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Understanding the diagnosis of prostate cancer

Abstract

- Prostate cancer continues to be the most commonly diagnosed cancer, and the second leading cause of cancer death among Australian men.
 - Prostate-specific antigen testing is personalised (not dichotomous in nature) and its interpretation should take into account the patient's age, symptoms, previous results and medication (eg, 5-alpha reductase inhibitors such as dutasteride).
 - Multiparametric magnetic resonance imaging of the prostate has been proven to have a 93% sensitivity for detecting clinically significant prostate cancer. It has the potential to decrease unnecessary prostate biopsies by around 27%.
 - International Society of Urological Pathology (ISUP) grade 1 (Gleason score 6) has been shown to have very little, if any, risk of metastasis
 - ISUP grade 1 (Gleason score 3 + 3 = 6) and low percentage ISUP grade 2 (Gleason score 3 + 4 (< 10%) = 7) can be offered active surveillance. The goal of active surveillance is to defer treatment but is still curative when required.
 - With better imaging (magnetic resonance imaging and emerging prostate-specific membrane antigen positron emission tomography-computed tomography) and transperineal prostate biopsy more men can be offered screening after discussion of risks and benefits, knowing that overdiagnosis has been minimised and radical treatment is reserved for only the most aggressive disease.
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With the constant expansion of data and knowledge, the landscape of prostate cancer is continually changing and being refined.¹ Currently, prostate cancer is estimated to be the most commonly diagnosed cancer among men and the third leading cause of cancer death in Australia. Consequently, there is a wide range of treatments from active surveillance to radical treatments such as surgery and radiation therapy. The challenge for clinicians lies in balancing the early detection of aggressive cancers with the overdiagnosis and treatment of indolent cancers; screening is therefore still largely patient driven and not population based. Further, patient symptoms, comorbidities, lifestyle and autonomy should be taken into account in the creation of a holistic management plan.

In this article, we summarise and discuss the most recent literature and guidelines pertaining to prostate cancer diagnosis and also explore factors that lead to either active surveillance or treatment for low to intermediate risk disease. PubMed, Google Scholar and the Cochrane Library were searched for publications from inception to August 2020 regarding important topics in prostate cancer diagnosis and risk stratification. An emphasis was placed on using evidence from prospective multicentre studies. A combination of published data, current guidelines, expert reviews and our experience was

then used to formulate a summary of what is applicable in contemporary clinical practice.

Prostate-specific antigen

Serum prostate-specific antigen (PSA) and digital rectal examination (DRE) are still the fundamentals of prostate cancer investigation and risk stratification. PSA is a protein that is detectable in normal prostate tissue, benign hypertrophic tissue, as well as malignant prostate tissue.³ It is therefore not specific for prostate cancer but can be elevated in benign prostatic hyperplasia, prostatitis, after prostate massage, and following prostate biopsy.⁴ Despite this, PSA is still an effective tool in triaging men for diagnostic prostate biopsy.⁵

The interpretation of a PSA result is complex. The PSA threshold of 4 ng/mL has traditionally been used for detecting prostate cancer⁵ but this has received criticism both for being too high and too low. Thompson and colleagues found that a significant number of men with prostate cancer had a PSA level < 4 ng/mL,⁶ showing that using a dichotomous PSA result may miss potentially lethal cancer.

PSA is a continuous variable with several factors that affect test results. Age is an important factor when considering a PSA result. A study found median PSA levels to be 0.7 ng/mL and 0.9 ng/mL in men aged 40–49 years and 50–59 years, respectively, without diagnosed prostate cancer.⁷ Baseline PSA levels between median and 2.5 ng/mL were associated with a 14.6-fold and 7.6-fold increased risk of prostate cancer in the respective age groups.⁷ Another study found median PSA was 1.6 ng/mL, 1.8 ng/mL and 2.2 ng/mL in men aged 70–74 years, 75–79 years and 80–84 years, respectively, without diagnosed prostate cancer.⁸ Age-specific reference ranges have been published and trialled in an attempt to standardise PSA results.^{9–14} However, these should be used with caution as they may potentially miss clinically significant cancers in older men.¹⁵

Other considerations when interpreting PSA results include use of 5- α reductase inhibitors (a treatment for benign prostatic hyperplasia), which have been shown to decrease PSA levels by about half.^{16,17} However, instead of simply doubling the PSA result, some studies have shown that 5- α reductase inhibitors and indeed surgical treatment for benign prostatic hyperplasia can increase sensitivity of PSA for prostate cancer detection,^{18–20} so any increase from PSA nadir should prompt further investigation. Prostate size, infection and inflammation can also skew PSA levels. Infection should be treated and PSA retested to obtain an accurate result.^{21,22}

Further, PSA density (total PSA/prostate volume) can be taken into consideration for risk assessment. Early results show PSA density may be particularly helpful in decisions for patients with equivocal magnetic resonance imaging (MRI) results.²³ Of note, PSA kinetics — velocity (difference in PSA per year) and doubling time (number of months for PSA to double) — have a more prominent role in relapsed and advanced prostate cancer; however, at this stage there is no evidence supporting its use in diagnosis.²⁴

Free-to-total PSA ratio and Prostate Health Index

Isoforms of PSA have been investigated to improve PSA specificity while maintaining sensitivity for predicting prostate cancer. Patients with prostate cancer have been shown to have higher protein-bound PSA and lower free PSA.²⁵ This was validated in a multicentre prospective study which found that a score of < 25% free-to-total PSA detected 95% of cancers while avoiding 25% of unnecessary biopsies. The score was also an independent predictor of prostate cancer on multivariate analysis (odds ratio, 3.2; 95% CI, 2.5–4.1; $P < 0.001$) compared with total PSA by itself (odds ratio, 1.0; 95% CI, 0.92–1.11).²⁶ Importantly, this study only included men with PSA levels of 4–10 ng/mL and a negative DRE result.

Other isoforms including proPSA, intact PSA and benign PSA have been described and incorporated to form algorithms for diagnosis. The Prostate Health Index (PHI)²⁷ is most commonly used, while others are very expensive and unavailable in Australia (eg, the 4K score). PHI is a mathematical score which uses three isoforms of PSA to predict the probability of prostate cancer on biopsy. The 4K score²⁸ is a score based on four PSA isoforms and also encompasses DRE, age and previous biopsy results if available. A recent systematic review and meta-analysis showed that the pooled sensitivity for all studies was 0.89 and 0.74 for PHI and 4K score, respectively.²⁹ However, using algorithms to reduce unnecessary biopsies from analysis of a simple blood test has not translated to routine use in Australia.

Guidelines for PSA screening

PSA screening is a highly debated topic and applies to men who are asymptomatic with no previous diagnosis of prostate cancer. Guidelines currently recommend against population-based screening and state that men must be well informed of the risks of prostate cancer investigation (Box 1) before proceeding.^{30–32} Box 2 summarises the European, United States and Australian guidelines on PSA screening.

Guidelines for PSA testing

European guidelines acknowledge PSA as a continuous variable with no agreed defined standards and recommend offering risks calculators (PHI or 4K score), imaging or additional urine- or serum-based biomarkers for patients with a PSA level of 2–10 ng/mL and a normal DRE result to avoid unnecessary biopsy. They also caution against the use of free PSA because it can be affected by several pre-analytical and clinical variables.³⁰

Australian guidelines use 3 ng/mL as a threshold for offering a repeat PSA test (recommended to be performed within 1–3 months), then recommend offering biopsy for patients with PSA levels > 5.5 ng/mL, or 3–5.5 ng/mL with free-to-total PSA < 25% on repeat test. PSA velocity and PHI are not recommended as adjuncts to PSA.³²

Digital rectal examination

Even in the PSA testing era, DRE still provides valuable information in the diagnosis and staging of prostate cancer.³³ Its utility, however, is clinician dependent and difficult to standardise. Often DRE is not sufficiently taught in medical school and clinicians who do not perform many DREs may not have the confidence or skills to perform it effectively.³⁴ Australian guidelines do not recommend DRE as a routine addition to PSA testing in asymptomatic men; however, DRE can be performed at a clinician's discretion.³² The DRE will remain an important part of diagnosis as it can detect some cancers even in patients with low PSA levels.^{35,36}

Multiparametric MRI of the prostate

Multiparametric MRI has revolutionised the prostate cancer diagnostic pathway in the past decade. Previously, prostate cancer diagnosis relied on an elevated PSA level and subsequent transrectal ultrasound-guided (TRUS) biopsy. Prostate multiparametric MRI is now used as the initial evaluation of an elevated PSA level and has resulted in a decrease of many "unnecessary benign" biopsies³⁷ while also improving the accuracy of prostate biopsy results.

The diagnostic strengths of multiparametric MRI have been well documented in recent practice-changing studies. A large, prospective, multicentre study compared the diagnostic accuracy of multiparametric MRI and TRUS biopsy. For detecting clinically significant Gleason scores ≥ 7 (see below for an explanation of Gleason scoring), prostate cancer multiparametric MRI had a sensitivity of 87% and negative predictive value of 72%, both of which outperformed TRUS biopsy (sensitivity, 60%; negative predictive value, 65%).³⁸ TRUS biopsy still had higher specificity and positive predictive value compared with multiparametric MRI, indicating that biopsy is still needed following multiparametric MRI to confirm cancer. The main outcome from this study showed that if patients received a multiparametric MRI before biopsy then this might allow 27% of men to avoid an unnecessary primary biopsy and increase the detection of clinically significant cancers by 18%.³⁸

The ability to locate the suspected prostate cancer lesion with multiparametric MRI has allowed more targeted biopsy techniques, which has improved the accuracy of biopsy results. Previously, TRUS biopsies were performed in a systematic grid-like fashion but had potential adverse effects such as infection or urosepsis, and significant false negative rates of 30–40%.^{39,40} An international, multicentre randomised trial compared MRI-targeted with standard biopsy for prostate cancer diagnosis.⁴¹ The results showed that the detection rate of clinically significant cancer (defined as Gleason score ≥ 7) with MRI-targeted biopsy was 12% higher than with standard biopsy. Moreover, the detection rate of clinically insignificant cancer (defined as Gleason score ≤ 6) was 13% less than standard biopsy. The MRI-targeted biopsy arm had a median of four core biopsies taken compared with 12 in the standard biopsy arm.⁴¹ Overall, this revealed that under- and

overdiagnosis was reduced with an MRI-triaged target biopsy with less cores needed for this increased accuracy.

The utility of a multiparametric MRI lesion for predicting clinically significant prostate cancer has now been classified using the prostate imaging reporting and data system version 2 (PI-RADS v2) (Box 3).⁴² Analysis of PI-RADS v2 compared with histological results have shown that this scoring system has a lower sensitivity for low volume, low grade disease and may also be a predictor of downgrading from a Gleason score of $3 + 4 = 7$ from biopsy to a score of $3 + 3 = 6$ at prostatectomy.⁴³⁻⁴⁵ For larger, more suspicious multiparametric MRI lesions (PI-RADS v2 score, 4–5), PI-RADSv2 was shown to be a predictor of clinically significant cancer with a sensitivity and specificity of 73.7–77.0% and 71.4–77.3%, respectively.⁴⁶

The importance of multiparametric MRI has been recognised globally. Current guidelines suggest that multiparametric MRI be used for patients to aid in decision making for biopsy or repeat biopsy.^{30,32} In Australia, this has culminated in government-subsidised multiparametric MRI for patients with suspicion of prostate cancer for diagnosis (Box 4).

Transperineal biopsy of the prostate

For many years, traditional TRUS-guided biopsy broke the fundamental surgical principle of sterile technique by passing the biopsy needle through “dirty” rectal mucosa to reach the prostate, leading to increased post biopsy infection rates of up to 10%.⁴⁷ The new transperineal biopsy technique dramatically decreases this potentially fatal complication.^{48,49}

The transperineal approach is a guided approach of the biopsy needle through sterilised perineal skin into the prostate, which completely avoids rectal flora. This technique has been shown to decrease infection rates to almost zero^{48,49} while maintaining at accuracy at least as high as TRUS biopsy.⁵⁰ Further, the risk of complications can be further decreased, as transperineal biopsy can also be performed under local anaesthetic with good effect.⁵¹ Such factors prompted a recent call for transperineal biopsy to become the new standard of care.⁵² In Australia, and much of the world, this transition is widely recognised, with many urology units already implementing or looking to implement this technique in routine clinical practice.⁵²

Grading of prostate cancer

Gleason score remains the mainstay of histological classification for prostate cancer. Donald Gleason first described the scoring system in 1966. He detailed and summarised the patterns of glandular differentiation seen on histological staining and developed a scoring system of patterns from 1 to 5. The two most predominant patterns seen were added together to give a final Gleason score (eg, Gleason $3 + 4 = 7$).⁵³ The Gleason score

is now included in most guidelines globally and is endorsed by the World Health Organization as the standard approach to histological grading.⁵⁴

In addition to the Gleason score, the International Society of Urological Pathology (ISUP) 2014 consensus accepted a prognostic five-grade system (Box 5),⁵⁵ to give patients a better understanding of aggressiveness and risk of progression. The ISUP grade has also been referred to as grade-group by some pathologists, which can be confusing. Nevertheless, the ISUP grade or grade-group categorises Gleason scoring into five distinct prognostic groups.⁵⁵ What the ISUP grade better illustrates is that Gleason 6 out of 10 cancer (ISUP grade 1) is a less aggressive form of cancer with a small risk of progression. It also indicates that Gleason 7 out of 10 cancer can be split into two prognostically different cancers (ISUP grade 2 and 3).⁵⁶

Active surveillance

Gleason pattern 3 cancer has different genomic properties compared with Gleason pattern 4 and 5.⁵⁷ Gleason score $3 + 3 = 6$ cancer has a low metastatic potential and a very low risk of mortality. A study of 14 123 cases found that zero cases of Gleason score 6 cancer had lymph node metastases at radical prostatectomy.⁵⁸ Another study of 12 389 cases reported a 0.2% 15-year prostate specific cancer mortality rate for Gleason scores < 6 (ISUP grade 1) after a radical prostatectomy. This knowledge forms the foundation of the modern day initial approach of active surveillance protocols for Gleason $3 + 3$ malignancy.

Active surveillance combines PSA, DRE and prostate biopsy to closely monitor a patient's prostate cancer, with the conversion to active treatment if progression occurs.³⁰ It is a highly debated topic and is the subject of much research. Criteria for inclusion include patients with ISUP grade 1 disease, PSA levels < 20 ng/mL, and clinically localised disease tumour stage (1–2). Contemporary criteria also include some ISUP grade 2 patients with low percentage of Gleason pattern 4 ($< 10\%$). Other factors to consider are the volume of cancer and number of biopsy cores taken. Early results suggest multiparametric MRI results also have a role for inclusion and monitoring of patients on active surveillance.⁵⁹ Patient autonomy, comorbidities and life expectancy also need to be taken into account. Clearly, there are many variables that inform the decision for active surveillance and there are no standardised inclusion criteria. Therefore, this decision should be made by a specialist with experience.

Regarding protocols for active surveillance, after initial investigations and confirmatory biopsy, men should receive 6-monthly PSA testing and DRE, and further biopsy every 1–3 years depending on level of suspicion.³² However, this is a dynamic space which will change with more prostate imaging experience and longer follow-up of active surveillance cohorts.

Prostate-specific membrane antigen positron emission tomography–computed tomography

Prostate-specific membrane antigen (PSMA) is a type 2 transmembrane glycoprotein expressed in prostate tissue as well as salivary glands, lacrimal glands, renal tubular cells and the small intestine. Its expression has been shown to be increased in prostate cancer, particularly in higher grade metastatic disease, making it a good biological target for detecting smaller lesions. In Australia, PSMA positron emission tomography–computed tomography (PET–CT) scans are widely available, enabling the running of the largest randomised controlled trial of PSMA PET–CT to date,⁶⁰ which demonstrated its superiority for primary staging compared with conventional scans (CT scan of the abdomen and pelvis and whole body bone scan).

The accuracy of PSMA PET–CT for characterising cancer within the prostate and its role in diagnosis of prostate cancer is currently in the early stages of investigation. A retrospective study of 205 men found no difference between PSMA PET–CT and multiparametric MRI in detecting all primary tumours, clinically significant tumours or transition zone tumours.⁶¹ Another study also found PSMA PET–CT to have greater sensitivity, specificity, negative predictive value and positive predictive value in intermediate grade cancers (ISUP grade 2–3) compared with multiparametric MRI; a combination of the two modalities increased accuracy slightly.⁶² Comparing the concordance between biopsy and radical prostatectomy histology in 144 men, PSMA PET–CT was found to incrementally improve tumour location compared with multiparametric MRI.⁶³

The PRIMARY trial seeks to identify the value of PSMA PET–CT in detecting clinically significant prostate cancer in men undergoing initial biopsy. This is an Australian-led multicentre, prospective, cross-sectional study investigating pelvic-only PSMA PET–CT in combination with multiparametric MRI against targeted prostate biopsies. It aims to recruit 600 men to provide level 1 evidence about imaging accuracy, the avoidance of overdiagnosis, and health economic analysis of pelvic-only PSMA PET–CT in the diagnostic setting.⁶⁴

A multidisciplinary approach

Given its complex nature, the search for improved outcomes has been somewhat of a call to arms, with many health specialties banding together to progress the development of prostate cancer management. Men diagnosed with prostate cancer are extensively discussed in multidisciplinary forums where radiologists, nurses, urologists, radiation oncologists and medical oncologists may all partake in offering decision choices. These meetings have been shown to make high impact changes for around one-quarter of cases, especially in patients with advanced cancer.⁶⁵ Multidisciplinary meetings also facilitate cross-referrals from specialty to specialty in a timely, upfront manner.⁶⁵ The nature of multidisciplinary meetings allows for a holistic approach to patient care and management, with experts from many fields providing knowledge that influences decision making.

Conclusion

The diagnosis and risk stratification of prostate cancer has seen major advancements in technology and changes in patterns of care in diagnosis and management over the past two decades (Box 6). New imaging modalities, risk calculators, biopsy techniques and management strategies have created an arsenal of information to aid in clinical decision making. The dilemma of overdiagnosis and overtreatment in Australia has decreased over the last decade but continues to hold back more widespread screening. The avoidance of unnecessary biopsies by imaging and the implementation of active surveillance for men with lower risk disease have emerged as a way to combat this problem. Men and their medical practitioners need to revisit prostate cancer in light of this new contemporary landscape.

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[Boxes]

1 Risks of early detection of prostate cancer

- Overdiagnosis — diagnosis of prostate cancer that would never have become symptomatic in the patient's lifetime
- Potential complications from diagnostic prostate biopsy — pain, infection
- Overtreatment — treatment of prostate cancer that would never have become symptomatic in the patient's lifetime
- Potential complications from curative treatment — erectile dysfunction, urinary incontinence, bowel symptoms
- Psychological harms

2 Guidelines for prostate-specific antigen (PSA) screening

	European Association of Urology ³⁰	US Preventative Services Task Force ³¹	Prostate Cancer Foundation of Australia ³²
Who to offer PSA screening	Well informed men with at least 10–15 years' life expectancy	Well informed men aged 50–69 years	Well informed men aged 45–69 years
Who not to offer PSA screening	Men with < 15 years life expectancy — unlikely to benefit	Men aged > 70 years	Men aged > 70 years
Early PSA screening	Well informed men at elevated risk of prostate cancer aged > 50 years; aged > 45 years with family history of prostate cancer; or African-Americans aged > 45 years	na	Well informed men aged 45–69 years estimated to be 2.5–3 times higher than average risk* Well informed men aged 40–69 years estimated to be 9–10 times higher than average risk †
How often to screen	Individualised strategy	na	PSA test every 2 years

* Due to presence of risk factors such as a brother diagnosed with prostate cancer, particularly if diagnosed at < 60 years of age. † Due to presence of risk factors such as father and two brothers diagnosed with prostate cancer.

3 Prostate imaging reporting and data system (PI-RADS) version 2: five-point scale for the likelihood of multiparametric magnetic resonance imaging predicting clinically significant prostate cancer⁴²

Category	Likelihood	Clinical significance
PI-RADS 1	Very low	Clinically significant cancer is highly unlikely to be present
PI-RADS 2	Low	Clinically significant cancer is unlikely to be present
PI-RADS 3	Intermediate	Presence of clinically significant cancer is equivocal
PI-RADS 4	High	Clinically significant cancer is likely to be present
PI-RADS 5	Very high	Clinically significant cancer is highly likely to be present

4 Prostate cancer diagnostic tests: Medicare rebate availability

Test	Medicare rebate
PSA	Available for one PSA test per year for any man A man with previously diagnosed prostatic disease is entitled to Medicare rebate for an unlimited number of PSA tests
Free-to-total PSA ratio	Available to follow up a PSA result that lies: <ul style="list-style-type: none"> at or above the age-related median but below the age-related, method-specific 97.5% reference limit (one test per 12-month period); or at or above the age-related, method-specific 97.5% reference limit but is < 10 µg/L (four tests per 12-month period)
Prostate Health Index	No rebate available
Multiparametric MRI	To obtain rebate, referral must be from urologist, radiation oncologist or medical oncologist Available for one multiparametric MRI per year for a patient suspected of having prostate cancer based on: <ul style="list-style-type: none"> suspicious DRE; or being aged < 70 years, with results of at least two PSA tests performed within an interval of 1–3 months > 3.0 ng/ml and a free-to-total PSA ratio < 25%, or repeat PSA > 5.5 ng/ml; or being aged < 70 years whose risk of developing prostate cancer based on family history (first degree relative with prostate cancer or suspected <i>BRCA1/2</i> mutation) is at least double the average risk, with results of at least two PSA tests performed within an interval of 1–3 months > 2.0 ng/ml and a free-to-total PSA ratio < 25%; or being aged >70 years, with results of at least two PSA tests performed within an interval of 1–3 months > 5.5 ng/ml and a free-to-total ratio < 25% Available for multiparametric MRI 12 months after diagnosis and then every 3 years thereafter; or if at any time there is clinical concern for patients: <ul style="list-style-type: none"> under active surveillance following confirmed diagnosis with biopsy histopathology; or not planning or undergoing treatment for prostate cancer
PSMA PET-CT	No rebate available

PSA = prostate specific antigen; PSMA PET-CT = prostate-specific membrane antigen positron emission tomography-computed tomography; MRI = magnetic resonance imaging.

5 International Society of Urological Pathology (ISUP) prostate cancer grades and Gleason score equivalents⁵⁵

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

6 Pathway for diagnosis, staging and treatment of prostate cancer

[ong_mja20.00783_gr]

CT = computed tomography; MRI = magnetic resonance imaging; PSMA PET = prostate-specific membrane antigen positron emission tomography.

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