

# PROSTATE CANCER FOR THE GENERAL PRACTITIONER

PSA booklet edition II

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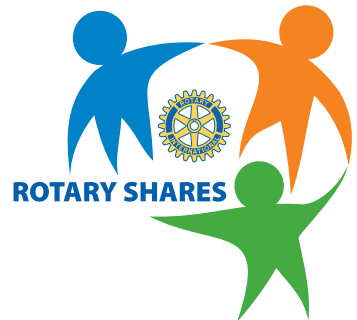
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**The University of Sydney**

# Forewords

Prostate cancer is one of the most important men's health issues. In Australia prostate cancer is the third most common cause of death among men. Yet testing for possible prostate cancer remains the subject of some confusion and controversy.

Phillip Stricker, one of Australia's leading urologists and specialists in prostate cancer treatment, and Kerry Phelp, a well respected general practitioner and former President of the Australian Medical Association, have combined their talents to produce a clear outline of their recommendations.

As Phillip and Kerry point out, there are no cut and dried answers to many of the questions about prostate cancer screening investigations and treatment, but as general practitioners we need to be prepared to discuss prostate cancer testing with our male patients. This booklet will assist Australia's general practitioners to work more effectively with our patients to manage both requests for testing for prostate cancer and the interpretation of test results.

## **Professor Michael Kidd**

Head of the Discipline of General Practice  
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I am pleased to be asked to write a foreword to the second edition of this useful guide to the PSA for the general practitioner.

Twelve years ago I was diagnosed as having prostate cancer. Having led a healthy life, I was shocked at the use of the 'C word' and quite ignorant of the nature of prostate cancer. From general reading and casual conversations, I was fairly familiar with the existence of breast cancer and gynaecological cancers, their symptoms and potential consequences. In my lifetime there had been a revolution in the public awareness about these cancers and their treatments. When I was younger, breast cancer for example was rarely mentioned in public, particularly in mixed company. But due to the efforts of many individuals and groups, the reticence to discuss such personal matters had been replaced

with widespread public discussion and informative articles in the press.

No such change had occurred for prostate cancer which remained largely unmentionable even in all-male company, let alone in the media. In fact, at the time I was only vaguely aware of the function, specific location and size of the prostate. It was news to discover that each year about the same number of men die from prostate cancer as women die from breast cancer. I found myself wondering how I, an intelligent, well educated adult male could be ignorant of something so important for my health and sexual life. I also found myself wondering why the conspiracy of silence that had prevailed around normal female sexual functioning and related disorders in my youth still existed among men.

These concerns were put aside as, after seeking the information needed to understand the diagnosis and make a decision about treatment, I faced the reality of having a radical prostatectomy. However, after recovery I joined a small prostate cancer support group at St. Vincent's Hospital. This group met and decided that men needed to be better informed about the disease and treatment options.

We found that, like us, many of those diagnosed with prostate cancer were ignorant about the nature of the disease before they were diagnosed and that they had experienced great difficulty in finding GPs or specialists to explain, in words they could understand, the seriousness of their situation and what treatment would be most appropriate and why. There also seemed to be a remarkable lack of accessible published information. Many felt angry; they felt that the medical system had let them down. Facing imminent death, some asked, 'Why didn't my own doctor suggest I be tested?' Others wondered, retrospectively, whether they had had the best available treatment when the advice they had received at the time of diagnosis was so inadequate.

From these concerns a number of initiatives resulted in the formation of the Prostate Cancer Foundation of Australia. PCFA has achieved a remarkable amount of public support and now provides millions of dollars annually for prostate cancer research. Importantly PCFA and other concerned groups have worked together to raise public awareness about prostate cancer and its treatments. While there is still much to

accomplish, there is now a wide range of published materials available to men who are diagnosed, as well as informative web sites, videos, toll free help-lines and an increasing number of support groups across the country.

GPs are the gatekeepers of the PSA test. There is now increasing evidence that early diagnosis can save lives. Therefore GPs need to be informed of the benefits and limitations of the PSA test, to inform those clients who are in the appropriate risk and age categories that the test may be appropriate for them, and to be ready to answer, in helpful and informative ways, the questions that clients may ask. An increasing proportion of clients will come well informed and initiate such discussions themselves but there are still many who will know little or nothing. In all cases, the general practitioner is a vital first step in guiding them in the most appropriate path to healing and support.

The authors are eminent clinicians in their field and present the best current available knowledge in a form designed to be most useful to the GP. The Prostate Cancer Foundation of Australia is proud to be associated with the republication and distribution of this widely used booklet. This is another vital step in increasing public awareness of the disease and ensuring quality of treatment.

**Professor Dexter Dunphy AM**

Visiting professor UTS

Director PCFA

Chair of the Public Awareness and Education Committee

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# Introduction

This booklet is a guide for general practitioners faced with the question of how best to manage consultations with men who present for a general check-up or who have particular concerns about prostate cancer.

The understanding of prostate cancer continues to be in the stage of rapid evolution. In the space of a few short years it has gone from being seen as a disease of elderly men who would likely die of some other cause, to become a disease that every man should know about. If you have any doubt about this at all, consider that not only is prostate cancer the most commonly diagnosed cancer in males, it is also the second most common cause of male cancer deaths (1). 18,000 Australians were diagnosed with prostate cancer in 2006 and just under 3,000 men died of prostate cancer in the same year. Approximately 13% of all men will be diagnosed with prostate cancer in their lifetimes. 2-3% of Australian men will die each year of prostate cancer (1).

Prostate cancer is different from most other cancers. What makes it different is the lack of symptoms in early disease, the extremely variable course and the different ways of managing it. As early prostate cancer has no symptoms, only active testing will lead to the detection of prostate cancer when it is still contained within the prostate gland (localised). Further, the variable natural history of the condition means that some patients with screen-detected cancers may have a relatively indolent cancer and end up receiving treatment unnecessarily. Although even low grade tumours can progress over 20 years (2). Finally, there are a number of different and effective treatments for localised prostate cancers. How effective each particular treatment is will differ from case to case and from person to person. It will also differ from doctor to doctor depending on their level of experience and expertise in managing prostate cancer. These issues have led to a perceived lack of consensus among expert bodies regarding programs targeting the early diagnosis of prostate cancer (3).

## **There are three ways to decrease the death rate from prostate cancer:**

- Prevention
- Early detection and treatment
- Successful treatment of advanced disease



# Reasons for Testing

PSA testing has been responsible for the earlier detection of disease and the increase in curative treatment. There is an increasing body of evidence suggesting that the use of PSA testing leads to the detection of cancers at an earlier and more curable stage.(5)

Furthermore, there is increasing evidence that the falling death rate from prostate cancer can at least in part be attributed to the efforts of testing and early treatment(6). In countries with a high uptake of PSA testing there has been a consistently lower death rate from prostate cancer(22). This is most evident in the Tyrol in Austria where there has been a provisional policy for free PSA testing from 1993 to the current year with an almost 80% uptake in the Tyrol but not in the rest of Austria. In the Tyrol in 2005 the death rate from prostate cancer was half that of the rest of Austria where PSA testing was not routine policy(4). The final confirmation of the degree of benefit of PSA testing will only, however, be determined by the European and American randomised controlled trials due to report between 2008 and 2009 (7,8). Even in these trials there is some concerns about contamination of the control group(20). Given these emerging indicators, it would seem unacceptable to withhold from or not discuss the option of prostate cancer testing with appropriately selected groups of men.

Testing, however, is not a perfect science for the following reasons:

- some cancers are latent and slow growing and do not require treatment (over-diagnosis)
- some cancers are incurable even with early detection
- all treatments have potential side-effects
- a PSA test can be abnormal when cancer is not present
- a PSA test can be normal, even when cancer is present

Over-diagnosis occurs to a different extent depending upon what age group one tests and the number of people ultimately receiving treatment. Over-diagnosis can be minimised by:

- appropriate selection of patients for PSA testing
- the use of active surveillance for small well-differentiated cancers in the older age group and
- the assurance of high quality effective treatment in appropriate patients.

Under-diagnosis also occurs to a varying extent and this can be minimised by having a lower PSA threshold and a lower PSA

velocity in younger patients (9). Although all treatments carry potential for side-effects such as impotence and incontinence, there has been significant improvement in surgical and radiotherapeutic techniques such as better nerve sparing techniques, laparoscopic robot assisted techniques, brachytherapy and conformal radiotherapy. The frequency of side-effects has decreased markedly. It has also become clear that side-effects can be minimised by treatments being performed by more experienced units (15). Furthermore, treatments are more likely to be successful if cancers are detected earlier as there is a lower chance of a positive surgical resection margin and a higher chance of potency and continence preservation if nerve sparing surgery can be used in cases where the cancer is contained.

Furthermore we know more accurately how to select patients for active surveillance and with improving clinical judgement, these less threatening cancers are more likely to be identified as such at the time of diagnosis and less likely to be treated. Increasingly, they are monitored with treatment instituted at a later stage and only if it becomes necessary. Identifying these so called 'latent cancers' more accurately is the subject of intense current research.

Finally, PSA is not a perfect test and is not specific to prostate cancers. For example, only 1:3 patients with a PSA between 4 and 10 will prove to have cancer. A recent Australian audit detected cancer in 40% of patients with a PSA between 4-10. (personal communication USANZ) Furthermore, 20% of patients with a PSA of less than 4 will prove to have cancer. (10) This issue is being

addressed by yearly monitoring of PSA and watching the PSA velocity thus picking up cancers at an earlier stage even when the total PSA is within the normal range (9).

Around the world, the official view on prostate cancer testing differs from country to country. The Urological Society of Australasia's position is: "Individual men, aged 50 - 70, with at least a ten-year life expectancy, should be able to be screened by annual D.R.E. and PSA testing after appropriate counselling regarding the potential risks and benefits of investigations and the controversies of treatment." It should be left to the individual doctor to decide whether to advocate testing in a man not requesting it. Population screening of asymptomatic men is not recommended (11). The Cancer Council Australia and The RACGP recommend a patient centred approach emphasising an informed and shared decision process.

However, there are multiple other organisations, including the American Urological Association, the American Cancer Society, the United States Preventative Services Task Force, the National Cancer Institute, the American College of Physicians, the American College of Family Physicians, the Centre for Disease Control, the U.S. Department of Veterans Affairs and the National Comprehensive Cancer Network, all of which have various recommendations that have been published. Some of these organisations feel there is insufficient evidence to support prostate cancer population screening, whilst others recommend testing after appropriate informed consent (3,12).

Recently, the Cancer Council Australia, the Australian Prostate Cancer Collaboration, the Urological Society of Australia and New Zealand, the Prostate Cancer Foundation of Australia and Andrology Australia have produced a guide for General Practitioners on this important topic. The guide aims to help GPs support their patients in making informed decisions about PSA testing. It is available at the Andrology Australia website: <http://www.andrologyaustralia.org/docs/PSAdecisioncard20041007.pdf>

The following are some general facts on prostate cancer:

- Incidence is 13% in Australia.
- Death rate is 2-3% in Australia.
- Inherited prostate cancer accounts for 10% of all prostate cancer patients.

- 40% of patients diagnosed with prostate cancer under the age of 55 have a strong family history of the disease.
- Family history increases the risk of prostate cancer (table 1).
- There are no proven effective preventative measures for prostate cancer.
- Advanced cancer has no cure.
- Early prostate cancer has no symptoms.
- For early detection of prostate cancer, a PSA blood test and a digital rectal examination are both needed. The chance of cancer given a positive PSA test is 40%. The chance of cancer given both abnormal PSA and digital rectal examination tests is at least 50%. Cancer of the prostate can be present with a normal PSA.

| <i>Table 1</i>  |          |
|---|----------|
| <b>Prostate Cancer Risk and Family History</b>                      |          |
| Average incidence   | 10 - 15% |
| 1 first degree relative   | 20 - 30% |
| 2 first degree relatives  | 50%      |
| 3 close degree relatives:<br>risk approaches                        | 100%     |
| All patients with a family history should be considered "high risk" |          |

- The falling death rate in communities that test for prostate cancer is likely attributable, at least in part, to early detection and treatment and better treatment of advanced disease.
- The longer a patient's life expectancy, the more likely they are to benefit from testing. Testing is most likely to benefit men between 50 and 75 years of age and between 40 and 75 years of age with a family history.
- Chemoprevention has not been found to reduce the incidence of aggressive prostate cancer.
- Complementary therapies such as vitamin E, vitamin D, selenium, Lycopene, green tea, phyto-oestrogens and diet may have a role to play in prevention but evidence is still uncertain (table 2).

Table 2

### Recommended Preventative Strategy

1. Low saturated fats
2. Low calorie intake
3. No obesity
4. Selenium (100 - 200mcg/day)
5. Lycopenes 6mg/day
6. Vitamin E (< 400 I.U/day)
7. Vitamin D3 ( $\leq$  10,000 I.U/day)
8. Fish oil/Omega 3 fatty acids 4,000mg/day or > 3 serves of fish a week
9. Soy Isoflavins
10. Zinc 10mg
11. Healthy heart diet (Mediterranean)

# Pathology

Prostate cancer occurs when the tissue of the prostate gland changes. The extent of the change defines the degree of cancer and, therefore, the prognosis. When a cancer develops, the glands multiply and change their architectural pattern. This range of patterns has been classified under the Gleason grading system named after the pathologist who first designed the system.

## Gleason grade and score

The Gleason grading system recognises five patterns of grades of cancer (fig 2).

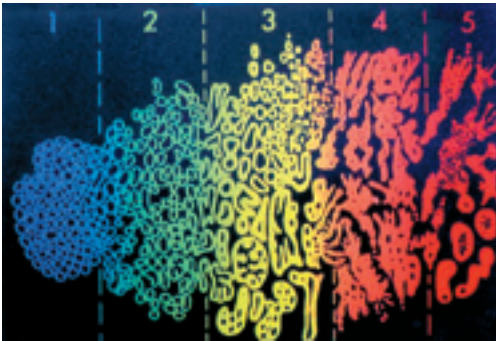


Fig 2 - Gleason Score  
There are five Gleason grades as above. The commonest 2 grades in the biopsies are added together to give the Gleason score on a scale of 2 to 10.

The Gleason score indicates how aggressive the cancer is and how fast it is growing. The higher the score the more aggressive the tumour.

These are given a number from 1 to 5. However, the pattern of any one cancer can be mixed and the prognosis for any patient depends upon this mixed pattern. The two most common or dominant patterns are each given a separate number and then the two numbers are added to give the Gleason Score, e.g. 3+4=7. The Gleason Score can, therefore, be between 2 and 10. In general terms, grade 1 and 2 are rarely reported as they are either rare or such slow growing tumours that they are insignificant. In general terms, a Gleason Score 3+3=6 tumour has a relatively good prognosis; a Gleason 7 tumour is intermediate and a Gleason 8 to 10 tumour has a poor prognosis. In the Gleason 7 category a Gleason 4+3=7 tumour is a worse tumour than a Gleason 3+4=7 as there is more Gleason 4-pattern than 3-pattern in the former.

## Cancer stage

As well as the pattern of architecture of growth (the grade), the extent of cancer felt on digital rectal examination is also important in estimating a prognosis. The extent of cancer is referred to as the cancer stage (fig 3). Stage 1 (T1) cancers cannot be felt on DRE; stage 2 (T2) cancers can be felt, but still feel to be within the prostate; stage 3 (T3) are felt to have extended outside the prostate and stage 4 (T4) are felt to be well outside the prostate, invading adjacent organs, e.g. the bladder or pelvic wall.

## Latent or occult tumours

We know some cancers are so small and progress so slowly that they are unlikely to be a real threat (latent or occult tumours). Generally, these so-called insignificant tumours are defined as tumours of  $<0.5\text{cc}$  with a Gleason Score of 6 or less (fig 4).

## Spread of prostate cancer

Prostate cancer generally spreads through the lymphatic system or blood stream. Most commonly, it spreads to the pelvic and iliac lymph glands or via the bloodstream to bones. Spread is rare when the PSA is  $< 10$  and the Gleason Score is  $< 7$ . When the PSA is  $> 10$  or the Gleason Score  $> 7$ , it is wise to do an abdo-pelvic CT scan and bone scan to assess the presence of pelvic lymph gland enlargement or bony secondaries. If either of these scans shows the presence of metastases, clearly this would influence management.

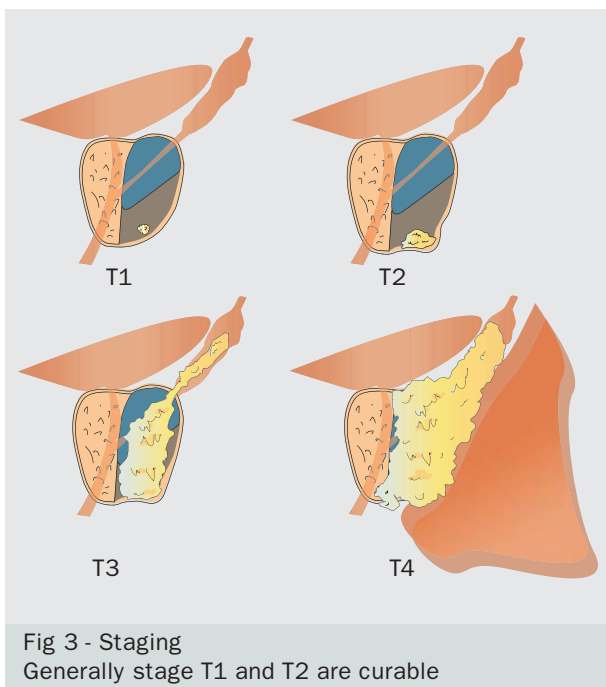


Fig 3 - Staging  
Generally stage T1 and T2 are curable

## Digital rectal examination

The normal prostate feels small, has two lobes, is symmetrical and firm (rubbery), but not hard. The enlarged, benign prostate is large, smooth, spongy and symmetrical. Prostate cancer feels hard in consistency. One should be suspicious of cancer when one feels a nodule, general hardness or gross asymmetry of the prostate (fig 5).

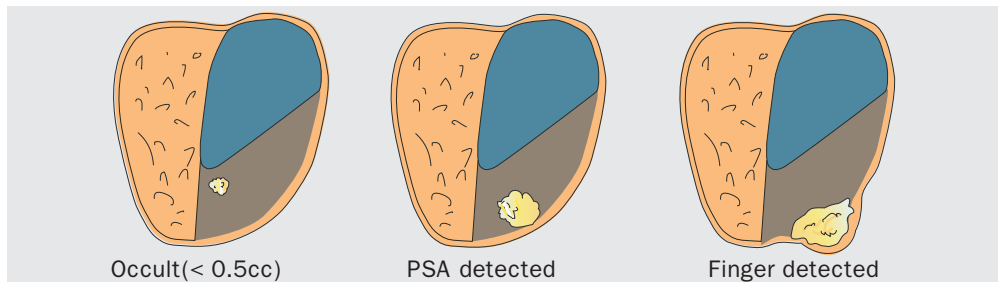


Fig 4 - Latent and significant cancers

Latent (insignificant or occult) tumours are usually defined as tumours less than  $0.5\text{cc}$  with a Gleason score of 6 or less. PSA and digitally detected tumours tend to be bigger and more aggressive tumours.

## Prostate biopsy

A prostate biopsy is a sampling of the prostate (fig 6) generally using a biopsy gun which takes multiple samples from the prostate in up to 20 sites. The procedure is often performed under light anaesthetic or local anaesthetic. It can be done transrectally or transperineally. A biopsy carries a very small risk of serious infection.

## Pathology report

The pathology report on needle biopsies will indicate the presence of cancer, predict

the Gleason Score, the location of the cancer within the prostate and note any feature that might indicate whether the cancer is confined to the prostate. The pathology report on a radical prostatectomy specimen will give more complete and accurate information on the presence and location of the cancer, the Gleason Score, whether there is extra-prostatic extension and whether the tumour has spread to the surgical resection margins or surrounding tissues.

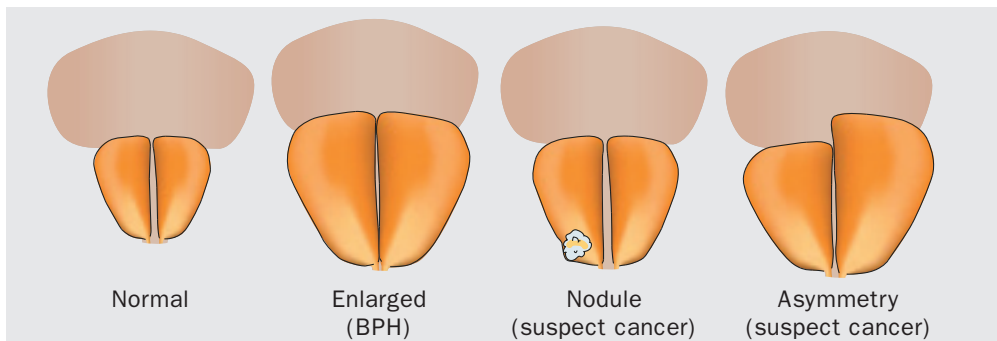


Fig 5 - DRE findings

One should suspect prostate cancer if there is a hard nodule or asymmetry. Size alone does not indicate cancer.

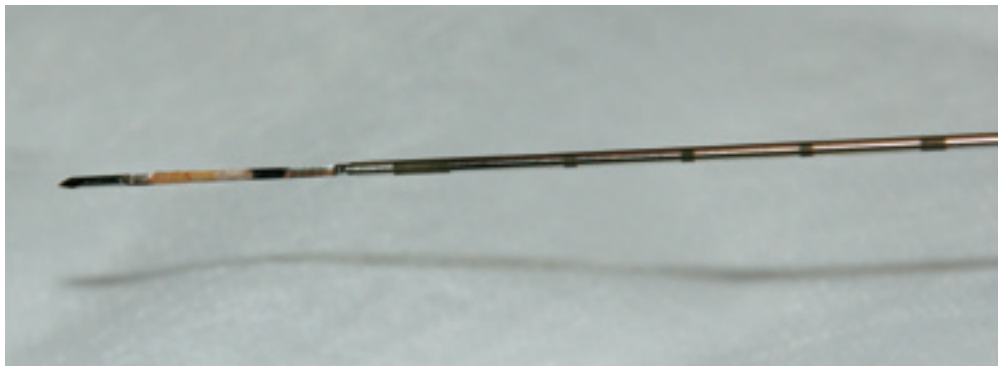


Fig 6 - Needle biopsy of prostate tissue

# Discussing PSA Testing

As with any area of medical practice as recommended by the NH and MRC, it is necessary to provide sufficient information for each and every intervention so that a patient can understand the rationale for it.

## Informed consent

Although a formal structured informed consent is generally reserved for more invasive procedures than PSA testing, each individual requires some informed consent. Generally one should establish the patient's main concerns (such as family history of prostate cancer, urinary symptoms), provide some basic information about prostate conditions and prostate cancer, clarify the risk of the individual, have a brief discussion about the pros and cons and finally clarify the patient's values and whether they are comfortable with PSA testing. The PSA decision card\* may be a useful written document in this context.

By consulting their doctor, patients are not specifically consenting to procedures such as a PSA test and a digital rectal examination that are reasonable in the opinion of the doctor. So the procedures need to be explained, preferably with some written information as the issues are complex. The patient should give verbal consent. If even after reasonable explanation the patient declines all or any part of the testing, this should be recorded in the patient's notes.

Good clinical judgement and an excellent patient doctor relationship with continuity of care remains a critical component of the informed consent process. All men who could benefit from PSA testing should be made aware of the test and the degree of detail provided, clearly needs to be individualised. Certainly, men who ask for PSA testing should not be discouraged or, worse still, denied it.

## The decision process

It is preferable that men requesting a PSA test be provided with written information. A PSA decision card\* which has been endorsed by numerous organisations is a useful tool to help in this regard.

### The decision process should:

#### a) clarify the patients concern.

Are they worried about their urinary symptoms or truly concerned about cancer?

#### b) provide basic information.

What is a prostate and what is prostate cancer, how accurate is the PSA test and the fact that both the PSA and digital rectal examination test need to be used.

#### c) provide an estimate of risk.

What is their lifetime risk, what is their lifetime risk of dying of prostate cancer, do they have a family history in which case a single first degree relative with prostate cancer diagnosed before age 70 will increase

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\* <http://www.andrologyaustralia.org/docs/PSAddecisioncard20041007.pdf>

the risk by double whereas two first degree relatives will increase the risk fivefold.

A single PSA at the age of 40 can be used to estimate the lifetime risk of developing prostate cancer (13,14). Furthermore, although the chance of finding cancer of the prostate increases with age, the chance of dying from cancer falls as one gets older. Generally, one needs at least a 10-year life expectancy and preferably a 15-year life expectancy, to benefit from early detection. Men aged 50 - 75 are most likely to benefit from early detection, although men from 40 - 75 with a significant risk factor, e.g. family history, are likely to benefit.

**d) explain the pros and cons of early detection. The pros:**

- Early prostate cancer has no symptoms and PSA testing can detect prostate cancer before there are symptoms, thus increasing the chance of detecting prostate cancer at a curable stage.
- Prostate cancer may progress over time. Modern treatments have a high cure rate for the majority of tumours detected by testing.
- Prostate cancer that has spread beyond the prostate gland is more difficult to cure.
- The side-effects of treatment are fewer with early diagnosis and treatment, e.g. patients with earlier localised cancers can be offered nerve-sparing surgery or brachytherapy.

- Treatment of localised prostate cancer by surgery reduces the development of metastatic disease and mortality from prostate cancer compared with simple observation.
- Treatment of advanced cancer has significant side effects.
- Most cancers detected in patients with a > 15 years life expectancy are significant tumours, i.e. likely to cause significant morbidity or mortality if the cancer is left untreated.
- A very low PSA level (< 1 ng/ml) and normal digital rectal examination are very reassuring.
- Side-effects of treatment, e.g. incontinence, impotence and rectal damage, as a result of radical prostatectomy, brachytherapy or radiation treatment, have all considerably reduced in incidence over the last two decades, particularly from high-volume treatment centres (15).

**The cons:**

- PSA is not specific to prostate cancer. A PSA test can be abnormal when there is no cancer e.g. only 40% of patients with a PSA of 4 - 10 will prove to have cancer. Furthermore, 20% of patients with a PSA of < 4, will prove to have cancer (10).
- Some cancers grow slowly and are not a threat to life. These cancers may be treated unnecessarily, leading to the

risk of unnecessary side-effects. All treatments have potential side-effects and can affect quality of life.

- There is no clinical trial evidence yet that PSA testing programs save lives, although this may change in the future when two large trials from Europe and the U.S.A. report their results (7,8).
- Even with early detection, cure cannot be guaranteed.
- In a small number of people prostate biopsies can lead to serious infection. However, this can be minimised by a careful technique and antibiotic prevention.
- As with many cancers, if prostate cancer is diagnosed, treatment decisions may be quite difficult and patients will often need time for careful consideration and may need several opinions.

#### **e) explain treatment side-effects.**

Potentially curative treatments for localised prostate cancer include:

- radical prostatectomy via the open, laparoscopic or robot-assisted laparoscopic route.
- radiation therapy, including external beam therapy and brachytherapy.

These treatments are associated with a risk of impotence and, less commonly, urinary incontinence and bowel side-effects such

as radiation proctitis. The prevalence and profile of side-effects vary for the different treatments. More recent results, particularly from high-volume units, have shown considerable improvement in all three of these side-effects. Incontinence and bowel problems are particularly uncommon, whilst impotence has been markedly reduced by better techniques of nerve-sparing surgery.

#### **f) help clarify patient values.**

It may be useful to give examples of the reasons men have given who have had or not had the PSA test. The PSA decision card also has a good section on what is important to men, to try and help them make up their minds. For example, a man focussed on minimising the chance of dying or developing advanced prostate cancer is clearly a candidate for testing, whilst a man who feels his chance of developing prostate cancer is low and who is particularly concerned about potential treatment side-effects, or is not convinced of the effectiveness of testing, may choose not to be tested.

#### **g) describe the sequence of events related to testing.**

As part of an effort to detect prostate cancer at an earlier and more curable stage, you will have a program of regular blood tests. It is always done in association with a finger examination of the prostate. The blood test measures the PSA (Prostate Specific Antigen) level. If it is abnormal, further tests, monitoring or a biopsy may be necessary. As most of these cancers tend

to progress slowly, a period of monitoring the PSA level may be required, to improve the accuracy of predicting whether or not prostate cancer is present. A biopsy may then be required. Prostate cancer is only diagnosed via biopsies. This would require referral to a specialist (urologist). Other conditions of the prostate may increase the PSA level and therefore not all biopsies will confirm prostate cancer. These other conditions are benign and may require no treatment. Small cancers and awkwardly placed cancers may not be detected at the first biopsy, so regular PSA testing should continue, even after a negative biopsy, to avoid missing these tumours in the future.

If a biopsy is recommended, this carries a very small risk of serious infection. This can, however, be minimised by newer techniques and antibiotics. The procedure is often performed under light anaesthesia or local anaesthetic. If a cancer is detected, there are many treatments, ranging from surgical removal, insertion of radioactive seeds and external beam radiotherapy, among others. Surgery can be performed by the open, laparoscopic or robot-assisted laparoscopic route. As each treatment may have side-effects (impotence, incontinence and bowel problems) as well as differing cure rates, the treatment must be selected to treat the individual patient's needs.

The factors that should be taken into consideration before any treatment is recommended include: the type of cancer, prostate symptoms, prostate size, age,

general health, particular personal priorities and preferences and the experience of the institution. A patient may need to seek second opinions before making a treatment decision. Most cancers detected at an early stage are, indeed, curable.

**h) include decision confirmation.**

Ask what further questions the patient may have and whether he wants to be tested immediately or on another visit. It should be noted that a digital rectal examination can be performed on the same day as the PSA. It is important to emphasize that prior to a PSA test there should be no ejaculation within 48 hours. Finally, another appointment for discussion of the results should be set up at this time.

# Using the PSA Test

## What is PSA?

PSA (short for a protein called prostate specific antigen) is a chemical made exclusively in the prostate. It is detected in very high concentrations in the ejaculated fluid. This is normal. When the prostate is abnormal, some of the chemical leaks into the bloodstream and can be detected in the blood test. Levels of up to 4ng/ml are generally normal in the bloodstream (although younger men have lower limits) but levels above this suggest that something is wrong with the prostate. The conditions that cause an elevated PSA are prostate cancer, prostatic enlargement and prostatitis. PSA, therefore, is specific to the prostate, but not to prostate cancer.

## Which patient to test?

- Men between age 50 and 70 (or 75 if a 10-year life expectancy).
- Men between 40 and 75 if at high-risk or very anxious.

## Men at high-risk are:

- Men with a family history of prostate cancer.
- Afro-American men (relevant to U.S.A.).
- Men with a PSA persistently  $> 0.6$  at age 40.

If a man is particularly concerned about prostate cancer his PSA can be tested at age 40 (prior to benign prostatic enlargement), to predict the likelihood of his developing prostate cancer during his lifetime. A man is 3.5 times more likely to develop prostate cancer if his PSA is  $> 0.6$  at age 40, compared to a man with a level of  $< 0.3$  at the same age (13).

## How to test?

### a) Take a blood sample

The PSA test is done via a blood test (fig 7). Venipuncture can be done specifically for the purpose of PSA testing or as part of a comprehensive, preventative health check, including screening for hypercholesterolaemia and blood sugar, depending on the context of the consultation. Advise men to avoid ejaculation, either by masturbation or intercourse, for 48 hours prior to testing. Blood is collected in a clotting tube. The PSA test can be done at the same visit as the DRE without affecting the PSA result.

**b) Conduct a digital rectal examination**

Be sure to advise the patient in advance of what the examination involves and what he is likely to feel. Lay the patient on his left side with his knees curled up (fig 8). Put on disposable gloves and use plenty of lubricant. Take plenty of time, allowing the anal muscle to relax as fully as possible before inserting your finger. Never push before the anus has relaxed. Feel for the smooth, anterior swelling about 3 - 5cm inside the anus. The normal prostate feels small, has two lobes and is symmetrical and firm (rubbery) but not hard. The enlarged prostate is large, smooth and spongy. Prostate cancer feels hard in consistency (usually only one section of the prostate, e.g. a nodule). Obvious prostate asymmetry may also suggest the presence of prostate cancer.

**c) Frequency of testing**

Annual testing is normally recommended. Follow-up intervals, however, for the detection of early prostate cancer, may vary depending on the initial result of the PSA test. The Medicare Benefit Schedule for PSA, as of November 2004, allows one patient episode in a 12-months period. Consider second-yearly testing if the PSA is < 1 (16).

**d) Refer for a biopsy (fig 9) if:**

- a DRE is abnormal.
- the PSA is above the age specific reference range (see table 3). This should be repeated for confirmation.
- the rate of rise of PSA is > 0.5ng/ml per year in the young (9) or > 0.75ng/ml per year in patients over 60 years (17) even if the PSA is below the age specific reference range. This is particularly important in younger patients with a family history, undergoing annual testing, where the PSA level may be well within the normal range.

**e) Consider careful monitoring if:**

- the PSA is between 4 and 10 in a man over 60 with an enlarged, benign feeling prostate and a high Free/Total PSA Ratio (> 25%).
- the PSA has gone up by more than 0.5 ng/ml but less than 0.75 ng/ml in one calendar year in a man over 60 years.



Fig 7



Fig 8

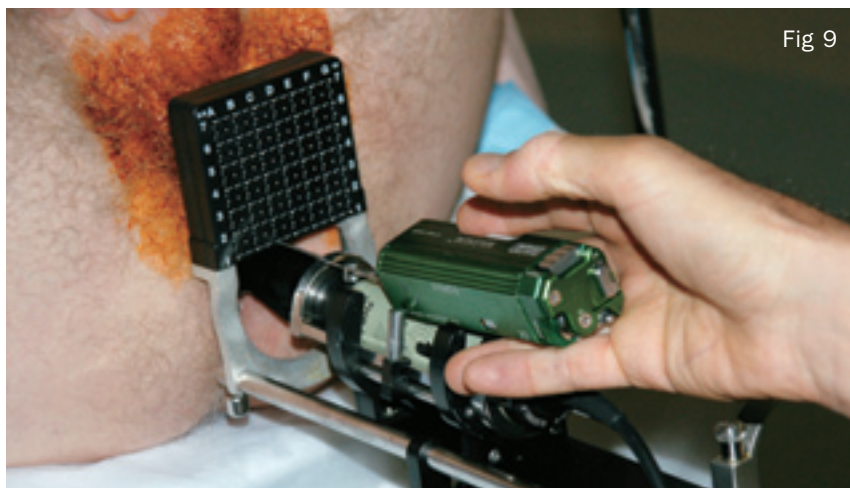


Fig 9

# Interpreting the PSA Test

## 1. PSA at age 40

An isolated PSA reading at the age of 40 will predict the likelihood of prostate cancer in a man's lifetime. A man is 3.5 times more likely to develop prostate cancer if the PSA is  $> 0.6$  at 40, compared to a man with a level of  $< 0.3$  (13).

Table 3

### PSA level by age as an indicator for biopsy

| Age     | 50th centile | Normal PSA level |
|---------|--------------|------------------|
| 40 - 49 | 0.65         | $< 2.0$          |
| 50 - 59 | 0.85         | $< 3.0$          |
| 60 - 69 | 1.39         | $< 4.0$          |
| $> 70$  | 1.64         | $< 5.5$          |

## 2. Age-specific reference ranges

Younger men tend to have lower PSA levels because their prostates are smaller. Hence, adopting a lower PSA level when deciding to refer younger men for biopsy avoids missing curable cancers in those who stand to benefit the most from early diagnosis. As a general guide, when deciding whether to refer for a prostate biopsy, the above table (table 3) may be useful. The normal PSA levels represent the 95th percentile of the upper limit of normal.

## 3. PSA in upper limit of normal

Men with a PSA above the 50th percentile, particularly young men, should be encouraged to have annual review with an 'eye on' PSA velocity and discuss prevention strategies, e.g. dietary regulation, regular exercise and possibly supplements.

## 4. PSA level and the likelihood of prostate cancer

The following table (table 4) represents the likelihood of detecting prostate cancer at different levels of PSA at all ages.

Table 4

### PSA level and likelihood of prostate cancer

| PSA level | Incidence of prostate cancer |
|-----------|------------------------------|
| 1 - 2.5   | 15%                          |
| 2.5 - 4   | 20%                          |
| 4.0 - 10  | 33%                          |
| $> 10$    | $> 50\%$                     |

## 5. PSA velocity

The change in PSA over time is the most accurate way to predict prostate cancer. Over time, the PSA goes up very slowly as men age. If the PSA goes up by more than

0.5ng/ml per year in younger patients or 0.75ng/ml if over 60 years this is predictive of prostate cancer. Furthermore, if the PSA has been steady for a long time and suddenly rises, this should be taken seriously. Not only does PSA velocity identify tumours before the PSA is outside the age-related ranges, but it is also a strong predictor of the likelihood of cure. More aggressive tumours have faster PSA velocities and these tumours need to be detected as soon as possible. It has been shown that a PSA velocity of more than 2ng/ml per year predicts the risk of death from cancer, irrespective of the treatment. Clearly, one needs to detect cancers before the PSA velocity exceeds 2ng/ml per year (18).

## 6. Free/Total PSA Ratio

Table 5

| Free-to-total PSA              |                              |
|--------------------------------|------------------------------|
| F/T ratio                      | Incidence of prostate cancer |
| 0 - 10%                        | 56%                          |
| 10 - 15%                       | 28%                          |
| 15 - 20%                       | 20%                          |
| 20 - 25%                       | 16%                          |
| > 25%                          | 8%                           |
| For PSA in the range of 4 - 10 |                              |

Some of the PSA in blood is called Free PSA (i.e. unbound to blood proteins). In patients with prostate cancer the amount of Free PSA is very low. It is much higher in benign prostatic conditions, e.g. benign prostatic hypertrophy (BPH) and prostatitis for reasons that are not entirely clear. The ratio of Free to Total PSA can therefore assist in distinguishing between men with prostate cancer and those with other benign conditions of the prostate (table 5), thus helping to avoid unnecessary biopsies by up to 20%. From the perspective of a G.P. the Free/Total PSA Ratio should be requested if the PSA test returns a result of between 4 and 10 in the over 60 year old age group. This group, if the Free/Total Ratio is > 25%, particularly if the prostate is enlarged, can be monitored rather than referred for immediate biopsy. The Free/Total PSA Ratio adds very little diagnostically if the Total PSA is > 10, as the incidence of prostate cancer is so high at this level.

The other use of the Free/Total PSA Ratio is in the under 50 year old age group, particularly where there is a very strong family history of prostate cancer. In this group, even if the PSA is within the normal range, a Free/Total PSA Ratio of < 10% is highly suspicious of cancer.

## 7. DRE plus PSA

Combining the findings of DRE and PSA gives a more accurate indication of the likelihood of prostate cancer, as shown in the following table (table 6).

### 8. PSA and prostate size

If the prostate gland is enlarged and the PSA is elevated only a little, above the 95th percentile, you can feel reasonably assured that there is no cancer present. This is particularly so if the Free/Total PSA Ratio is > 25%. However, if the PSA is elevated and the prostate is small, you should be much more suspicious of an underlying cancer.

### 9. Non-cancer causes of an increased PSA

- Benign prostatic enlargement
- Recent ejaculation (can remain altered for up to 48 hours)
- Urinary infection
- Urinary retention or catheterization
- Prostatitis

- Vigorous prostate massage (not routine digital rectal examination).
- Prostate biopsies.
- Long-distance bicycle riding (controversial).

### 10. Prostate and urinary infection

Prostatitis typically has symptoms of mild dysuria, irritative urinary symptoms and ejaculation discomfort. Some cases of subclinical prostatitis have virtually no symptoms at all. If prostatitis is likely, one should wait at least three months before repeating the PSA test. If the patient has significant acute urinary symptoms, e.g. dysuria, nocturia, frequency or ejaculatory pain, a four-week period of an antibiotic, e.g. a quinolone should also be recommended and then the PSA repeated after three months. It must be noted that resolving prostatitis can lead to a very low Free/Total PSA Ratio, which should not cause alarm as long as it settles over the ensuing 3 to 6 months.

**Table 6**

| PSA level by age as an indicator for biopsy |                |                                      |
|---|----------------|--------------------------------------|
| DRE   | PSA            | Approx. incidence of Prostate Cancer |
| normal                                      | negative (0-4) | 6 - 20%                              |
| abnormal                                    | negative (0-4) | 15 - 25%                             |
| normal                                      | positive (> 4) | 23 - 40%                             |
| abnormal                                    | positive (> 4) | > 56%                                |

Most cases of prostatitis do not have a positive confirmation of bacteria in the urine. In the event of a positive urine test and an elevated PSA (bacterial prostatitis) it is recommended that a four-week course of a quinolone antibiotic be used and the PSA repeated at three and six months. If the PSA does not return to normal after six months, referral for a biopsy should be considered.

## 11. Medications and PSA

Finasteride and Dutasteride will halve the level of PSA. If a patient is taking these medications you should double the PSA reading to get an indication of the patient's true PSA level. High dose Phyto-Oestrogens may also decrease the PSA level, but Saw Palmetto and almost all the other herbal treatments, as well as Alpha-blockers, do not have any effect on the PSA level.

## 12. Close observation of slightly elevated PSA in the older age group

This is justified for men over 65, whose PSA is only slightly above the 95th percentile. This is particularly so if the Free/Total PSA Ratio is high. In this group the test may need to be repeated six-monthly initially, and if it is stable, annually. It is important to not let the PSA get over 10ng/ml or let the PSA velocity exceed 2ng/ml/yr, as this will decrease the chance of curing cancer if it is present.

## 13. Repeat the PSA test

The PSA tests can vary day-to-day in any one individual. The cause of this is largely unknown. An isolated PSA reading is subject to many inaccuracies, not the least of which are laboratory error, hour-to-hour fluctuation, sexual excitement or ejaculation or subclinical prostatitis. Before referral for biopsy, it is essential to repeat the PSA test, to confirm persistent elevation. It is also recommended that a micro-urine be done at the same time as the repeat test. It should be mentioned that one should always use the same laboratory for consistency.

## 14. Age

In men under 50, with a family history of prostate cancer, one should allow a much lower threshold for recommending biopsy. The younger man with an early cancer is the patient most likely to benefit from treatment.

In men over 65, and certainly over 70, one should increase the threshold for levels of PSA before recommending a biopsy. Testing over age 70 is unlikely to save lives, unless the man is in excellent health with a > 15 year life expectancy.

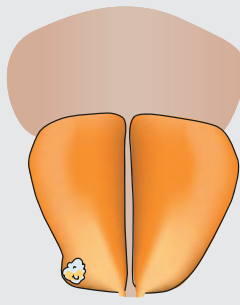
## 15. Lower urinary tract symptoms and PSA

In the current era, symptoms of urinary obstruction e.g. hesitancy, poor flow, post-micturition dribbling and a feeling of incomplete bladder emptying, bear no relationship to the possibility of early prostate cancer, being almost always due to benign prostatic enlargement. The presence of obstructive symptoms does not require antibiotics and should not, in itself, elevate the PSA level unless the prostate is enlarged. Note that, in the past and prior to PSA testing, most prostate cancers grew sufficiently large to cause obstructive symptoms before they were detected. These more advanced cancers were rarely curable and led to the popular tendency to associate obstructive symptoms with prostate cancer (see figure 10).

## 16. PSA testing after negative biopsy

If a biopsy has been performed and prostate cancer not detected, patients should have

(a) BPH  
Obstruction with  
early tumour



(b) Advanced  
incurable cancer  
with obstruction

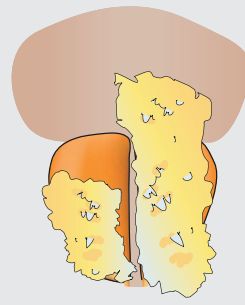


Fig 10 – Urinary obstruction

(a) Symptoms of urinary obstruction are due to benign prostate enlargement and not due to prostate cancer in cases of early curable cancer.  
(b) In the past more advanced cancers led to obstruction.

ongoing PSA monitoring. This is to detect cancers which may have been missed in the biopsy process, or cancers which may develop in the future. False negatives are currently much less likely due to more extensive biopsy techniques with a minimum of 12 biopsy cores. Testing should be done annually, unless the pathology report confirmed abnormal cells, e.g. prostatic intraepithelial neoplasia (P.I.N.) or atypical small acinar proliferation (A.S.A.P.) or highly suspicious cells for malignancy.

In the presence of these abnormal cells, PSA testing should be done at 3 - 6 monthly intervals, with a view to early re-biopsy. In the absence of these cells, PSA velocity can help decide on the need for re-referral for consideration of a repeat biopsy. Recent research has suggested a new test (PCA3) may more accurately predict the presence of cancer in the presence of a previous negative biopsy. Nomograms have also been suggested to stratify the likelihood of cancer (21).

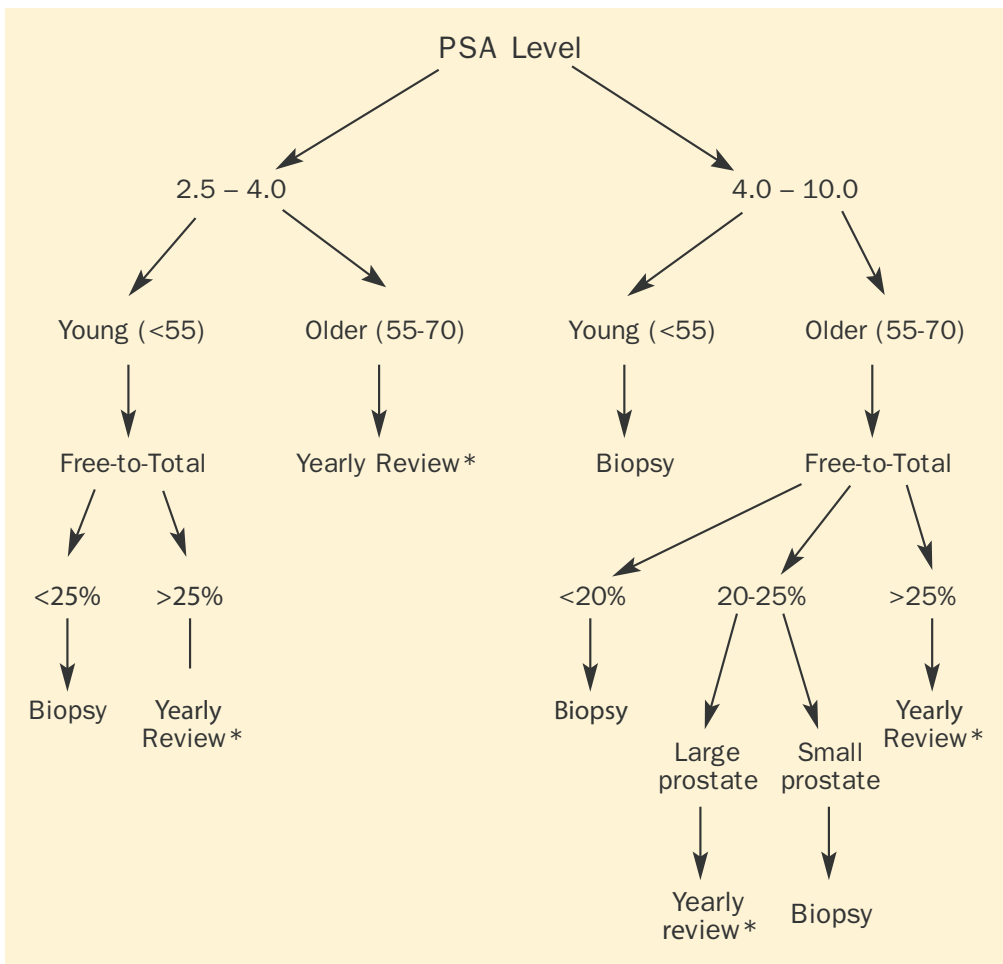
### Take home messages:

- Always repeat the PSA prior to referral, particularly if there are other causes for the increased level.
- Ensure no ejaculation for 48 hours prior to PSA testing.
- Be more vigilant in the young, particularly those with a family history.
- Use the same laboratory.
- Tailor the PSA testing to the individual (age, anxiety, family history, prostate size and PSA velocity).

# PSA Algorithm

In the presence of a normal DRE and after being careful to exclude other possible causes of temporary elevations of the PSA level (recent ejaculations, bike riding, prostatitis, etc) the following algorithm

is suggested as a practical means of interpreting the PSA results. However, it is recommended that the PSA is repeated to ensure accuracy and that good clinical judgement is always used.



\* Yearly Review - repeat PSA yearly and recommend biopsy if PSA velocity is excessive (i.e. > 0.75ng/ml/yr if over 55 and > 0.50ng/ml/yr if < 55 )

Fig 11 - PSA Algorithm  
 The Algorithm is suggested as a reasonable means of diagnosing important cancers and minimising over-diagnosis (personal recommendation of P. Stricker). However, if in any doubt, consult your urologist.

# Treatments

There are many treatment options available for patients diagnosed with localised prostate cancer. These options include:

## a) Radical prostatectomy

In all its forms includes nerve-sparing and non-nerve-sparing radical prostatectomy. These operations can be performed via the open retropubic route (fig 12), laparoscopically or laparoscopically with robot-assistance (fig 13) which is increasingly being utilised internationally.

## b) Radiotherapy

Options include conformal external beam radiotherapy, brachytherapy with seeds (fig 14) and high-dose rate brachytherapy with wires.

## c) Active Surveillance

## d) Hormone therapy

## e) Other less established options

Options such as High Intensity Focused Ultrasound (HIFU) or Cryotherapy.

With each individual it is important to discuss all these treatment options including their cure rates, the side-effects of each treatment, the institution's and surgeon's particular expertise and the individual factors that may influence the choice of therapy.

In general, there are five factors to consider when deciding on treatment. These include:

- Tumour factors
- Prostate factors
- Local factors
- Patient factors
- Institution factors

Detailed discussion of treatment management decisions is beyond the scope of this book. It is recommended that books, DVDs and websites about treatment options be consulted prior to making a decision (appendices 1 & 2). It is also important to take one's time in making a decision, to be aware of all the treatment options, to possibly seek second opinions, to have appropriate sexual expectations and occasional sexual counselling and to give enough time for the treatment to be tailored appropriately to maximise the chance of a successful outcome (19).



Fig 12



Fig 13

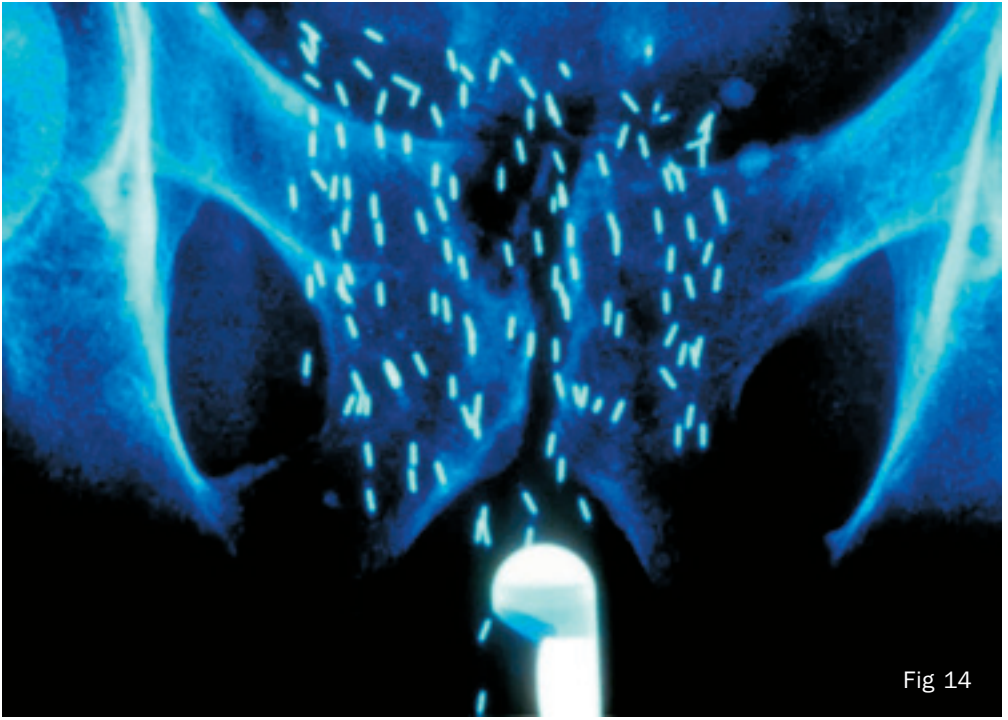


Fig 14



Fig 15

# PSA Recurrence After Definitive Therapy

PSA levels fall to different levels after various treatments. Subsequent rises (depending on the treatment) represent a PSA recurrence which occurs in 20-30% of all cases and may lead to clinically important cancer recurrence.

## 1. After radical prostatectomy

(fig 12 and 13) The PSA level should essentially drop to  $< 0.05$  within six weeks of surgery. Any level above 0.1, and definitely above 0.2, suggests a clinical failure and should mandate referral back to the Urologist. The ultra-sensitive assays of PSA which measure levels below 0.1 remain of uncertain significance. However, relentless increase at this level is highly suspicious of a recurrence. If the PSA is rising even at these low levels, this may be an indication for salvage radiotherapy, particularly if there was a positive surgical margin.

## 2. After radiotherapy

(fig 16) The PSA level generally plateaus below 1ng/ml and ideally below 0.5. It should then not rise. A failure is deemed to have occurred if the PSA levels go up on three successive occasions (Astro definition) or go above 2ng/ml (Phoenix definition). The more popular definition is

now the latter. This can generally only be assessed after 2 - 3 years because it takes that long for the radiotherapy to have the full effect on the PSA and tumour.

## 3. After brachytherapy

Brachytherapy (fig 14) is a form of radiotherapy where radio-isotope pellets are inserted directly into the prostate. Post-treatment the PSA often takes 2 - 4 years to reach its lowest point and may bounce around as it goes down to its plateau level, which is generally below 0.5.

After high intensity focused U/S (HIFU), or cryotherapy PSA levels should drop very rapidly, usually within six weeks, to levels below 0.5 and preferably below 0.1. After partial treatment, the PSA may fall to a level of  $< 2$  and as long as it plateaus at this level and does not rise on three consecutive occasions (Astro definition), this is reassuring.



Fig 16

# Case Histories

These are some short case histories to illustrate common clinical problems.

## Case 1

A 48 year old man with a family history of prostate cancer has regular PSA levels and these have been 0.7, 0.9, 1.0 and 1.7 over the previous four years.

## Comment

The most recent PSA velocity was above normal for a young man (0.5ng/ml per year) and this shows an increased risk of prostate cancer. This high-risk individual should be referred for consideration of a biopsy. If, on the other hand, the PSA remains stable, there is a very low risk of cancer. Regular PSAs in this high-risk group establish a base-line with the ability to map the PSA velocity and early detection of aggressive tumours.

## Case 2

A 60 year old man has mild dysuria, a PSA of 15 and increased white cells in the urine.

## Comment

This patient is likely to have prostatitis, particularly if the prostate is tender and he has ejaculatory pain. A four-week course of a quinolone antibiotic and repeat PSA in 3 and 6 months should confirm that symptoms have disappeared and that the PSA has settled back to the age-specific

reference range. It can, however, take up to, or occasionally even longer than, six months for the PSA to normalise.

## Case 3

A 68 year old man has a PSA level of 5.6 with an enlarged, benign-feeling prostate and a Free/Total PSA Ratio of 25%.

## Comment

As this is an older man, with only slight PSA elevation and benign enlargement which likely explains this elevation, it is reasonable to monitor this man. A simple annual PSA is all that is required and if the PSA were to go up by > 0.75ng/ml per calendar year, or if the Free/Total PSA Ratio drops precipitously, he should be referred for consideration of biopsy.

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## Appendix one

# Useful Websites

### **Andrology Australia**

www.andrologyaustralia.org

### **The Cancer Council Australia**

www.cancer.org.au

### **The Cancer Council NSW**

www.cancercouncil.com.au

### **The Lions Mens Health Website**

www.prostatehealth.org.au

### **The National Cancer Institute**

www.cancer.gov/cancertopics/factsheet

### **National Comprehensive Cancer Network**

www.nccn.org

### **Prostate Cancer Foundation of Australia**

www.prostate.org.au

### **Think GP**

www.thinkgp.com.au/education

### **The Urological Society of Australia**

www.urosoc.org.au

### **St Vincent's Prostate Cancer Center \***

www.prostate.com.au

## Appendix two

# Useful Books and DVDS

## Books

### **Your Guide to Prostate Cancer**

by Prem Rashid - available from the PCFA

### **The Prostate: An Owners Manual**

by Peter Scardino and Judith Kelman -  
available from Amazon

### **Dr Patrick Walsh's Guide to Surviving Prostate Cancer**

by Patrick Walsh - available from Amazon

### **Understanding Prostate Cancer:**

**A guide for people with cancer, their families and friends**

- available from the Cancer Council NSW

### **Localised Prostate Cancer:**

**A guide for men and their families**

- available from the Cancer Council

## DVDS

### **So I Have Prostate Cancer, What Now?**

**A guide for men and their partners**

- available from the PCFA

### **Prostate Cancer, How Do I Choose ?**

by Phillip Stricker - available from the PCFA  
and the St Vincent's Prostate Cancer Centre

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\* A PDF version of this book can be downloaded from: [http://www.prostate.com.au/8+support/downloads/pc\\_gpguide.pdf](http://www.prostate.com.au/8+support/downloads/pc_gpguide.pdf)

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