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Current Diagnostics for Prostate Cancer

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Abstract: How prostate cancer is diagnosed and staged is an ever-evolving field. It plays a fundamental role in ensuring the appropriate therapeutic options are offered to the patient whilst preventing overdiagnosis and overtreatment. Despite the numerous advances in the field, a suspicion of prostate cancer continues to arise from digital rectal examination and measurement of serum prostate specific antigen (PSA). Additional derivatives of serum PSA along with urinary biomarkers and multiparametric magnetic resonance imaging can then help to risk stratify patients in order to appropriately counsel them on the risks and benefits of a prostate biopsy. After a diagnosis of prostate cancer is reached, further staging may be required and can be achieved by a variety of imaging techniques such as computed tomography (CT), bone scintigraphy, and prostate specific membrane antigen-based positron-emission tomography/CT. In this chapter, we review the current role of these and other diagnostic tools in prostate cancer.

Keywords: diagnosis; imaging; prostate biopsy; prostate cancer gene 3; prostate-specific antigen

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INTRODUCTION

Diagnostic tools for prostate cancer have undergone significant advancements in recent years to improve the accuracy of prostate cancer detection and avoid over-diagnosis and subsequent overtreatment. Despite this, a suspicion of prostate cancer continues to arise from a raised serum prostate specific antigen (PSA) level, and/or a digital rectal examination (DRE). However, an elevated PSA alone should no longer necessitate a prostate biopsy. The use of diagnostic adjuncts can help to predict the presence of clinically significant prostate cancer thereby avoiding unnecessary biopsies in a proportion of patients.

DIGITAL RECTAL EXAMINATION (DRE)

DRE can be used as an inexpensive diagnostic tool to check the prostate for cancer and to give an assessment of the prostate volume. It has the ability to detect prostate cancer with a volume of >0.2ml, if situated in the posterior peripheral zone, and can be used to raise suspicion irrespective of PSA. However, there is a high degree of interobserver variability, and a normal DRE does not eliminate the risk of a significant prostate cancer (1). An historical prospective multicenter trial found 18% of prostate cancers were detected solely by DRE (2), nowadays this figure is thought to be less. Nevertheless, an abnormal DRE is an indication for a prostate biopsy irrespective of the PSA.

PROSTATE-SPECIFIC ANTIGEN (PSA)

PSA is, broadly speaking, an organ-specific glycoprotein secreted by the prostatic epithelium which may be elevated in a variety of conditions, both benign and malignant. Higher levels of PSA indicate a greater likelihood of prostate cancer. A PSA cut-off of ≤4ng/ml was originally proposed as a normal level in men aged 50–70 years. However, analysis of men with a PSA level of ≤4.0ng/ml in the Prostate Cancer Prevention Trial (PCPT) found 15% had clinically significant prostate cancer (3). Therefore, the ability to detect prostate cancer at any PSA level means that no cut-off thresholds for PSA can be used with absolute confidence. Furthermore, a single elevated PSA reading cannot be relied upon due to normal biological fluctuations. A population-based study found that 30% of men with an abnormal PSA had a return to normal PSA on their next reading (4). This highlights the importance of obtaining a confirmatory PSA reading a few weeks after the first reading. The unreliability of PSA means instead the urologist must take into consideration additional factors to determine if the patient should proceed to biopsy, which may include PSA derivatives.

Age-adjusted PSA

Serum PSA readings do not account for the normal age-related PSA changes. The Olmstead county population study demonstrated that serum PSA increases with

TABLE 1 **Recommended age specific serum PSA reference ranges (5)**

Age (years)	Serum PSA reference range ng/ml
40 – 49	0 – 2.5
50 – 59	0 – 3.5
60 – 69	0 – 4.5
70 – 79	0 – 6.5

age and recommended age-specific reference ranges (Table 1) (5). Therefore, if the decision to proceed to further diagnostic tests for prostate cancer is being based solely on a PSA reading, the patients age should be accounted for in order to appropriately counsel them and avoid an unnecessary biopsy.

PSA density

In addition to changes in PSA with age, the Olmstead county population study also demonstrated an increase in PSA with increasing prostate volume (5). To account for this, PSA density can be calculated as the total PSA divided by prostate volume. An increased PSA density is associated with a higher risk of prostate cancer, with a generally agreed cut off value of between 0.12–0.15 ng/ml/cc (6). A prospective multi-center study in patients undergoing an extended template biopsy has found PSA density to be more predictive than total PSA for detecting prostate cancer (7).

PSA kinetics

Changes in PSA over time can be assessed as PSA velocity (change in PSA over time, ng/ml/year) and PSA doubling time (number of months for the PSA to increase two-fold). Whilst PSA kinetics are useful for prognostic purposes after patients have received treatment, they currently have no role in the diagnostic setting (8).

Free and total PSA

Total PSA readings include the sum of all detectable forms of PSA, including PSA bound to protease inhibitors and free PSA. For reasons that are unclear, the percentage of free PSA has been demonstrated to be lower in patients with prostate cancer compared to those with benign disease (9). A multi-center prospective study evaluated men with a benign prostate gland on palpation and a total PSA level of 4 to 10 ng/ml. The study found the probability of prostate cancer in men aged 65 to 75 years was 55% when the free/total (f/t) PSA ratio was 0.1 and reduced to just 9% when the f/t PSA ratio was >0.25 (10). Therefore, in these select patients with a benign prostate gland and PSA of 4 to 10 ng/ml measuring

free PSA may help to avoid unnecessary imaging or biopsy; but it should be used cautiously as it can be affected by other factors including prostate volume and most patients' f/t PSA ratio falls between 0.1 and 0.25 (11).

ADDITIONAL SERUM TESTS

Additional assays are now commercially available measuring a panel of kallikreins. The use of these tests aims to reduce the number of unnecessary prostate biopsies.

Prostate health index

The prostate health index (Phi) test uses a formula to combine the results of total PSA, free PSA and [-2]proPSA ([-2]proPSA/free PSA x √tPSA). It has been shown to have greater specificity and sensitivity than any of its individual components (12). Furthermore, it has been demonstrated to improve the prediction of clinically significant prostate cancer (aggressive histopathology per Epstein criteria or ≥ Gleason 7) in men with a PSA between 4 and 10 ng/ml (13). The use of Phi has the potential to reduce unnecessary biopsies; however, it has not been widely adopted partly due to the pre-analytical stability of [-2]proPSA. For an accurate [-2]proPSA reading, it is recommended that the serum is separated within 3 hours of the sample being taken as the reading increases with clotting time (14).

Four kallikrein score

Similar to the Phi test, the 4 Kallikrein (4K) score has also been shown to be a predictor for prostate cancer which can be used to avoid unnecessary biopsies (15,16). It combines four kallikrein markers (total PSA, free PSA, intact PSA and kallikrein-like peptidase 2 [hK2]) with patient age, DRE findings and prior biopsy status. A direct comparison of the 4K score and Phi found both tests to be equally predictive of prostate cancer and clinically significant prostate cancer (17).

URINE TESTS

In addition to serum tests, several urinary biomarkers for prostate cancer have been described. These include urinary measurements of prostate cancer gene 3, TMPRSS2:ERG, and SelectMDX test.

Prostate cancer gene 3

Prostate cancer gene 3 (PCA3) is a prostate specific non-coding mRNA that is over expressed in prostate cancer and detectable in urine collected after prostatic massage (18). Initial investigations into the use of PCA3 were performed in men with a previous negative biopsy and persistently elevated PSA levels. These early

studies suggested that using a PCA3 cut off score of 35, the test had a sensitivity of 58% and specificity of 72% and was superior to PSA in predicting the biopsy outcome (19–21). However, the ability of the test to predict clinically significant prostate cancers found variable results. Fewer studies have evaluated the use of PCA3 to direct the need for an initial biopsy. One prospective multicenter study in men with a PSA between 2.5 and 10 ng/ml found a sensitivity of 64% and specificity of 76% and similarly found it superior to PSA in predicting biopsy outcome (22). However, further research is still required in the biopsy naïve patient to understand the use of PCA3 in this setting. Consequently, whilst initial research suggests that PCA3 may be useful in predicting the presence of prostate cancer, particularly in patients that have had a previous benign biopsy, it remains unclear whether it can be accurately used to detect clinically significant disease, what cut off levels should be used, and with the extra expense of performing the test, what clinical benefit it truly offers (23).

TRANSMEMBRANE SERINE PROTEASE 2:ERG

The *ERG* gene is a transcription factor of the ETS family which has been observed to be overexpressed in prostate cancer as a result of its fusion to the transmembrane protease serine 2 gene (*TMPRSS2*) (24). *TMPRSS2:ERG* fusion transcripts can be detected in urine with a sensitivity of 37% and specificity of 93% (25). Further studies have shown improved diagnostic ability when combined with the PCA3 test (Michigan-Prostate score [MiPS]) (26). However, this is still under investigation and it is likely that the discovery of *TMPRSS2:ERG* will have a bigger role as a potential therapeutic target than for diagnostics.

SelectMDX test

Similar to PCA3 and *TMPRSS2:ERG,* the SelectMDX test is based on the presence of mRNA biomarkers in urine namely *HOXC6* and *DLX1*. Combining the presence of these biomarkers with traditional clinical risk factors (PSA, PSA density, DRE, age, history of prostate biopsy and family history), the SelectMDX test has the ability to detect clinically significant prostate cancer (27). Further analysis has demonstrated that the use of SelectMDX may lead to a reduction in unnecessary biopsies and overtreatment (28). However, with the advent of prostate magnetic resonance imaging (MRI), a clear role for all these urinary biomarkers in prostate cancer diagnostics is uncertain. Future research will need to focus on how these biomarkers may be effectively integrated to avoid unnecessary and costly imaging.

IMAGING

The role of imaging in prostate cancer diagnostics is rapidly evolving and can be used to identify clinically significant prostate cancers and avoid unnecessary biopsies.

Transrectal ultrasound (TRUS)

Prostate cancer can appear as a hypoechoic lesion on conventional B-mode TRUS; however, this is a non-specific finding. A large prospective study found no significant difference in the detection of prostate cancer from biopsies of patients with or without hypoechoic lesions (25.5% versus 25.4%) (29). This indicates a hypoechoic lesion itself is not associated with an increase in cancer prevalence and B-mode TRUS alone is not diagnostic of prostate cancer. Nevertheless, it serves a vital purpose in identifying the prostate in order to perform biopsies.

Additional variations in ultrasound (US) imaging have also been assessed for their usefulness in diagnosing prostate cancer. Color doppler US (CDUS) measures blood flow and therefore has the potential to detect prostate cancer as a result of increased tumor vasculature. An early evaluation of CDUS found it was able to diagnose up to 70% of prostate cancers but generally performed better in high-grade disease and when used in combination with the conventional B-mode TRUS (30). However, a further study has shown the use of CDUS in targeted prostate biopsies did not improve prostate cancer detection rates when compared with standard TRUS (31). Contrast enhanced US (CEUS) uses microbubble contrast agents to detect increased microvasculature in the prostate. Its use in detecting prostate cancer has been shown to improve the sensitivity when compared to unenhanced CDUS (32). Sonoelastography is based on the principle that there are significant differences in the elastic properties of benign and malignant prostate tissue. The technique estimates the response of tissues under harmonic mechanical excitation using Doppler ultrasound to detect areas of abnormal stiffness (33). The initial study investigating its use found sonoelastography was able to detect 84.1% of prostate cancers (34).

Whilst each of these US techniques has shown promise in initial studies to improve the detection of prostate cancer, combined imaging is reported to offer the most benefit. Multiparametric US (mpUS) consisting of a combination of B-mode, sonoelastography and CEUS improved the sensitivity for clinically significant prostate cancer to 74% from 55%, 55% and 59%, respectively (35). Nevertheless, the use of US in prostate cancer diagnostics is unclear particularly with the recent evolving role of multiparametric-MRI (mp-MRI) which is more accurate than mpUS (36).

Micro-ultrasound is the only US technique that has shown promise in rivalling mp-MRI. Traditional TRUS operates at frequencies of 6–9 MHz whilst micro-ultrasound is a new modality that operates at 29 MHz. This improves image resolution by 300% allowing for the detection of subtle changes in ductal anatomy. Early results of this technique have demonstrated an improvement in the detection of clinically significant prostate cancer and that it may be able to detect lesions missed on multiparametric-MRI (mp-MRI) (37,38). Although further research is required to understand the exact role micro-ultrasound will have in prostate cancer diagnostics.

Multiparametric magnetic resonance imaging

The European Society of Urogenital Radiology recommends mp-MRI for the detection of prostate cancer should include a combination of high-resolution T2 weighted images and at least two functional MRI techniques; diffusion weighted

imaging (DWI) and dynamic contrast enhanced (DCE) imaging (39). Prostate cancer typically manifests as a round low signal intensity focus on T2-weighted MRI, high signal intensity on DWI at high b-values and classically demonstrates early enhancement on DCE-MRI. The Prostate Imaging-Reporting and Data System (PI-RADS) provides a structured way to report each lesion by allocating a score between 1 and 5 that predicts its chance of being a clinically significant prostate cancer; with 5 indicating a very high likelihood for the presence of clinically significant prostate cancer (40). A meta-analysis assessing the diagnostic accuracy of mp-MRI for prostate cancer found it to have high specificity and sensitivity, 88% and 74%, with a variable but high negative predictive value ranging from 65–94% (41). Furthermore, a comparison of pre-operative MRI to radical prostatectomy histopathology found prostate cancer detection rates increased with both tumor volume and increasing Gleason score (42). One of the main uses of mp-MRI is to identify a target to biopsy to improve the detection of clinically significant prostate cancers (43). This will be discussed further in the chapter along with its use in staging. In addition, a prebiopsy mp-MRI can also be used to avoid undertaking biopsies in patients with no visible lesions. The PROMIS trial found that using a mp-MRI and only performing a prostate biopsy on patients with PI-RADS lesions of ≥3 could have avoided a biopsy in 27% of patients (44).

RISK CALCULATORS

The use of risk calculators can help to combine diagnostic tests to predict an individual patients' risk of clinically significant prostate cancer and potentially reduce unnecessary investigations. One such validated risk calculator is that developed from the PCPT cohort. The PCPT predictive model was initially developed to combine the patients' age, race, family history, serum PSA, DRE and prior biopsy status to produce a risk score for having both low- and high-grade prostate cancer on a biopsy (45). Further developments now provide the option to include free PSA, urinary PCA3 and *TMPRSS2:ERC* into the PCPT calculator (46,47). Other risk calculators also include mp-MRI findings. A systematic review has identified that over 100 prediction models exist in the literature, although not all of these have been validated and currently no single model has shown superiority over another (48).

PROSTATE BIOPSY

The modern era of prostate biopsies began with the systematic sextant method in which initially 6 and subsequently 12 ultrasound guided biopsies were taken from 6 sites (apex, middle and base of each lobe) (49). Currently, TRUS guided prostate biopsy can be performed via either a transrectal or transperineal approach. A meta-analysis comparing the two biopsy approaches found the diagnostic accuracy to be comparable, however, the transperineal approach was associated with a lower risk of fever and rectal bleeding (50). Following the publication of the landmark PROMIS study, a prebiopsy mp-MRI is now the gold standard to perform

targeted biopsies (44). A subsequent Cochrane review found this approach increases the number of significant cancers detected while reducing the number of insignificant cancers diagnosed (43). Different methods for performing targeted biopsies of lesions identified on mp-MRI exist; direct in-bore targeted biopsy, fusion biopsy, and cognitive targeted biopsy.

Direct in-bore targeted biopsy

Direct in-bore MRI targeted biopsy in which the biopsies are performed in the MR scanner using real time MRI guidance. A prospective matched cohort study comparing this technique with a 10-core TRUS biopsy found a significantly improved correlation with histology at radical prostatectomy (88% versus 55%) (51). However, this is a labor intense and costly procedure, taking up 2–3 hours of scanning time. It requires administration of a general anesthetic with the patient in the scanner potentially creating difficulty with airway management.

MRI fusion biopsy

An MRI-transperineal or transrectal fusion target biopsy is where software is used to merge the MRI image of the prostate with the TRUS image in real time to accurately direct biopsies. Several different systems are available including Artemis, Biopsee and Koelis Trinity. The system records the site of biopsy confirming that the selected target has been sampled and is useful for future reference. This approach takes some extra time as the prostate and lesion requires contouring but is faster and less expensive than the direct in-bore biopsy technique. The main potential source of error is in the co-registration of the MRI and TRUS images. The prostate images are obtained in different positions; MRI in supine and TRUS either in the left lateral or lithotomy with the hips flexed which rotates the prostate within the pelvis. Image registration is either rigid or elastic. Rigid image registration overlays the MRI images onto the TRUS images without any adjustment for possible deformation during the procedure such as from patient movement. Whilst elastic registration does compensate for this deformation and, therefore, would be anticipated to be more accurate. However, a meta-analysis comparing rigid and elastic registration found no significant difference in the detection of clinically significant prostate cancer (52).

Cognitive targeted biopsy

Finally, cognitive targeted biopsy or visual registration are where the MRI images are reviewed by the urologist who then performs the biopsies, either via a transperineal or transrectal route, using TRUS guidance aiming to sample the general location of the suspicious lesion. This is the simplest, fastest, and cheapest method to perform MRI-targeted biopsies. However, the accuracy is highly dependent on operator experience and training requiring good knowledge of prostate zonal anatomy on both MRI and TRUS images. Furthermore, in cases of negative template biopsy for quality control there is no ability to check whether the target was sampled (53). Despite this, a comparison of cognitive targeted to systematic biopsies found no statistically significant difference in the detection

of clinically significant prostate cancer and found fewer insignificant cancers were detected (54).

What is the preferred biopsy approach?

There is clear evidence that MRI targeted biopsies improve the detection of clinically significant prostate cancer and results in fewer insignificant lesions being detected. So far studies have failed to demonstrate any of the different MRI targeting techniques described to be superior to another (55,56). Targeted biopsies can be taken via a transperineal or transrectal approach with the former having a reduced risk of sepsis (50). Other factors to consider when performing a biopsy include anesthetic and position. Biopsies can be performed under general or local anesthetic. The local anesthetic technique has been shown to have good patient tolerability without the associated risks of a general anesthetic and with reduced operative time and patient recovery (57). Furthermore, biopsies under local anesthetic can be performed in the lithotomy or left lateral decubitus position, with the latter associated with improved pain scores (58).

STAGING

Once a diagnosis of prostate cancer has been reached, the patient requires clinical staging in order to direct the appropriate treatment.

Multiparametric magnetic resonance imaging

In addition to directing the need for a prostate biopsy, mp-MRI can be used for local staging of prostate cancer. T2-weighted imaging can be used to look for extracapsular extension (ECE) (T3a), seminal vesicle invasion (SVI) (T3b) and invasion into other organs (T4). Pooled data from a meta-analysis has demonstrated mp-MRI has high specificity but poor sensitivity in detecting ECE, 91% and 57%, and SVI, 96% and 58%, respectively (59). The use of mp-MRI to assess the prostate for suspicious lesions also indirectly provides an assessment of nodal disease. However, similar to its use in local staging, mp-MRI has also been shown to have poor sensitivity for the detection of nodal disease. A meta-analysis found a pooled sensitivity of 39% and specificity of 82% with significant study heterogeneity (60). Accordingly, mp-MRI can therefore not be completely relied upon for local staging for the presence of lymph node metastases.

Computed tomography

The use of computed tomography (CT) in the detection of lymph node metastases has also been shown to be an unreliable method. Similar to mp-MRI, a meta-analysis found a good specificity at 82% but a poor sensitivity of 42% (60). The main drawback in the use of CT and mp-MRI to detect lymph node metastases is their reliance on nodal enlargement which is not always present (61).

Choline positron emission tomography CT

The use of choline positron emission tomography (PET) CT is based on high uptake of the radiotracer believed to be due to the increase in membrane phosphatidylcholine in cancer cells (62). Its use in prostate cancer diagnostics has largely been evaluated in its ability to detect lymph node metastases which has found variable results. However, its utilization in high-risk prostate cancer has demonstrated a significantly improved specificity and sensitivity suggesting it may be useful under these conditions for the detection of nodal metastases (63). Although, with the developments in ^{68}Gallium (^{68}Ga) labelled prostate specific membrane antigen (PSMA) PET-CT, it is unclear whether choline PET-CT will have a role in the future of prostate cancer diagnostics.

Bone scan

Bone metastases are most frequently looked for using a technetium Tc 99m methylene disphophonate (Tc 99m MDP) bone scan. PSA, Gleason score, and clinical stage are all significant predictors of bone metastases. It is suggested that a staging baseline bone scan should be performed in patients with intermediate (PSA 10–20 ng/ml or Gleason score 7 or cT2b) or high-risk prostate cancer (PSA >20ng/ml or Gleason score 8–10 or cT2c/3/4). By using these criteria, it was found that staging baseline bone scan could be avoided in approximately 81% of patients with a negative predictive value of 99.6% (64).

Prostate specific membrane antigen-based PET CT

^{68}Ga PSMA PET-CT shows great promise in improving prostate cancer diagnostics. PSMA is over-expressed on the cell membrane of nearly all prostate cancer cells with expression levels increasing according to the stage and grade of tumor (65). A meta-analysis comparing ^{68}Ga PSMA PET CT with MRI for the diagnosis of lymph node metastases in patients with intermediate or high-risk prostate cancer found ^{68}Ga PSMA PET CT to have a higher sensitivity (65% versus 41%) (66). A further meta-analysis has also demonstrated ^{68}Ga PSMA PET-CT to have the highest sensitivity and specificity for the diagnosis of bone metastases when compared with choline PET-CT, MRI, and bone scintigraphy (67). A recent multicenter randomized study also found ^{68}Ga PSMA PET-CT in men with high-risk prostate cancer (Gleason grade group 3–5, PSA ≥20 or clinical stage ≥T3) was superior to bone scan and CT, with a 92% accuracy. Importantly, this improved method of staging resulted in more frequent changes to the patients' management plan, and it therefore has the potential to offer the most appropriate first line therapy in addition to avoiding unnecessary treatment (68).

CONCLUSION

The integration of these diagnostic tools for prostate cancer enables the urologist to risk stratify patients and appropriately direct the diagnostic path. There have been significant improvements in the detection of clinically significant prostate

cancer in addition to preventing overdiagnosis as well as improvements in staging. However, further advances to improve the sensitivity of staging investigations and streamlining of the pathway are required to make this both clinically and cost-effective.

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