Advances in prostate cancer

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Background
Prostate cancer is a common tumour type in Australian men.

Objective
The aim of this article is to review important changes in prostate cancer diagnosis and management over the past five years, particularly as they pertain to general practice.

Discussion
The management of prostate cancer has changed significantly in recent years, particularly the use of imaging, with the introduction of prostate magnetic resonance imaging as routine in the diagnostic pathway, and the increasing use of prostate-specific membrane antigen positron emission tomography for early stratification in the salvage setting for failure of primary treatment in localised disease. In addition, upfront combinations of androgen deprivation therapy with other systemic treatments have yielded significant gains in overall survival for patients with metastatic disease. There has also been an increasing recognition of the association between germline DNA repair defects and progressive disease, and interest in the potential to identify patients for therapies that target these defects. There have been significant changes in how prostate cancer is diagnosed and managed in the past five years, with the introduction of new clinical pathways that were unprecedented just a decade previously.

Detection

Although randomised controlled trial data suggest that prostate-specific antigen (PSA) testing results in a small reduction in prostate cancer mortality, its widespread use in case-finding is controversial because of the low specificity of the test, the morbidity of prostate biopsy, and the risks of overdiagnosis and overtreatment of clinically insignificant cancers.[1] Advances in prostate magnetic resonance imaging (MRI) go some way to addressing the issues of overdiagnosis through improved risk stratification. These advances include the incorporation of multiple MRI techniques ('sequences'), such as diffusion-weighted and contrast-enhanced images, as well as the development of the Prostate Imaging Reporting and Data System (PIRADS), which is a five-point standardised reporting system for MRI-detected abnormalities, where 1 = clinically significant cancer highly unlikely to be present, and 5 = clinically significant cancer highly likely to be present.[2] Higher PIRADS scores are often associated with tumours of higher volume and grade, and meta-analysis of MRI performance indicates a pooled sensitivity of 0.89 and specificity of 0.73 for prostate cancer.[3] In contrast, the sensitivity of traditional imaging modalities (eg computed tomography [CT] and ultrasonography) in this setting is low.

The PSA testing guidelines published by the Prostate Cancer Foundation of Australia/Cancer Council Australia (and endorsed by the National Health and Medical Research Council) contain detailed information about who should be offered PSA testing and the supporting evidence.[4] In brief, for men at average risk of prostate cancer with a reasonable life expectancy (>7 years) who have been informed of the benefits and harms of testing and have decided to proceed with regular testing, PSA testing should be offered every two years between the ages of 50 and 69 years, with further investigation offered if the PSA exceeds 3.0 ng/mL (typically an early repeat PSA with a free/total ratio in the first instance). For men to be able to access Medicare Benefits Schedule (MBS)–funded prostate MRI, the scan must be ordered by a specialist urologist, radiation oncologist or medical oncologist, and patients must fulfil certain clinical criteria. For example, men aged <70 years who have a benign digital rectal exam (DRE) need two elevated PSA readings of >3 ng/mL (interval between tests 1–3 months) in additon to a free/total ratio <25% or a repeat PSA >5.5 ng/mL, highlighting the importance of repeating PSA before embarking on further investigation. Different criteria exist for those with higher prostate cancer risk or those on active surveillance.[5] The increasing availability of prostate MRI does not alter recommendations regarding to whom PSA testing should be offered.

One advantage of visualising areas of abnormality prior to biopsy is that these areas can be specifically targeted, reducing the sampling error inherent in systematic biopsies. This can be done by taking extra cores under transrectal ultrasound guidance from the abnormal area identified on the MRI ('cognitive fusion'), using coregistration software that

can overlay regions of interest from the MRI onto the ultrasound image, or via an 'in-bore' biopsy, where the biopsy is taken with real-time MRI. The latter has the advantage of being able to directly image the needle sampling the area of interest, providing confidence that the appropriate area has been biopsied. Adding targeted cores to a systematic biopsy increases the detection of clinically significant cancer,[6,7] although the findings are not universal.[8] However, the utility is much greater for patients with a prior negative biopsy for whom a clinical suspicion remains.[9]

Although a systematic template biopsy is usually performed at the same time as targeted cores are taken, there has been some debate as to whether this is required. Performing target-only biopsies increases the number of clinically significant cancers identified by 20% when compared with whole-gland sampling and consistently decreases the number of insignificant tumours detected. It is also associated with fewer biopsy cores taken and, in some studies, fewer complications.[10–12] However, omitting a systematic biopsy resulted in failure to diagnose clinically significant cancer in 2.1% of patients (0.0%–12.4%),[13] and a combination approach is optimal for significant cancer detection (although with higher rates of insignificant cancers diagnosed as a trade-off).

Another area of interest is whether MRI can be used as a triaging tool. The reported negative predictive value of MRI is high, with median values of 82.4% for any prostate cancer and 88.1% for clinically significant prostate cancer,[14] although the confidence intervals are quite wide. Adopting this approach in the PRostate Evaluation for Clinically Important disease: Sampling using Image-guidance Or Not? (PRECISION) study allowed 28% of men to avoid a biopsy, but oncological outcomes have yet to be reported to indicate if this approach is safe in the long term.[12] Introduction of an MRI-based triage system to prostate biopsy into one Australian public teaching hospital resulted in 47% of men avoiding biopsy altogether, with clinically significant cancers being diagnosed in 60.5% of men with a 'positive' MRI, and considerable savings from a healthcare perspective.[15] At this stage, MRI is not recommended as an initial screening tool. When considering the interpretation of MRI, it is imperative to consider the individual patient's risk of prostate cancer based on their family history, PSA and DRE. Omission of biopsy is recommended only in low-risk cases and should be based on shared decision making with a well-informed patient.[16]

One important consideration for the use of MRI is the potential for variability among readers (reporting radiologists). An agreement rate of 78% between central and local reports seen in one large multicentre randomised trial,[12] reinforces the importance of ensuring scans are performed and reviewed at experienced centres.[9]

Active surveillance

Active surveillance aims to defer curative treatment for patients with low-risk, clinically localised prostate cancer to minimise treatment-related toxicity without compromising survival. It employs a predefined program of regular monitoring (with PSA, DRE and repeated biopsy) to allow for delayed intervention at a stage when the disease is still potentially curable. Currently there is no consensus regarding the optimal surveillance schedule.[17] Given that MRI improves the accuracy of biopsy, it is now recommended before confirmatory biopsy for all active surveillance patients if not already done prior.[16] At this stage, MRI has not replaced biopsy in active surveillance, and further research is required to clarify how it might be best incorporated into schedules to potentially reduce the number of biopsies needed.

Recurrent disease

Biochemical recurrence (BCR) occurs in 27–53% of patients after primary curative therapy and is defined differently depending on the modality of primary treatment: following radiotherapy, PSA needs to be >2 ng/mL higher than the PSA nadir level; after prostatectomy, any detectable PSA represents the presence of disease.[18] A proportion of men with BCR will progress to metastases and death; others will have local recurrence and may be curable with salvage treatment (ie salvage radiation for patients who underwent prostatectomy, or salvage prostatectomy following primary radiotherapy).

The key to determining who will benefit from local versus systemic therapy depends on the ability to determine the site of relapse. Given that recurrent disease can be detected biochemically often well before it is identifiable radiologically by CT or bone scan, treatment decisions regarding who should proceed with salvage are often imprecise, with many patients exposed unnecessarily to the morbidity of treatment without any therapeutic benefit. Prostate-specific membrane antigen (PSMA) positron emission tomography (PET) imaging has had a significant impact on decision making in this space.

PSMA is an enzyme expressed on the cell surface of prostate epithelium and other tissues, and sites expressing the protein can be imaged by detecting binding of radiolabelled PSMA ligand by PET. PSMA-PET has greater sensitivity for low-volume metastatic prostate cancer than traditional staging (combined CT and bone scan), with metastatic deposits being detectable even at PSA levels <1 ng/mL.[19] Patients with a scan that is negative for metastatic disease (with or without evidence of uptake locally) may have a better response to local salvage treatment, whereas those positive for metastatic disease may be better served with systemic therapies. There is also interest in the use of PSMA-PET (CT or MRI) as a primary staging modality for patients with intermediate- and high-risk disease prior to definitive local therapy (replacing the standard staging CT and bone scan), with early evidence suggesting greater sensitivity.[20] It is currently not funded for this indication, although this may change if prospective comparative studies are positive.[21]

Another area of ongoing interest is the concept of oligometastatic disease, which is well established in other tumours and posits that some patients with a limited number of metastases (<3 or <5, depending on the author) may represent a

'curable' metastatic state. Early detection with molecular imaging may allow these sites to be specifically targeted with local treatment, thus avoiding or delaying the need for systemic therapy. Results from stereotactic ablative body radiotherapy (an image-guided hypofractionated radiation technique that can be used to give very high doses of radiation to a target volume with usually minimal toxicity)[22] or salvage surgery in this setting show some promise, but long-term outcomes and the ideal patient characteristics have yet to be determined.

Metastatic disease

Established metastatic prostate cancer is incurable; for 80 years, castration/androgen deprivation therapy (ADT) was the standard treatment, followed by palliation once patients inevitably no longer responded (castration-resistant prostate cancer [CRPC]). This changed in 2004 when the taxane chemotherapeutic agent docetaxel was reported to prolong survival for patients with metastatic CRPC.[23] This has been followed by the approval of a slew of new systemic agents over the past 15 years, all of which are administered in combination with ADT and have been shown to improve survival,[24] further increasing the therapeutic options available to patients (Table 1).

First-line therapy

The biggest paradigm shift has been the finding that upfront administration of combination therapy at the time of diagnosis of metastatic disease (metastatic hormone-sensitive prostate cancer) confers a far greater overall survival benefit (approximately 10–18 months) than chemotherapy or androgen signalling–targeted inhibitors started at the onset of castration resistance (approximately 2–4 months).[24] This was first shown with six cycles of chemotherapy (docetaxel),[25] but has since also been shown with newer androgen signalling–targeted inhibitors such as abiraterone,[26] enzalutamide[27] and apalutamide.[28] There is some evidence that combination treatment of ADT with docetaxel has greater effect in patients with high-volume disease (visceral metastases or >4 bone lesions with >1 beyond the vertebral bodies and pelvis);[25] however, this is not universal[29] and appears less pronounced with androgen signalling–targeted inhibitors. The choice of agent is usually determined by patient factors (Table 2). For medically fit patients, docetaxel in addition to ADT is the usual starting point (predominantly as a result of MBS funding restrictions in Australia).

Subsequent therapy

For patients who were initially treated with ADT alone, those with progressive CRPC may be offered either chemotherapy (docetaxel) or androgen signalling–targeted inhibitors on the basis of multiple factors including previous response to ADT, fitness for chemotherapy and specific patient factors (Table 2). Early reports suggested that detection of a particular splice variant of the androgen receptor (ARv7) in circulating tumour cells may identify patients who are resistant to androgen signalling–targeted inhibitors.[30] However, this process has produced mixed results in validation studies[31] and is not widely used clinically. Post-chemotherapy, there is no compelling evidence that one agent is superior to another, and patient factors are again the main drivers of choice. For example, abiraterone might be less preferable in a patient with diabetes who has poor glycaemic control because of the need for concomitant steroids. For patients who have failed two lines of treatment (usually docetaxel followed by an androgen signalling–targeted inhibitor), very recent evidence suggests that second-line chemotherapy withcabazitaxel results in better clinical responses than the alternative androgen signalling–targeted

Table 1. Systemic treatment options

Timing of treatment	Agent
Metastatic hormone-sensitive prostate cancer	Docetaxel
	Abiraterone
	Enzalutamide
	Apalutamide
Non-metastatic castration-resistant prostate cancer	Enzalutamide
	Apalutamide
	Darolutamide
Metastatic castration-resistant prostate cancer	Docetaxel
	Cabazitaxel
	Abiraterone
	Enzalutamide

Table 2. Agents currently available in Australia

Agent	Mechanism of action	Adverse effects
Chemotherapy		
Docetaxel	Taxane chemotherapy	Myelosuppression, neuropathy, fatigue, nausea/vomiting/diarrhoea, peripheral oedema
Cabazitaxel		
Androgen signalling–targeted inhibitor		
Abiraterone	CYP17A1 inhibitor (prevents androgen synthesis)	Hypertension, hypokaelaemia, fluid retention, cardiac disorders, liver function test abnormalities (low-dose prednisolone is co-administered to reduce mineralocorticoid excess)
Enzalutamide	Androgen receptor inhibitor	Fatigue, seizures, back pain, arthralgia, peripheral oedema, headache, hypertension
Apalutamide		Hypertension, rash, gastrointestinal upset, fatigue, hypothyroidism, fracture, falls, QT prolongation

inhibitor (eg treatment with abiraterone if already treated with enzalutamide and vice versa).[32]

Germline testing

There is growing interest in genetic testing for risk stratification and treatment selection in prostate cancer. Patients who harbour germline defects in genes involved in the repair of DNA damage (such as *BRCA2*) are at an increased risk of developing certain cancers, including prostate cancer, when compared with patients without defects. Accumulating data indicate that such mutations are more commonly seen in patients with metastatic disease,[33] suggesting that testing may be useful to determine the risk of progression early in the disease course. For example, patients with germline *BRCA2* with low-risk prostate cancer may be unsuitable for active surveillance because of a risk of high rates of DNA damage accumulation leading to rapid clinical progression.[34] Patients with these defects also respond better than those without defects to certain systemic therapies such as PARP inhibitors (eg olaparib), which show promise but have yet to be approved.[35]

Genetic testing is not yet a part of routine prostate cancer care in Australia, and although several commercially available genetic biomarkers exist, their routine use in clinical practice is not supported by urological guidelines. As yet, there is no consensus regarding who should be tested and when testing should be offered.[36] Some suggest consideration of genetic testing in those with prostate cancer diagnosed under the age of 65 years, or patients with relevant family history such as cancers related to hereditary breast and ovarian cancer syndrome or Lynch syndrome (hereditary non-polyposis colorectal cancer).[37]

Identification of germline mutations has significant implications for the families of patients, as this DNA is passed on to children. Referral to a genetic counsellor for assessment, and to provide patients with information to determine if testing is right for them and their families, is important. Patients should be aware that testing may have insurance implications, highlight the risk of other cancers (that the patient may not anticipate) and identify variants of unknown significance that require ongoing follow-up in case they are revealed to be important at a later date.

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