



Michael Izard

Early management of prostate cancer

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Prostate cancer is now the commonest cancer diagnosed in Australia. In 2005 there were 5913 men diagnosed with prostate cancer in New South Wales alone (31% of male cancers; 17% of all cancers).¹ However, that year there were only 980 deaths from prostate cancer in NSW, and so prostate cancer dropped to be the fourth commonest cause of cancer death, ahead of breast cancer with 877 deaths.¹ This discrepancy is a major cause of the angst experienced in the detection and management of prostate cancer. What is needed is a way to separate the significant prostate cancers from the insignificant ones, and accept that identifying them is a very different issue to managing them aggressively.

Screening

There is a divergence in professional organisation recommendations about prostate cancer screening. Some organisations recommend screening, such as the Urological Society of Australia and New Zealand.² Other organisations, such as The Royal Australian College of General Practitioners, suggest that there is insufficient evidence to recommend routine screening for prostate cancer.³

Recent literature has added further confusion, providing ammunition for both camps on whether or not to screen. In 2009, two large studies published their interim results. The American Prostate, Lung, Colorectal and Ovarian Cancer Study trial⁴ was criticised as heavily

flawed in its selection of men already screened by prostate specific antigen (PSA) (and thus removing many of the already present malignancies). In this study 82% of the 'screened' arm were actually screened, while 52% of the 'control' arm also chose to have their PSA measured. Unsurprisingly, little difference in outcome was shown. The European Randomised study for Screening in Prostate Cancer (ERSPC)⁵ showed an advantage in survival to men who were screened, with a relative reduction in death from prostate cancer by 20%. This translates into an overall reduction of seven per 10 000. Neither trial is ideal; the ERSPC was an amalgamation of trials from different countries, with slightly different entry and design criteria, but most were screened with PSA on a 4 yearly basis, perhaps too long an interval. For a small benefit in survival there were many more men treated (497 vs. 223). The data is interim, and still too short for a truly valid answer.⁶

This quality of life after treatment is being reviewed in the European study, but by the time the data emerges it is possible that both surgical and radiation treatment techniques will have advanced and we will have difficulty extrapolating from this 'old' information to these newer techniques. Radiation oncology now uses conformal radiotherapy and intensity modulated radiation therapy (IMRT) techniques,⁷ and with the introduction of tomotherapy (or 'RapidArc'),⁸ there is steadily reducing radiotherapy morbidity. Surgical techniques with laparoscopic and robotic options may reduce their side effect rates.⁹ Yet other techniques exist that are still experimental (eg. cryotherapy or high intensity focused ultrasound [HIFU]).

At times there is an assumption that active management by either surgery or radiotherapy can be avoided with the judicious use of hormonal manipulation once the man is symptomatic with progressing disease. This overlooks that hormonal therapy carries its own set of side effects, both physical and psychological. It forgets that what might hold true for an infirm octogenarian does

not hold true for a man in his 50s or 60s when hormonal manipulation as a primary treatment may rob him not only of quality life, but of one (possibly two) decades of life as well.

PSA, PSA doubling time, PSA velocity and free to total ratio

Given the limitations of PSA screening, other options are being actively investigated. Studies, such as the Baltimore Longitudinal Study of Aging,¹⁰ have shown that men over 75 years of age with a PSA of <3 are unlikely to die of prostate cancer. It is also clear that cancers start with a low volume, hence a low PSA does not mean that there is no cancer in younger men. As such, a PSA of <4 in the younger man is not 'safe'.^{11,12} Approximately 25% of men with a PSA of 3–4 already have prostate cancer,¹² although the significance of that malignancy is the crux of the issue (the ERSPC used an upper limit of normal as three, and identified more cancer as a result). The doubling time of a PSA rise may depend on whether the disease is confined within the gland or if it has metastasised, and this applies both before and after radical treatment. There is controversy, but it is generally agreed that a PSA doubling time (PSA-DT) of 1 year or more is indicative of a tumour confined to the prostate, while a PSA-DT of 6–10 months or less is suggestive of metastatic disease.¹³

When the PSA is <10, it may be helpful to use three broad groupings based on its rate of rise, ie. PSA velocity (PSA-V). If the PSA-V is <0.3 ng/mL/yr then there is probably little cause for concern that significant prostate cancer present. Conversely, if the PSA-V is rising at a rate of >0.75 ng/mL/yr then there should be concern that malignancy might be present and further investigation considered. Biopsy has been recommended if the rate of rise is >1.0 ng/mL/yr.¹⁴ The PSA-V impacts with PSA-DT, as a rise in PSA of >1.0 ng/mL/yr implies a volume of disease that is becoming clinically relevant.

The free to total PSA ratio (FTTR) has been clearly shown to be a useful aide in discriminating

between a high PSA due to malignancy against a high PSA due to other causes.¹⁵ If the FTTR is >25%, then malignancy is either unlikely or unlikely to be of clinical significance. Catalona's trial¹⁵ showed 'that the 25% cutoff detected 98% of cancers for subjects aged 50–59 years, 94% for subjects aged 60–69 years, and 90% for subjects aged 70–75 years'.

From this it can be seen that serial PSA values, including the FTTR, can provide useful information; far more than a PSA reading in isolation (Table 1). By monitoring the value, the velocity and DT, and perhaps the decline in the FTTR, men can be identified to pass to the next step of prostatic biopsy and identification of malignancy. Ideally, we should dissociate this step from a societal assumption that identification of such a malignancy automatically progresses the man to treatment.

Understanding choices

The consultation that delivers the diagnosis is often where treatment options are proffered. As such, it is not reasonable to assume that everything has been fully comprehended. Having the patient return (or see another clinician) to repeat treatment options allows a better understanding, and consequently more control over the process. A second opinion could be provided by the surgeon, but perhaps a radiation oncologist might provide another perspective. Obviously this puts burdens on the health system and patient, but it should at least

be considered and used where possible. Support groups such as the Prostate Cancer Foundation of Australia and Lions Australia can also be of assistance. All choices should be proffered: active surveillance, cancer chemoprevention with finasteride,¹¹ hormonal manipulation, radical prostatectomy, external beam radiotherapy (EBRT) (in one of its guises) or brachytherapy. It is here, at this point, that the dissociation of diagnosis from treatment is required, and it is here that input from a second opinion to re-emphasise this and answer questions may be invaluable.

Radiotherapy options

There is an increasing lexicon of radiotherapy choices, perhaps best explained by a radiation oncologist. External beam radiotherapy has progressed significantly with better computers and better imaging, such that doses of 70–80 Gy (compared to the 60–66 Gy of 10 years ago) can now be given with much reduced toxicity. This need for a higher dose has been shown in a recent meta-analysis to be of benefit¹⁶ using techniques such as IMRT and RapidArc tomotherapy or image guided radiotherapy. Brachytherapy techniques also aim to deliver these higher doses, with ~90 Gy equivalent doses from either permanent implants (low dose rate seed implantation) or temporary implants (high dose rate implants which are usually given with EBRT). Brachytherapy has an advantage over external techniques of being able to finesse

the dose away from the rectum to reduce or avoid the rectal morbidities seen with techniques used 10 years ago. These options have been shown to have very good long term control^{17,18} but all have positives and negatives, which are best discussed in a tailored and individual basis.

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Table 1. Brief guide to PSA interpretation	
Single PSA level	
PSA <3 in man aged >75 years	Patient unlikely to die from prostate cancer
PSA 3–4	25% may have prostate cancer
Free to total PSA ratio (FTTR)	
FTTR >25%	Prostate malignancy unlikely or unlikely to be of clinical significance
PSA velocity (PSA-V)	
PSA <10 and PSA-V <0.3 ng/mL/yr	Little cause for concern of significant prostate cancer
PSA <10 and PSA-V >0.75 ng/mL/yr	Malignancy may be present. Consider further investigation
PSA <10 and PSA-V >1.0 ng/mL/year	Prostate biopsy recommended
PSA doubling time (PSA-DT)	
PSA-DT of >1 year	Tumour (if present) likely to be confined to prostate
PSA-DT <9 months	Suggests metastatic disease