Personalising prostate cancer care

Part 1. Advances in diagnosis

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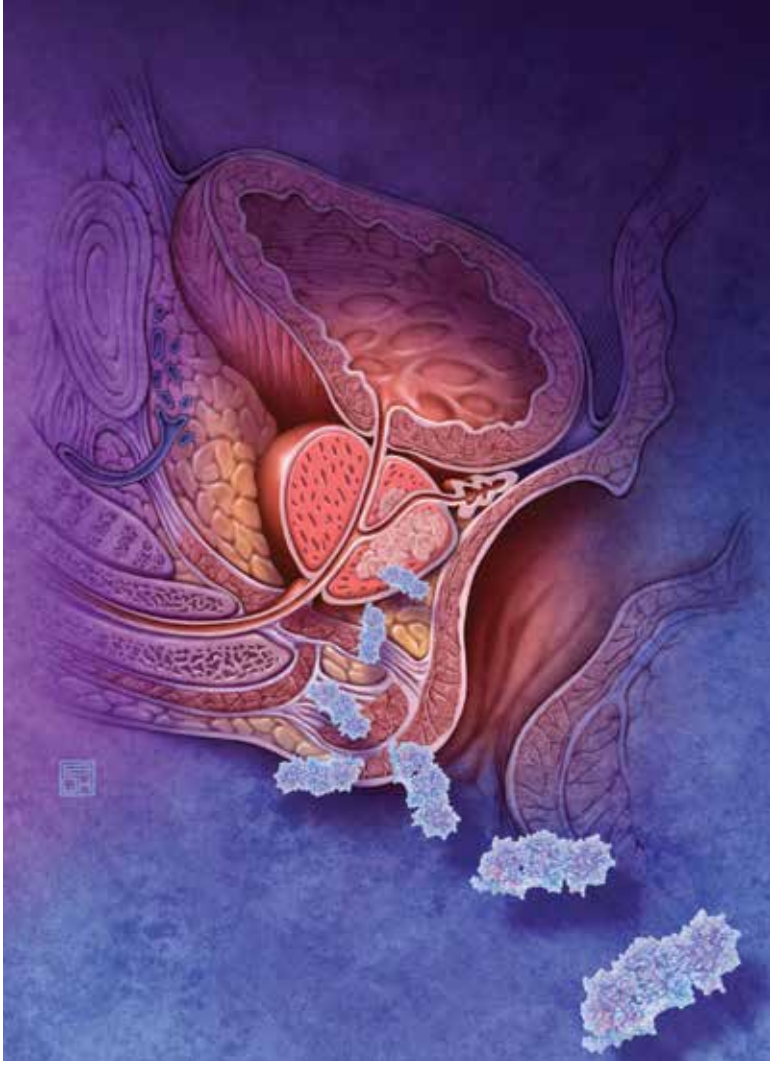
Recent advances in detection and diagnosis of prostate cancer include updated guidelines on PSA testing and early management, multiparametric MRI, transperineal biopsy, genetic testing of tumours and a simplified grading system.



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Prostate cancer remains the second most commonly diagnosed cancer in Australian men (after skin cancer).[1] The diagnostic pathway and management options continue to evolve, and we are on the cusp of being able to deliver truly personalised, tailored therapy. This is the first article in a two-part series that summarises recent changes in the care of patients with prostate cancer. Here we discuss advances in investigation and diagnosis of patients with possible prostate cancer. In the second article, we will discuss current treatment options for patients with prostate cancer.

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Early detection of prostate cancer

Updated guideline on PSA testing and early management

A consensus guideline, *Clinical Practice Guidelines for PSA Testing and Early Management of Test-Detected Prostate Cancer*, was recently developed by the Prostate Cancer Foundation of Australia and Cancer Council Australia and approved by the NHMRC.[1] It

KEY POINTS

- Prostate cancer is the second most commonly diagnosed cancer in Australian men and has potentially significant implications for quality of life.
- Updated Australian guidelines on prostate-specific antigen (PSA) testing and early prostate cancer management were published in 2016.
- Multiparametric MRI of the prostate has an emerging, important role in both prostate cancer detection and management.
- Prostate biopsy remains a fundamental component of the diagnostic pathway; transperineal biopsy minimises infection risk and may challenge the 'gold standard' of transrectal biopsy.
- Genetic testing of prostate cancer tissue may help differentiate significant from insignificant cancers.
- A new prostate cancer classification system has been proposed to simplify the Gleason scoring system.

SUMMARY OF THE 2016 AUSTRALIAN CLINICAL PRACTICE GUIDELINES ON PROSTATE-SPECIFIC ANTIGEN (PSA) TESTING*[1]

- There is no evidence to support a national PSA 'screening program' for all men; instead PSA testing is a decision that requires open discussion between men and their doctors
- Men who are considering PSA testing require information on its benefits and harms
- Men of average risk of prostate cancer, who after being fully informed decide to undergo regular testing, should be offered PSA blood tests every two years from age 50 to 69 years
- In general, if the total PSA level is greater than 3 ng/mL then further investigation for prostate cancer should be offered
- Men aged 70 years or older should be advised that the harms may outweigh the benefits of PSA testing in their age group
- Men with a family history of prostate cancer in their father or one brother have a 2.5 to 3 times greater risk of disease. In this group of men, who after being fully informed decide to undergo regular testing, PSA blood tests should be offered every two years from age 45 to 69 years
- Men with a family history of prostate cancer in their father and two or more brothers have a 9 to 10 times greater risk of disease. In this group of men, who after being fully informed decide to undergo regular testing, PSA blood tests should be offered every two years from age 40 to 69 years
- Digital rectal examination (DRE) is not recommended for asymptomatic men as a routine addition to PSA testing in the primary care setting
- DRE is still an important part of the work-up before biopsy after referral to a urologist or other specialist
- PSA testing is not recommended for men who are unlikely to live another 7 years because of other health issues

* Adapted from: PSA Testing Guidelines Expert Advisory Panel. Clinical practice guidelines for PSA testing and early management of test-detected prostate cancer (2016).[1]

has been endorsed by the Urological Society of Australia and New Zealand as well as the Royal Australian College of General Practitioners. This guideline is the first of its type and should help GPs work in accord with the evidence in this highly controversial area. The key points of the guideline are summarised in the Box.

Prostate specific antigen (PSA) testing in the 50 to 69 years age group is supported by evidence and generally is suggested every two years for men who have been fully educated about the benefits and harms. In the authors' opinion, digital rectal examination (DRE), although not supported by strong evidence, can still be performed by experienced practitioners. Some DRE-detected tumours secrete low amounts of PSA, and therefore DRE remains relevant.

It is important to obtain informed consent from patients before any PSA testing. Although there is now some level 1 evidence from randomised controlled trials that PSA testing may decrease prostate cancer-specific mortality in the appropriate population, there is equally compelling level 1 evidence that PSA testing results in overdetection and overtreatment.[2,3] It is therefore crucial to inform patients about the likelihood of developing significant prostate cancer in any individual situation and equally to emphasise the risk of detecting insignificant tumours and the effect that may have on quality of life.

Multiparametric MRI

Multiparametric MRI (mpMRI) has had a major impact on the diagnosis and management of prostate cancer. This technique involves combining three imaging sequences:

- T2-weighted imaging to define the anatomy and structure of the prostate
- diffusion-weighted imaging to detect and characterise tumours, including an apparent diffusion coefficient map of the prostate (as most significant prostate cancers are denser than surrounding tissue)
- dynamic contrast enhanced imaging to map cancer vascularity.

Multiparametric MRI is discussed in the January 2017 issue of *Medicine Today*.[4] Results are reported on a five-point scale indicating the likelihood of a clinically significant prostate cancer.

There is increasing evidence that mpMRI of the prostate could be a valuable secondary screening tool to aid in the detection of aggressive cancers while reducing overdetection of low-grade lesions.[5,6] The technique will hopefully distinguish between patients with an elevated PSA level who are appropriate for monitoring and those who require prostate biopsy. We have found that mpMRI of the prostate by experienced practitioners has a negative predictive value of 92% and a sensitivity of up to 96%.[7] The use of mpMRI before biopsy in certain population groups could therefore markedly decrease the need for biopsies. Furthermore, if biopsy is necessary then mpMRI could facilitate a more accurately targeted biopsy.

It should be noted that mpMRI should be performed and interpreted only by experienced practitioners. It is not currently eligible for a Medicare rebate, creating a cost burden for patients.

Our research group is currently developing an algorithm for use of mpMRI as part of active surveillance (close monitoring of low-grade prostate tumours). Other factors to be considered in the decision to undergo a prostate biopsy include risk factors such as a strong family history, genetic factors such as *BRCA* gene mutations, and PSA features, including PSA density, doubling time, velocity and free-to-total ratio.

A typical situation where mpMRI may aid in the decision whether to perform a prostate biopsy is in a patient approaching

the age of 70 years who has a slightly elevated PSA level, no other risk factors and a negative mpMRI result. In our opinion, this patient may avoid biopsy and instead be monitored closely with a very small risk of missing or delaying diagnosis of a significant prostate cancer. Further validation studies are needed before this practice can be adopted in the guidelines.

The major criticism of PSA testing previously has been overdetection and overtreatment. Multiparametric MRI goes some of the way towards addressing overdetection, and active surveillance goes some of the way towards addressing overtreatment.[8] Further studies are now needed that incorporate these two developments to assess their effect on previously refuted population screening programs.

Prostate biopsy

Prostate biopsy is supported by evidence in men with suspected prostate cancer based on history, examination and PSA testing. Core biopsies may be taken via transrectal or transperineal approaches with ultrasound guidance. The current clinical practice guidelines support 21 to 24-core sampling for initial diagnostic biopsies.[1] Some patients have concerns that prostate biopsy may promote tumour growth or tumour seeding along the needle tract. At this stage, there is no evidence to support the avoidance of biopsy for this reason.[9] Some tumours such as melanoma and transitional cell tumour of the kidney have been shown to implant along the site of a biopsy, but this has not been shown to be a significant factor for prostate cancer.

MRI-targeted biopsy

Multiparametric MRI has an increasingly important role in prostate sampling. Not only can a negative result on mpMRI potentially help patients with a slightly elevated PSA level avoid biopsy, as discussed above, but mpMRI identification of the target can help avoid undersampling during biopsy. Indeed MRI-targeted biopsies are now becoming more commonplace in tertiary centres.[10] They can be performed using MRI–ultrasound fusion (fusion of MRI images with ultrasound-guided biopsy through specialised software or visual estimation by the surgeon) or in-gantry (also termed in-bore) MRI-guided biopsy.

This raises the question whether MRI–ultrasound fusion biopsies or in-gantry MRI-guided biopsies may replace random biopsies. The evidence is that MRI-targeted biopsy detects more high-grade cancers and fewer low-grade cancers compared with standard template biopsy, but a small proportion of significant tumours may be missed in other parts of the prostate with targeted biopsy alone.[8,11] At this stage, therefore, a combination of a targeted approach (if mpMRI is available) and standard-of-care systematic random template biopsy is encouraged.[10,12,13]

Transperineal biopsy

Transperineal biopsy of the prostate, which minimises the risk of infection and allows template sampling of the prostate anteriorly and posteriorly, appears to be challenging the 'gold standard' of transrectal biopsy. The latter has the disadvantage of a risk of significant infection, particularly in the era of multiresistant bacteria. The commonly quoted incidence of infection after transrectal biopsy is 2 to 3%, with a proportion of these being serious infections necessitating intensive care.[14-16] Data from our centre and centres in Victoria support the notion that transperineal biopsy almost eliminates the risk of infection.[17,18] Furthermore, fusion of mpMRI with template biopsies appears to be much simpler for transperineal than transrectal biopsies.

Assessing clinical significance of prostate cancer

There are essentially two types of prostate cancer, those that are not life threatening (insignificant) and those that are life threatening (significant). Even significant cancers can take a long time to progress, and therefore patients with a life expectancy of less than 10 years generally do not undergo curative therapy. An insignificant prostate cancer is generally regarded as a Gleason 6 tumour, particularly if it is relatively low in volume. Tumours classified as Gleason 6 (equivalent to grade group 1 of the International Society of Urological Pathology [ISUP] system discussed below) are very prevalent in the normal population and can be detected incidentally when template biopsies are performed.

Gleason 6 tumours are now rarely treated and instead undergo initial active surveillance. There is one caveat, in that it is important to ensure that there has not been undersampling; this is addressed by a more thorough saturation biopsy or recently by using mpMRI. Multiparametric MRI has been useful in avoiding the detection of insignificant cancers, which tend not to show up on MRI imaging.[5,6] MRI has also been useful in detecting significant cancers in unusual anterior locations in the prostate, which are often missed at initial biopsy.[19]

Genetic testing of prostate cancer

Genetic testing of prostate tissue is becoming more popular in an attempt to improve differentiation of significant from insignificant cancers. Although Gleason 6 cancers are generally regarded as relatively harmless, a small proportion (about 10%) are still significant. Furthermore, some Gleason 7 tumours are insignificant in that they tend not to progress. Use of novel genetic biomarkers is attempting to address the challenge of accurate classification of tumours into significant and insignificant categories. Current commercially available genetic tests include the Oncotype DX Genomic Prostate Score and the Prolaris and Decipher tests.[20]

Simplified grading system for prostate cancer

A new classification of prostate cancers has been introduced. The ISUP grading system classifies prostate cancers as grades 1 to 5, replacing the older Gleason sum score that ranged from 6 to 10.[21] The relationship between the ISUP grade group and Gleason classification systems is shown in the Table.[21] In essence, Gleason 6 is now classified as

TABLE. RELATION BETWEEN ISUP GRADE GROUP AND GLEASON CLASSIFICATION OF PROSTATE CANCER[21]

ISUP grade	Gleason score
1	3+3 = 6
2	3+4 = 7
3	4+3 = 7
4	4+4 = 8 3+5 = 8 5+3 = 8
5	4+5 = 9 5+4 = 9 5+5 = 10

Abbreviation: ISUP = International Society of Urological Pathology.

ISUP grade 1, Gleason 3+4 = 7 as grade 2, Gleason 4+3 = 7 as grade 3, Gleason 8 as grade 4 and Gleason 9 to 10 as grade 5.

The ISUP grading system may be better received by patients, as a low-grade cancer labelled ISUP grade 1 may cause less anxiety than one labelled Gleason 6. The ISUP grade groupings also correlate well with long-term prognosis.[21] At this stage, Gleason 6 is still regarded as a low-grade prostate cancer rather than an indolent or benign tumour as a small percentage of Gleason 6 tumours seem to have significant abnormalities resulting in progression.

What next after a diagnosis of prostate cancer?

Many factors impact on decisions about tailoring therapy. These include patient factors, such as comorbidities, medications and life expectancy, quality of life priorities in terms of sexual and urinary function, and patient preferences and biases about surgery versus radiotherapy. Tumour factors are equally important, including tumour type, size, grade and site, as well as prostate factors such as prostate size and lower urinary tract symptoms. Logistical factors that come into play are the particular expertise of certain units and the geographic location of the patient. The next article in this two-part series will discuss advances in treatment of prostate cancer, including the complexities of curative versus noncurative approaches.

Conclusion

The diagnostic pathway for prostate cancer has evolved and been expanded beyond the traditional approach of clinical history taking, DRE, PSA testing and transrectal biopsy. PSA testing guidelines were recently updated, and new pathology reporting systems are helping to standardise and simplify practice in this area. The introduction of mpMRI into the diagnostic pathway may potentially reduce overdection of indolent disease, missed or undersampled significant disease and inaccurate risk group categorisation. Genetic testing is emerging with a potential role in differentiating significant cancer that needs treatment from insignificant disease. Active surveillance is challenging the issue of overtreatment. These advances may help contribute to truly personalised management of prostate cancer. MT

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A list of references is included in the website version of this article (www.medicinetoday.com.au).

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