Diagnosing prostate cancer

What GPs need to know

BACKGROUND
The symptoms and signs of prostate cancer usually manifest after it is too late to 'cure' the condition. General practitioners are ideally suited to diagnose this disease early and need to know the latest information about how best to identify and advise patients.

OBJECTIVE
This article describes the latest information about the natural history and detection of one of the commonest cancers in Australian men.

DISCUSSION
Prostate cancer rarely causes symptoms in the early stage and lower urinary tract symptoms (LUTS) are more likely to be due to benign prostate disease rather than cancer. Identifying asymptomatic prostate cancer requires both prostate specific antigen (PSA) and digital rectal examination as about one-fifth of men with prostate cancer have a 'normal' PSA. Although on currently available evidence population screening cannot be recommended, 'case detection' in men deemed to be at risk of prostate cancer is widely practised. Informed patient participation in this process is vital.

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Prostate cancer is, after lung cancer, the commonest cause of cancer related death in Australian men. Usually affecting men over 60 years of age and rare in those under 40 years, it accounts for more deaths in men than breast cancer does in women. In 2004, Australia recorded 10 512 new cases and 2852 deaths[1] – statistics likely to worsen as our population ages.

The only currently known definite risk factors are increasing age and a positive family history – although it is unclear whether the latter reflects a shared environment, a similar lifestyle or common genes. Although in the USA the incidence is known to be higher in African-Americans compared to caucasians,[2] similar racial statistics are not available for other populations. While the prevalence of microscopic or autopsy detected prostate cancer is similar among men of different ethnic groups, clinical incidence is low in Asians and highest in African-Americans and Scandinavians.[3] The influence of dietary and other factors on this finding is currently under investigation.

Pathology

Most prostate carcinomas are adenocarcinomas originating in the prostatic glandular acini. A system of histological grading known as the Gleason System is currently in use, because tumour grade is a valuable prognostic factor. The system, developed in the 1970s and based on the degree of architectural differentiation, assigns a primary pattern for the dominant grade seen, with a secondary pattern assigned for the nondominant grade. These patterns are designated 1 to 5, with '1' being the best differentiated and '5' the most poorly differentiated pattern. The overall Gleason Score, between 2 and 10, thus provides a relatively accurate picture of the aggressiveness of the disease.

Prostate carcinoma initially spreads to local nodes and structures before distant spread occurs. It extends locally through the compressed outer tissue of the prostate (described as the 'prostatic capsule'), the seminal vesicles and rectum. Metastasis occurs to local nodes, bone, supra-diaphragmatic lymph nodes and lung.

Natural history

Prostate cancers detected incidentally at transurethral resection of the prostate (TURP) are designated T1 tumours. These are then subclassified as T1a or T1b depending on whether less than 5% (T1a) or more than 5% (T1b) of the prostate chips are involved with cancer. While T1a tumours have a median time to progression of disease of 15 years, T1b tumours have a much quicker median time to progression of less than 5 years.

Tumours that are palpable rectally are designated T2. It is known that without treatment 90–100% of these will

progress within 15 years[4] – which explains the rationale for actively treating such cancers in men with a life expectancy greater than 10 years.

Palpable cancer extending beyond the prostate capsule is designated T3. The reported prognosis of these clinical stage 3 cancers is poor as most patients have occult metastases. When a cancer extends beyond the prostate into the lateral sulci or seminal vesicles, lymph node metastases are present in 30–50% of patients.[5]

Although this type of information helps us make decisions about how to manage patients with prostate cancer, we still cannot accurately predict which cancers will progress until the disease has extended beyond the prostate.

Clinical assessment

Prostate cancer rarely causes symptoms in early disease as most cancers arise in the periphery of the gland. Obstructive urinary symptoms such as hesitancy, poor stream and intermittency usually indicate benign prostatic hyperplasia. This is important as many patients with lower urinary tract symptoms (LUTS) present to their general practitioner concerned that they may have prostate cancer. In most cases, cancer is unlikely and patients can be investigated according to their symptoms. Bone pain represents advanced disease but is often the first symptom.

Digital rectal examination

Digital rectal examination (DRE) is an essential component of the physical examination when assessing the older man with urological problems. While a palpable irregularity of the gland has only about a 50% chance of being cancer, about a fifth of prostate cancers are associated with a normal PSA[6] and may only be detected on DRE.

Prostate specific antigen (PSA)

Prostate specific antigen is a glycoprotein produced predominantly by the prostate epithelium. It circulates in free and bound forms with levels varying by up to 20% over days. Several factors can increase serum PSA such as:

- prostate biopsy
- TURP
- prostatitis
- urinary retention, and
- ejaculation within an hour of the test.

Drugs such as finasteride, anti-androgen therapy, and radiotherapy can reduce PSA. It is important to note that DRE does not significantly alter PSA; neither do alpha blockers such as prazosin and tamsulosin.[7]

Among the modifications to the interpretation of the PSA test recently undertaken to try and improve its accuracy are the use of age specific reference ranges for PSA (*Table 1*). Attempts are also being made to refine the measurement of PSA to make it more sensitive and specific for detecting prostate cancer. None of these methods – the use of free to total PSA ratio, the measurement of PSA velocity, assessing PSA density, or using the Prost-Asure index[8-11] – are currently accurate enough for routine clinical practice.

As PSA in the blood exists both free and complexed to other proteins, measuring the percentage of free (or unbound) PSA and expressing this as a ratio compared to the total amount of PSA has proved useful in younger patients and in those with a PSA between 4–10 ng/mL. In prostate cancer most of the PSA is bound and hence the ratio is lower; whereas in benign prostatic hyperplasia the ratio is higher. It is currently believed that if the ratio is above 22–25%, the risk of prostate cancer is low. Further investigation is advocated for ratios below this amount, even if the total serum PSA is normal.

The PSA velocity measures the rate at which PSA values change over a period of time, with any change greater than 0.75 ng/mL per mL per year being of concern. A PSA level greater than that expected for the patient's age does not necessarily mean carcinoma – but certainly warrants further evaluation by an urologist.

It is important to reiterate that undergoing a DRE is important because 20–25% of patients with carcinoma of the prostate have a PSA level less than 4 ng/mL – which was the accepted 'normal' value in the past.

TRUS and biopsy

For further investigation of patients with abnormalities detected on DRE or with serum PSA greater than that expected for their age, transrectal ultrasound (TRUS) examination and biopsy are undertaken. It may also be required in patients who have a progressive increase in their PSA or evidence of advanced disease (eg. a positive bone scan) but no histological diagnosis.

Table 1. Age reference range for PSA

Age	PSA in ng/mL
40–49 years	<2.5
50–59 years	<3.5
60–69 years	<4.5
70+ years	<6.5

The procedure is performed in a radiology suite or, more commonly, in a facility such as a consulting suite, day surgery unit or operating theatre. Usually patients have a preparatory enema and rectal preparation such as a Betadine swab. The ultrasound probe is then placed in the patient's rectum and the prostate examined. It is now routine to perform 12–14 biopsies with a biopsy needle inserted into the prostate through the rectum.

All TRUS and biopsy procedures should be performed under antibiotic cover (eg. norfloxacin 400 mg orally twice per day for 3 days to include the day before, the day of, and the day after the biopsy). Even with antibiotic cover there is a 1% rate of gram negative sepsis after TRUS and biopsy. Most patients report some discomfort as a result of their biopsy and some may experience rectal bleeding.

Bone scan

Radioisotope bone scan is the most sensitive method for detecting bony metastases – which are usually distributed in the axial rather than the appendicular skeleton. The probability of a positive scan is very low if the PSA is less than 10 ng/mL – hence current recommendations that bone scans in these patients are unnecessary. Computerised tomography and magnetic resonance imaging (MRI) are of limited use, being unable to sensitively and specifically detect pelvic lymph node involvement and extra-prostatic disease. If the PSA level is high (>10 ng/mL) or if there is high grade disease on TRUS biopsy (Gleason score >7), lymph node sampling is usually performed at the time the patient undergoes surgery (radical retropubic prostatectomy).

Screening for prostate cancer

Population screening (in the manner of Pap tests and breast cancer screening) is not currently recommended in most countries. Currently there is no evidence from randomised controlled trials to demonstrate an increased survival resulting from intervention for early stage prostate carcinoma. There have been promising reductions in prostate cancer mortality in many countries, which may be attributed to the result of 'screening' that encouraged early detection and treatment. The most promising results showing population screening decreasing prostate cancer mortality (up to 40–50%) came from the Tyrol region of Austria, where (unlike other regions of Austria) screening has been freely available for over a decade.[12,13] The results of the Prostate, Lung, Colorectal and Ovarian cancer study (PLCO) in the USA and the European Randomised study for Screening in Prostate Cancer (ERSPC), expected by the end of this decade, are eagerly awaited, as they may provide data which strengthens the case for screening.

We are faced today with this dilemma: we do not yet have the results of properly constituted randomised controlled studies – yet there appears to be some epidemiologic data that prostate cancer mortality is being reduced, possibly as a result of testing.

Many groups therefore advocate an informed decision making process with regard to testing asymptomatic patients. They should be clearly informed of:

- what the PSA test involves and its pitfalls (in particular the false positive results of relying on serum PSA alone)
- the process by which a diagnosis will need to be made (adequate TRUS biopsy)
- the various treatment options available (including their potential side effects), and
- the potential diminished mortality rate that appears to result from this earlier detection and treatment.

When testing asymptomatic men for prostate cancer it is essential that both PSA and DRE are performed (because a normal PSA does not preclude prostate cancer) and that these men are clearly given the following information:

- the test may detect a cancer at a stage where curative treatment can be offered
- the test will fail to detect some early tumours
- treatment of early prostate cancer detected by PSA testing may incur risk and may not improve life expectancy in all men.

The Urological Society of Australasia, The Royal Australian College of General Practitioners and the Anti-Cancer Council of Victoria do not currently endorse population based screening for prostate cancer. However, they do not actively discourage the practice of providing access to 'screening for prostate cancer' (utilising annual PSA and DRE) for concerned patients who are otherwise in good health and have a life expectancy of greater than 10 years. In most cases this means men in the age range 50–65 years. Screening is also recommended for men at an earlier age who have a strong positive family history of prostate cancer. Hence, while population screening is not currently endorsed, case detection is considered acceptable practice at the primary care level.

What is more important than consensus agreement on the role of screening of entire populations for prostate cancer is that patients are informed at a primary care level of the options available to them in relation to PSA testing and the possible significance of the test result. Both PSA testing without the patient's informed consent as well as the deliberate omission of PSA testing in men with a life expectancy of more than 10 years without discussing the option of testing with them, are practices that should be actively discouraged.

Summary of important points

- Prostate cancer is the second most common cause of cancer death in Australian men.
- Prostate cancer rarely causes symptoms in the early stage.
- Lower urinary tract symptoms are more likely to be due to benign prostate disease rather than cancer.
- Although on currently available evidence population screening cannot be recommended, 'case detection' in men deemed to be at risk of prostate cancer is widely practised.
- Identifying asymptomatic prostate cancer requires both PSA and DRE as about 20% of men with prostate cancer have a 'normal' PSA.

Conflict of interest: none declared.

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