CHANGING STATUS OF INVESTIGATIONS FOR PROSTATE CANCER DETECTION

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Abstract

Before the introduction of serum prostate specific antigen for the early detection of prostate cancer, this condition was diagnosed at an advanced stage, with palliative androgen deprivation therapy the mainstay of management. Increasing use of prostate specific antigen testing has resulted in a significant stage shift from locally advanced/metastatic disease to early stage, lower volume prostate cancer. Prostate specific antigen testing provides the potential for life-threatening disease to be detected early enough for effective treatment. However, many asymptomatic men with low-risk prostate cancer have also had what were, in retrospect, unnecessary diagnostic procedures and treatments leading to management-related morbidity. This manuscript traces the changes that have occurred and are occurring to refine detection, with the integration of new technologies to uncouple diagnosis from management so that potentially curative treatment can be tailored to those who are most likely to benefit.

Clinical detection of prostate cancer is evolving at a rapid pace, with the levels of imprecision experienced until very recently in the process of being superseded. However, before considering any investigation, the basic question of whether a diagnosis of prostate cancer will benefit the patient should be addressed. Many men have co-morbidities, the gravity of which will lead to their premature demise and of which they are completely unaware. This poor appreciation of individual life expectancy is not just limited to patients, as many clinicians are overoptimistic and 'give patients the benefit of the doubt' when recommending investigations and treatments.[1] In addition, individual wishes with respect to quality of life should be respected,[2] in particular the importance some men place on sexual function, given the impact that all prostate cancer treatments can have on erectile ability and other bodily functions.

Because of the long natural history of prostate cancer, expectation of a 7-10 year life expectancy following treatment (and therefore, diagnosis) is considered warranted in terms of a survival. Consequently, many patients will not live long enough to achieve a survival benefit.[3-6] Life expectancy is certainly not the only consideration, but it is for survival reasons coupled with the acknowledged potential adverse effects of investigations and treatment, that selective, rather than mass population or opportunistic, prostate-specific antigen (PSA) screening is advocated.

Men proceeding for prostate cancer screening are assessed initially by total serum (PSA) testing with or without digital rectal examination (DRE), findings influencing a decision whether to proceed to biopsy for a histological diagnosis. As most prostate cancers detected are impalpable, transrectal ultrasound (TRUS) is employed to permit spatial positioning of, previously six (sextant) but now >10-12, random biopsy needles, as the majority of early prostate cancers are unable to be differentiated from non-cancerous tissue with grey-scale ultrasound imaging. Increasingly, the transperineal approach to biopsy is replacing the transrectal route since anterior lesions constitute up to 30% of malignancies and these can be missed with the transrectal approach, especially in larger prostates, identified as being greater than 30mL.[7,8]

Prostate-specific antigen

PSA is a member of the kallikrein family of proteases, with PSA (KLK3) protein present in seminal fluid and with very low levels normally in blood. Clinical use of PSA began in the 1980s, initially having been approved by the Food and Drug Administration in 1986 for monitoring of the disease status of prostate cancer patients. In 1994, it was endorsed for prostate cancer screening,[9] with this application having caused controversy largely because of false positive results for insignificant or non-life-threatening tumours. The PSA blood test is a continuous variable with no cut point.[10] As a result, very low levels do not

completely exclude prostate cancer, although the higher the serum PSA, the greater the likelihood of malignancy, particularly in the absence of clinical infection.[11]

Abnormal levels of PSA do not distinguish between cancer and non-cancer, or identify those patients with prostate cancer who will benefit from attempted curative treatment. An elevated serum PSA merely indicates an abnormality in the prostate, with most PSA increases not attributable to prostate cancer. Furthermore, for those in whom prostate cancer is detected, many have indolent disease that will not show evidence of clinical progression in the short to medium term.[12]

When identifying those likely to benefit from a prostate cancer diagnosis and therefore PSA testing, a family history, particularly in first-degree relatives, is well-recognised to predispose to a future diagnosis of prostate cancer, but a PSA >90th percentile for men <50 years is regarded as even more predictive than either family history or race.[13] Hereditary prostate cancers occur more commonly than any other tumour diagnosed, on average six years earlier than for sporadic cancer.[14] Those patients with a family history of germ-line mutations in the family-susceptibility genes BRCA1 and BRCA2, have a significantly increased susceptibility for developing this malignancy, tending to present at a younger age, have more aggressive disease and poorer survival outcomes.[15-19]

PSA is a labile enzyme that can be affected by a variety of factors. Recent ejaculation elevates serum PSA for up to 48 hours, with vigorous exercise, bacterial prostatic infection, recent instrumentation and benign prostatic hyperplasia also incriminated as causes for raised levels in sera. The prostate gland enlarges as men age, so that age-based reference ranges are provided by many laboratories.[20] Instrumentation of the prostate and urinary tract can also raise PSA levels.[21] Drugs that inhibit 5-ï-reductase activity result in a decrease in serum PSA, with both finasteride and dutasteride reducing PSA values by approximately 50%.[22,23] Once a nadir is reached by these drugs, which target the benign prostatic heperplasia component of prostatic enlargement, reducing its contribution to serum PSA levels, PSA becomes a more sensitive marker for prostate cancer. Marks et al reported a 71% sensitivity and a 60% specificity for prostate cancer detection for men receiving dutasteride, recommending that an increase in PSA of >0.3 ng/ml from nadir should be regarded as an indication for biopsy in these patients.[24]

Despite the introduction of variations to PSA (below), it is serum PSA itself that is used almost exclusively for triaging patients for further investigations.[25] Another important role that PSA serves is aiding patient reassurance, an aspect so often overlooked in critical assessments of clinical practice. A serum PSA <1 ng/mL in a man aged 60 years has been reported to indicate an extremely low risk of significant prostate cancer in his lifetime.[26,27] Although the likelihood of diagnosing prostate cancer is relatively low in men aged less than 55 years, a subgroup with PSA levels >95th percentile is particularly at risk of developing life-threatening prostate cancer,[13,25] and it is the 'young man cohort' under 65 years which is the one most likely to benefit from diagnosis (and treatment) because these men are more likely to live long enough.[28] An analysis of the Victorian Prostate Cancer database between 2001 and 2008 showed that, in keeping with the rest of Australia, 1/3rd of prostate cancers were detected in men aged less than 65 years and, among those detected in men aged less than 65 years, 76% were Gleason score less than or equal to 7.[29]

Variations on PSA

Attempts to improve the predictability of serum PSA for prostate cancer detection have included measuring the rate of PSA change or PSA velocity and the relationship of PSA level in serum to the size of the prostate or PSA density. In some cases this is extended to include measuring transition zone volume, the site of benign prostatic hyperplasia and a low likelihood of significant prostate cancer. Although serial serum PSA readings often rise and fall over a relatively short period, an increase in >0.75 ng/mL in a year has been equated to and is generally regarded as indicating an increased risk of prostate cancer.[9] However, because malignancy is only one cause of an elevation in PSA, this relationship is far from perfect.

Similarly, measurement of prostatic size by transrectal ultrasonography is less than accurate, although serial measurements may be helpful in managing patients on active surveillance for low-risk disease. Nevertheless, a PSA density >0.15 ng/mL per gram of prostate tissue is generally considered worrisome for prostate cancer. The free or unbound PSA in relation to total PSA level in serum is commonly measured with a higher free component related to a lower likelihood of prostate cancer. A free component of <9% is particularly associated with malignancy. Measurements of free or unbound PSA levels are considered more useful in younger men and those with PSA values between 4 and 10 ng/mL.[30]

More recently, the prostate health index has become available and promoted. This test, that stratifies patients into three groups indicating probability, is calculated by having the value of a truncated form of the PSA molecule (proPSA) as the numerator and the free PSA value as the dominator, multiplied by the total PSA level to give a prostate health index reading. In one study, for a PSA 2-10 ng/ml, sensitivity, specificity and AUC (0.703) of PHI exceeded those of total PSA and percentage free PSA. Increasing PHI was associated with an increased risk of prostate cancer.[31] It is reported to be better at predicting prostate cancer risk than total PSA,[32] particularly for obese men,[33] but its role in decision making has yet to be established in Australia and other countries.

Two publications from last year are also of particular interest, although not yet widely available for clinical use. Yoneyama et al reported that a prostate cancer-associated

aberrant glycosylation PSA assay in sera from 314 patients who underwent biopsy Dep(138 prostate cancer: 176 non-prostate cancer) with PSA of <10.0 ng/ml, provided a sensitivity of 95% with a specificity of 72%.[34] Secondly, Parekh et al measured 4 kallikrein proteins (total PSA, free PSA, intact PSA and human kallikrein 2) in blood from 1012 patients from 26 US centres prior to prostate biopsy-470 men (46%) were diagnosed with prostate cancer, 231 (23%) of whom had Gleason >7 lesions. The predictive accuracy of the 4Kscore showed a high level of discrimination in detecting Gleason >7 lesions, with an AUC of 0.82 with a sensitivity of 84% and a specificity of 75%.[35]

PCA3 Test

Multiple markers have been examined as indicators of prostate cancer, mostly in blood, urine or voided urine following firm DRE or prostatic massage. Of these, the 'PCA urine test' is best known.[36-41] This test analyses the first part of a specimen of voided urine after milking the prostate by firm digital rectal examination or prostatic massage to dislodge prostatic fluid and cells from the posterior part of the gland.[42] At the commonly used PCA3 score cut off of 35, the PCA3 test has been reported to improve detection of prostate cancer compared with PSA in a pre-screened population, but its role in initial assessment of patients suspected of having prostate cancer has yet to be established as a first-line, stand-alone investigation.[37,43] Addition of other RNA markers to the 'PCA3 urine test' such as the fusion gene TMPRSS2:ERG, has been reported in some, but not all cases, to improve prostate cancer prediction.[38-41,44,45] It is because of the limitations of PCA3 and other tests that Noviogendex and DDL Diagnostic Laboratory (the Netherlands) are developing a 4-gene panel (Quattro) commercially around PCA3 mRNA.

Multi-parametric MRI

Following the initial work of Zerbib and colleagues in 2005,[46] MRI techniques have been developed to fulfil an increasingly valuable role in identifying evasive anterior and other significant tumours that may be missed by 'blind' TRUS biopsies.[47] Diagnostic images are provided by T2 diffusion-weighted MRI (capitalising on the mobility of water affected by interaction with intracellular elements, macromolecules, cell membranes and microstructures with differences observed in several cancers) in T2-weighted images and early gadolinium blushing due to increased vascularity in tumours.[48]

The potential for multiparametric MRI (mpMRI) to increase detection and identify the site of significant cancers so that biopsies can be targeted, is being exploited increasingly in routine diagnostic approaches. A combination of anatomical (T2-weighted) images with at least two of the three functional MRI parameters (diffusion-weighted imaging, dynamic contrast-enhanced imaging and spectroscopy) has been estimated to identify approximately 90% of moderate to high risk lesions, although less reliable for detecting small (<0.5 cc) and lower risk tumours.[49,50] Using a structured scheme, prostate imaging-reporting and data system (PI-RADs),[51] PI-RADS 3 lesions are at intermediate risk of being malignant, PI-RADS 4 probably malignant and PI-RADS 5 highly suspicious of malignancy.[52] Although a small number of significant prostate cancers will be missed if only patients with PI-RADS 3-5 lesions are biopsied, over 80% of indolent/low risk tumour patients and the majority of those with a raised PSA who do not have cancer will be spared biopsies and its risks of adverse effects.

mpMRI is an expensive investigation requiring expert interpretation, so its benefits need to be maximised if it is to be used to triage all men suspected of harbouring significant prostate cancer. Since most patients with a raised PSA +/- an abnormal DRE will not have any detectable prostate cancer, let alone clinically significant prostate cancer, cost effectiveness, in addition to oncological and quality of life benefits, demand scrutiny. A recent study performed in the Netherlands assessed the cost-effectiveness of mpMRI and MR guided biopsy compared with TRUS biopsy. The authors concluded that the total costs of the MRI strategy were almost equal with those of standard of care, and that a reduction of over diagnosis and over treatment with the MRI strategy led to an improvement in quality of life.[53] These findings may not translate internationally, and a major concern with MR guided biopsy is the extra time in the MRI-suite with the potential to expand costs further in what is already an expensive diagnostic process. In some centres, information from business cases (without MR guided biopsy) has contributed to mpMRI being used routinely to stratify patients into those likely to have significant prostate cancer compared with those whose glands are unlikely to harbour a clinically-significant malignancy,[54] so PI-RADs mpMRI 1 and 2 patients do not routinely proceed to diagnostic biopsy.

With the rapid introduction of mpMRI into the diagnostic equation, a number of issues remain to be resolved. Among these is the risk of missing a clinically significant Gleason 7 or greater tumour by restricting biopsies in the first instance to PI-RADs 3-5 lesions, although current data suggest that this is <15% for normal PI-RADS 1 or 2 MRI. Another quandary needing to be addressed is which lesions to biopsy with the patient on the MRI machine. MRI in-gantry biopsy may improve the diagnostic accuracy in some small lesions, but is not required for most tumours identified on MRI, which usually can be targeted adequately by transperineal or TRUS techniques, especially with evolving MRI-TRUS fusion technology.

MRI-based imaging is becoming established as an essential part of the diagnostic strategy for prostate cancer. It is notable that most advances in mpMRI per se have been prostate-centric, as mpMRI alone fails to indicate regional and more distant spread of tumour. On complete removal of the gland (radical prostatectomy) however, approximately 40% of patients have extra-

prostatic extension in the surgical specimen and 25% show ongoing evidence of cancer activity via a rising serum PSA, indicating unidentifiable occult metastases.[54,55] MRI research to improve rates of detection, both within the gland and at the sites of metastases, is being pursued actively, with initiatives including examining potential new markers, field strength changes and sequence optimisation.[56,57]

Prostate-specific membrane antigen PET

Over the last few years, positron emission tomography (PET) has begun to be used to identify metastases. PET imaging reflects function/dysfunction, thus adding a further dimension to imaging when superimposed on to CT and MR images. Many PET tracers have been tested for use in the evaluation of prostate cancer patients based on increased glycolysis ((18)F-FDG), cell membrane proliferation by radiolabeled phospholipids ((11)C and (18)F choline), fatty acid synthesis ((11)C acetate), amino acid transport and protein synthesis ((11)C methionine), androgen receptor expression ((18) F-FDHT), and osteoblastic activity ((18)F-fluoride), with ligands in the form antibodies or smaller molecules such as peptides and aptomers also having been used to deliver detectable labels to the prostate. Combining CT or MRI with PET adds anatomical precision vital in targeting interventions, with the potential of not only demonstrating local extension and metastatic disease, but also improving identification of significant intraprostatic prostate cancer concurrently, highly relevant if focal treatments to the primary lesion are to be contemplated.

Of those candidates examined to date in prostate cancer, prostate specific membrane antigen (PSMA) and choline seem the best, with PSMA PET considered superior to choline PET.[58] However, comparing tracers and studies is difficult for a number of reasons, which include heterogeneity of cohorts, different reference standards used, some investigations using tracers combined with CT but others with MRI, and many studies lacking histological correlation of imaging findings.[59] Although PSMA PET is being used widely and appears more accurate to others available,[58] neither PSMA PET nor choline PET detects all metastatic lesions.[58,60]

Conclusion

The mode of diagnosis of prostate cancer is changing, with imaging increasingly establishing an important role in both diagnosis and staging. Prostate MRI has the potential to increase detection of clinically significant prostate cancers and, concurrently, also decrease identification of clinically insignificant low-risk prostate tumours, if biopsies are not performed on patients with normal MRI findings. However, MRI is expensive with investment in ever-improving hardware, post-processing software, together with upskilling of radiologists and urologists interpreting MRI images, requiring consideration in integrating MRI into the prostate cancer diagnostic algorithm. As a consequence, since the majority of men with an elevated PSA will not have prostate cancer detected with biopsies, the need for inexpensive and better triaging tests is more relevant than ever before, so that MRI can be reserved for those with a high risk of malignancy warranting treatment. However, the combination of triaging tests and imaging will increasingly aid urologists in their decision to pursue a diagnosis. Despite these advances, the most important decision remains: "Will the patient in front of me benefit from diagnosis and treatment?" A reflection back to the Hippocratic oath of 'first do no harm' can often aid in this decision.

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