
5. Same as 4 but ≥ 1.5 cm in the greatest dimension or definite extra prostatic extension/invasive behaviour

Diffusion-weighted imaging

1. No abnormality and ADC—apparent diffusion coefficient and high b value DWI
2. Indistinct hypo intense on ADC
3. Focal mildly/moderately hypo intense on ADC and isointense/mildly hyper intense on high b value DWI
4. Focal markedly hypo intense on ADC hyper intense on high b value DWI; <1.5 cm in the greatest dimension
5. Same as 4 but ≥ 1.5 cm in the greatest dimension or definite extra prostatic extension/invasive behaviour

Dynamic contrast enhancement

- Negative: no early enhancement or diffuse enhancement not corresponding to a focal finding on T2 and/or DWI or focal enhancement corresponding to a lesion demonstrating features of BPH on T2
- Positive: focal and earlier than or contemporaneously with enhancement of adjacent normal prostatic tissues and corresponds to suspicious finding on T2 and/or DWI

MR spectroscopy

Currently, MR spectroscopy is not included in PIRADS scoring.

A score is given according to each variable. The scale is based on a score from 1 to 5 (which is given for each lesion), with 1

being most probably benign and 5 being highly suspicious of malignancy (Tables 1 and 2):

- PIRADS 1: very low (clinically significant cancer is highly unlikely to be present)
- PIRADS 2: low (clinically significant cancer is unlikely to be present)
- PIRADS 3: intermediate (the presence of clinically significant cancer is equivocal)
- PIRADS 4: high (clinically significant cancer is likely to be present)
- PIRADS 5: very high (clinically significant cancer is highly likely to be present)

HistoScanning™

HistoScanning™ is an ultrasound-based technology in which the ultrasonic raw data is processed mathematically by the PHS technology, which is built on characterisation algorithms of patterns specific to non-malignant and malignant tissues. A volumetric tool is used to provide fine measurement of total prostate volume and total tumour lesion volume. The initial studies were promising [60, 61]; however, recent reports have questioned its credibility [62].

Elastography

The principle behind this technique is that the tissues differ in stiffness between the normal and prostatic cancer tissues. Strain elastography (SE) and shear-wave elastography (SWE) are two techniques used now. Studies have shown that the elastography targeted approach detects high-risk prostate cancer more reliably than sextant biopsy, requires a reduced number of cores for prostate cancer detection and enhances the overall sensitivity in the combined biopsy setting [63]. It can also be used in prior radical

Table 1 PIRADS 2.0 for peripheral zone (adapted from Turkbey et al.) [59]

DW MRI	T2W MRI	DCE-MRI	Overall PIRADS
1	Any ^a	Any	1
2	Any	Any	2
3	Any	—	3
		+	4
4	Any	Any	4
5	Any	Any	5

DW MRI diffusion-weighted magnetic resonance imaging, *T2W MRI* T2-weighted magnetic resonance imaging, *DCE-MRI* dynamic contrast-enhanced magnetic imaging, *PIRADS* prostate imaging reporting and data system

^a Any indicates a score of 1–5

Table 2 PIRADS 2.0 for transitional zone (adapted from Turkbey et al.) [59]

T2 W MRI	DW MRI	DCE-MRI	Overall PIRADS
1	Any ^a	Any	1
2	Any	Any	2
3	≤ 4	Any	3
	5	Any	4
4	Any	Any	4
5	Any	Any	5

T2W MRI T2-weighted magnetic resonance imaging, *DW MRI* diffusion-weighted magnetic resonance imaging, *DCE-MRI* dynamic contrast-enhanced magnetic imaging, *PIRADS* prostate imaging reporting and data system

^a Any indicates a score of 1–5

prostatectomy for index tumour localisation, measurement of tumour burden and local staging of the tumour. However, this has not proven superior to multiparametric MRI for the above use and further studies are needed.

Biomarkers Screening for Prostatic Cancer

Biomarkers help us in understanding a disease process, to develop various diagnostic and therapeutic modalities. MicroRNA (miRNA) are important components of gene expression and are particularly significantly active in cancer cells [64]. miRNA can be detected in both urine and blood samples. The aberrant miRNA produced by prostatic cancer can be used as biomarkers in identifying risk groups who require prostatic biopsy and also help us in developing molecule-based therapeutics [65–67]. miRNA 141 level use is promising [64].

The combination of TMPRSS2-ERG with PCA3 and serum PSA data has attained a specificity of 90% and sensitivity of 80% [68]. Other miRNA biomarkers include alpha-methyl acyl coenzyme A racemase (AMACR) detection in urine PSA.

Other biomarkers include proteomic profiling of other kallikrein markers [69], metabolic biomarkers like tissue choline [70–72], urinary sarcosine [73] and genetic profiling [74], and many others have been studied; none of which has now reached clinical use.

Conclusion

In the present era, with the development of newer biomarkers, indices and risk assessment tools, it is apt to classify patients into different risk groups considering their life expectancy, prior subjecting them to diagnostic testing. Radiological investigations help in guiding clinician in deciding the need for a biopsy. However, the parameters to define these risk groups are yet to be elucidated and studies should be targeted in establishing this in order to overcome the problems of routine screening like over diagnosis and over detection. One should refrain from using one size fits for all approach [75].

The PSA test as it stands now is still going to be the first line investigation. When values of PSA are in the grey zone, the PHI test and 4K tests may be used to decide on biopsies or in the setting of repeat biopsies. The role of MP MRI is still evolving and has the potential to be used both as a first line tool and in the repeat biopsy setting.

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