Localised prostate cancer
questions patients ask

The general population is now relatively well informed about prostate cancer. In fact, there is so much literature in the public domain on prostate cancer that it can be difficult to keep ahead of our patients. This article tackles some of the common questions general practitioners are faced with on a day-to-day basis and gives the evidence to support the answers.

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Prostate cancer is the leading male cancer diagnosis and the second most common cause of cancer-related death in men. The men's health movement has produced a well informed population such that men approach their doctor for advice not only on screening but also on prevention. The management of localised and metastatic prostate cancer is often a difficult dilemma even for uro-oncology specialists, and men diagnosed with prostate cancer face an increasing array of treatment options with a multitude of side effect profiles. The role of GPs in the decision making process is critical, as many patients will seek their GPs advice regarding which treatment will be right for them.

In this article, we hope to arm you with the current evidence to enable you to answer the tricky questions you are faced with on a day-to-day basis.

What is my risk of prostate cancer?

In Australia approximately 10,000 new diagnoses of prostate cancer are made each year, giving an lifetime incidence of about 10%; however, only 2 to 3% of men die from prostate cancer. This instantly highlights the nature of the problem: not all prostate cancer is clinically significant. We know from postmortem studies that about 30% of men over 50 years of age have prostate cancer but only 10% of cancers become clinically significant. The skill comes in screening only those men who are likely to benefit from finding the diagnosis and in treating only those with a significant cancer.

Inherited prostate cancer accounts for about 9% of all prostate cancer cases, and such patients often present at a younger age. Hereditary prostate cancer is due to genetic alterations in several putative oncogenes and is associated particularly with loci on the long arm of chromosome 1.[1] Sporadic

IN SUMMARY

- **There is now good evidence to support dietary changes that may reduce the risk of developing prostate cancer. These changes include reducing fat intake; taking selenium, lycopene and vitamin E supplements; and avoiding excess calcium.**
- **The aim of modern prostate cancer diagnosis is to use all the available information to ensure that only those patients with a significant cancer undergo biopsy.**
- **Not all patients with prostate cancer need treatment, and there are now useful nomograms to help determine those who really need treatment and those who can be actively surveyed.**
- **There are so-called 'ideal patients' for the different modalities of treatment. This helps in the guidance of patients to the best treatment for them.**

prostate cancer is associated with genetic polymorphisms (minor variations in inherited genes that alter their function) such that environmental or dietary factors may affect one individual more than another.

Compared with the overall lifetime risk of developing prostate cancer, the risk if there is a positive family history is:[2]

- 20% if a single first degree relative (father or sibling) has prostate cancer
- 50% if two first degree relatives have prostate cancer
- more than 90% if three first degree relatives have prostate cancer.

How can I reduce my risk of prostate cancer?

The incidence of histologically proven prostate cancer is similar around the world and between different ethnic groups. However, the incidence of clinically problematic prostate cancer differs vastly, suggesting that environmental factors are not initiators but may promote its progression. The best evidence for this comes from migration studies. Japanese and Chinese men have a higher risk of dying of prostate cancer if they move to the USA than their relatives who stay at home.[3] So what contributes to the development of prostate cancer and can we alter our risk? Much work has been done in this area, including dietary prevention and chemoprevention. There is some evidence based dietary advice we can give our patients on how they may reduce their risk of prostate cancer (Table 1).[4-8]

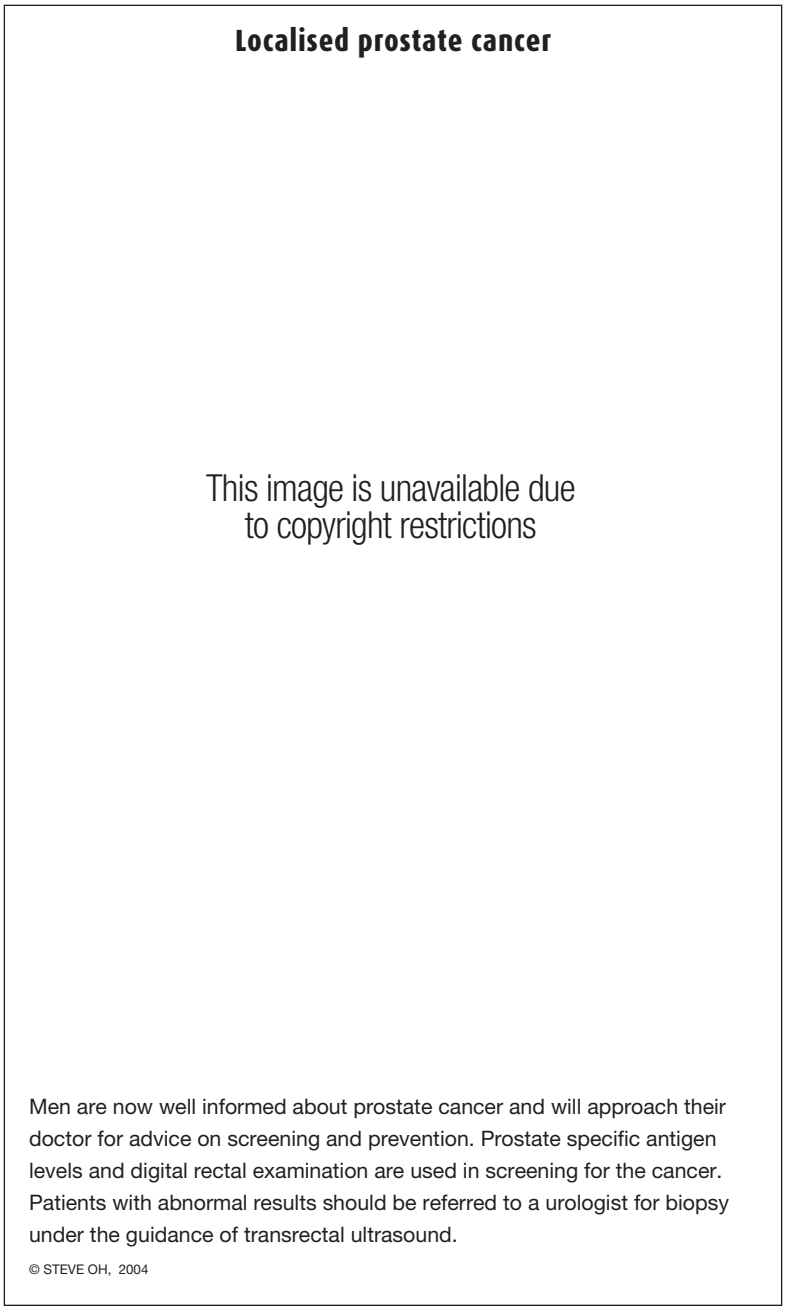
Fat intake

There is good evidence that a diet high in fat, especially fat from red meat, is associated with increased risk of developing prostate cancer and may even encourage progression.[7] One study has shown that a fat-free diet could reduce the growth of prostate cancer in a rat model.[9]

Selenium supplementation

Levels of the trace mineral selenium have been shown to be reduced in the soil of regions with higher rates of prostate cancer. Selenium supplementation has been shown to reduce the risk of developing prostate cancer by about 60% (level 1 and 2 evidence),[4] and so a daily supplementary dose of 200 μg is a sensible suggestion for all men seeking advice on how to lower their risk of prostate cancer. All the trials have used this dosage, and daily selenium supplementation of 200 μg is considered safe in countries where the soil is deficient in selenium, such as Australia. There is no evidence at present that selenium supplementation alters the course of the disease once diagnosed.

Localised prostate cancer



Men are now well informed about prostate cancer and will approach their doctor for advice on screening and prevention. Prostate specific antigen levels and digital rectal examination are used in screening for the cancer. Patients with abnormal results should be referred to a urologist for biopsy under the guidance of transrectal ultrasound.

Lycopenes and ketchup intake

Lycopene, a carotenoid present at high concentrations in tomatoes, is a potent antioxidant. In the Physicians Health Study, men with higher plasma lycopene levels at entry had a 25% lower risk of developing prostate cancer during follow up.[5] The good news is that lycopenes are also found in good quantities in New World red wines.

Calcium intake

Several studies have shown that a high calcium intake is associated with approximately a twofold increase in risk of prostate cancer (level 3 and 4 evidence).[8] Men should be advised to ensure that they have an adequate dietary intake of calcium and vitamin D and to avoid calcium supplementation unless there is an absolute indication for it.

Vitamin E supplementation

Vitamin E is another antioxidant. A prospective study of lung cancer incidence in smokers showed that vitamin E supplements decreased the incidence of prostate cancer by 32% and mortality by 41% compared with placebo (level 2 evidence).[6] Longer follow up of the same group gives less convincing results.[10] However, vitamin E supplementation is a good idea for those at risk, especially if they are smokers, and even for those already diagnosed.

Table 1. Dietary influence on prostate cancer

Dietary factor	Prostate cancer risk
Selenium supplements (200 µg/day)	Decreased by 63%[4]
High lycopene diet	Decreased by 25%[5]
Vitamin E supplements (50 mg)	Decreased by 32%[6]
High fat diet	Increased by almost twofold[7]
Excess calcium (>150 mg/day)	Increased by twofold[8]

Chemoprevention

A few studies have been undertaken to determine whether prostate cancer can be prevented by taking 5α-reductase inhibitors (finasteride and dutasteride). In a randomised placebo controlled trial of the effect of finasteride on the development of prostate cancer, there was about a 25% reduction in prevalence over the seven-year period,[11] but the rationale for treatment in this study has been heavily criticised. It has been suggested that by shrinking the central portion of the gland with 5α-reductase inhibitors, the outer zone, where cancer develops, moves more anteriorly. This accounts for the reduced detection at biopsy as the anterior portion of the gland is hard to access. Also, more worryingly, creating an androgen free environment within the prostate may be encouraging more aggressive disease. This was proposed because there were more cases of high grade prostate cancer in the treatment arm. Chemoprevention with finasteride is currently not recommended by most urologists.

Vasectomy and sexual activity

There has been much controversy surrounding increased risk of prostate cancer after vasectomy, but the most recent meta-analysis suggests that there is probably no causal relation (level 1 evidence).[12,13] It used to be thought that increased sexual activity was associated with an increased risk of prostate cancer, but a recent study has shown increased frequency of ejaculation may actually reduce the overall risk.[14]

Why, how and when should I be tested?

Why?

Prostate cancer screening is one of the most controversial areas in urology, but while mortality rates remain high, prevention attempts will continue. Population-based prostate specific antigen (PSA) screening in this country has been rejected by most Government reviews because of concerns that it would cause overdiagnosis and overtreatment and worsen quality of life, and it has not been proven to be cost effective.

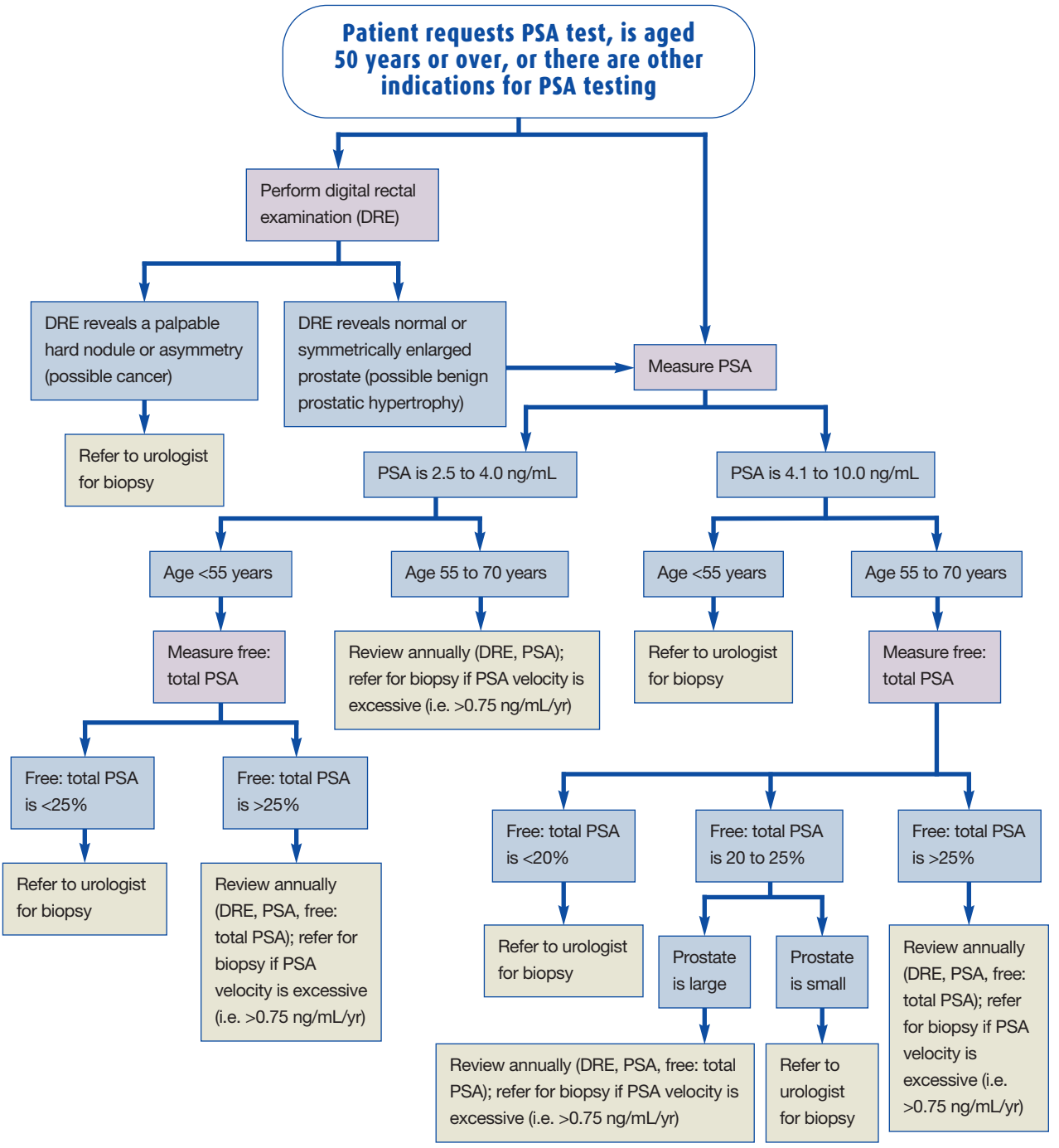
If all men in Australia aged 55 to 70 years were screened, about 15% would have a raised PSA level requiring prostatic biopsy, although 75% of these men would not have prostate cancer. So why should we advocate a screening program? The reason is that there is mounting evidence that it reduces mortality. The decreasing mortality rate of prostate cancer in countries such as the USA is attributed to screening and the introduction of radical prostatectomy. This is compared with an increase in mortality in countries without screening policies. Only one study has randomised between radical prostatectomy and watchful waiting. The eight-year data demonstrate that the incidence of metastases as well as cancer death rate is reduced in those undergoing surgery (although it will take 10 to 15 years to see a substantial difference in overall mortality).[15]

How?

The combination of PSA testing with digital rectal examination (DRE) has been reported to almost double the proportion of curable prostate cancers detected (that is, those that are pathologically organ-confined), when compared with an age-matched group whose cancers were detected with traditional DRE alone.[16] PSA and DRE now form the cornerstone of prostate cancer screening: a raised PSA level can pick up a nonpalpable tumour and an abnormal DRE can pick up a non-PSA producing tumour. It has been proven that the combination picks up more prostate cancer than either parameter alone. In addition, any patient with haemospermia should be tested for prostate cancer.

continued

An approach to PSA screening*



This algorithm is suggested as a reasonable means of diagnosing important cancers and minimising over-diagnosis (personal recommendation of P. Stricker). However, if in doubt, consult a urologist.

*Adapted from *PSA for the general practitioner*, by Dr Phillip Stricker and Professor Kerryn Phelps, 2004.

MedicineToday **PATIENT HANDOUT**

Screening for prostate cancer

Why do I need a blood test?

As part of an effort to detect prostate cancer at an earlier and more curable stage, you are about to have a blood test. This is always done in association with a finger examination of the prostate. The blood test measures the PSA (i.e. prostate specific antigen) level. If it is abnormal, further testing, monitoring or a biopsy may be necessary. As prostate cancers generally progress slowly, a period of monitoring the PSA level may be needed to improve the accuracy of predicting whether or not prostate cancer is present.

Does having a biopsy mean I have cancer?

If a biopsy is required, you will be referred to a specialist (a 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 in the future.

Biopsies carry a very small risk of serious infection but this can be minimised by using the newer techniques and antibiotics. The procedure is often performed under light anaesthesia or local anaesthetic.

What happens if cancer is detected?

If a cancer is detected, there are many treatments. These include surgical removal, insertion of radioactive seeds, external beam radiotherapy or simply monitoring, among others.

As each treatment may have side effects (such as impotence, incontinence and bowel problems) as well as differing cure rates, the treatment must be selected to meet the individual's needs. The factors that should be taken into consideration before any treatment is recommended include the type of cancer, the prostate symptoms, the prostate size, your age and general health and your personal priorities and preferences.

Most cancers that are detected at an early stage are indeed curable.

This patient handout has beenadapted with the authors' permission from *PSA for the general practitioner*, by Dr Phillip Stricker and Professor Kerryn Phelps.

When?

At present there is no national screening program in Australia and it is up to individual patients and GPs to request or suggest a PSA blood test. The position of the Urological Society of Australasia is that 'Individual men between 50 and 70 with at least 10 years' life expectancy should be able to be screened by annual DRE and PSA testing, after appropriate counselling regarding the potential benefits of investigations and the controversies of treatment.'[17]

The start age at screening should be reduced to 40 years if the patient is of Afro-Caribbean origin or has a positive family history. There is some good evidence that a PSA test at 40 years of age is of value because prostate cancer is seven times more likely to develop in a man whose PSA level is above 0.6 ng/mL at this age than in a man whose PSA level is less than 0.3 ng/mL. This has useful implications for how frequently a PSA test should be performed (Table 2).

How accurate is the PSA test?

PSA screening can cause patients a lot of unnecessary anxiety. Many attempts have been made to improve the test's accuracy, including determining free PSA level, PSA velocity, PSA density and complexed PSA level (some of these tests are research tools only and not freely available). The ratio of free to total PSA can assist in distinguishing between men with prostate cancer and those with benign prostate conditions. We find this a useful tool, helping to avoid unnecessary biopsies by up to 20% .

The specificity and sensitivity of the PSA test are far from ideal, so it is important that patients are appropriately counselled before they undertake a test as it can open 'a can of worms' that they may not be prepared for. We recommend the text in the patient handout sheet on this page as a minimum that the patient should read before agreeing to a PSA test. More information is contained in the booklet *PSA for the general practitioner*, by Dr Phillip Stricker and Professor Kerryn Phelps, from which the patient handout text is taken.[18]

Who to refer?

All patients between the ages of 40 and 75 years with a suspicious DRE should be referred to a urologist for biopsy irrespective of their PSA level. However, which

Table 2. PSA blood test frequency (men aged 50 to 70 years)

- If PSA >2 ng/mL, test annually
- If PSA 1 to 2 ng/mL, test every two years
- If PSA <1 ng/mL, test every four years

Table 3. Age specific PSA reference range[19]

Age (years)	Normal PSA level (ng/mL)
40 to 49	0 to 2.5
50 to 59	0 to 3.5
60 to 69	0 to 4.5
70 and over	0 to 6.5

patients should be referred in the presence of a normal DRE? It is important to take note of the age-specific reference ranges for PSA levels first suggested by Oesterling and colleagues in 1993 (Table 3).[19] Age-specific reference ranges make the test more sensitive in younger men in whom we do not want to miss cancer, and make it more specific in older men to avoid unnecessary intervention. The flowchart on page 23 suggests an age-specific approach to screening with the addition of free to total PSA ratio and PSA velocity. This algorithm avoids initial biopsy in some patients with the proviso that the PSA velocity is closely followed. Table 4 discusses a few issues regarding raised PSA levels.[20,21]

Biopsies are performed (under local or general anaesthetic) by imaging the prostate with a transrectal ultrasound probe and taking trucut biopsies through the probe (transrectal) or via the perineum (transperineal). The latter technique most likely has a lower incidence of sepsis.

What is clinically insignificant prostate cancer?

Many attempts have been made to predict who needs treatment for their cancer and who is likely to die from other causes first. The aim is to reduce the number of men subjected to unnecessary interventions and side effects.

Several groups of authors have defined insignificant prostate cancer.[22-24] If the volume of the tumour is less than 0.2 to 0.5 cm^3 and the Gleason score is 6 or less then it is highly unlikely to become clinically relevant in the next 15 years (the Gleason grading system describes the differentiation of prostate tumours). The shorter a patient's life expectancy, the larger the estimated tumour size can be without becoming clinically significant. This means that the calculated tumour volume can increase to 5 cm^3 in a man aged over 70 years and still not compromise life expectancy. Nomograms have been developed to predict the likelihood that a biopsy proven prostate cancer requires treatment (the Kattan nomograms – www.mskcc.org/nomograms/prostate). They use the percentage of prostatic cores that are positive for cancer along with the Gleason score and PSA level to produce an estimation of the chance that this cancer will become clinically significant in the next 15 years.

How to decide between treatments?

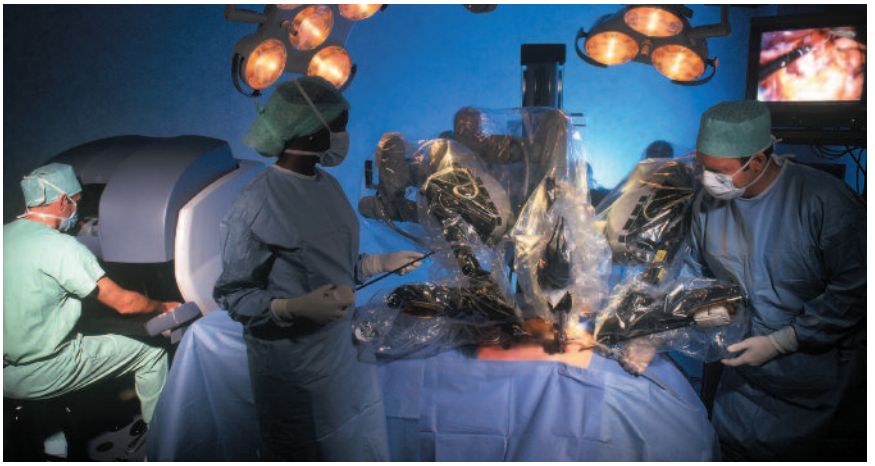
Three types of radiation therapy and two types of surgery are available for patients with localised prostate cancer. The surgical approaches – open radical prostatectomy (perineal and retropubic) and laparoscopic (including robotic) radical prostatectomy – need to be judged on the individual surgeon's ability to achieve negative surgical margins and maintain erections and continence, and not on the cleverness of the technology (Figure 1). There has been much interest in laparoscopic and robotic approaches recently but it must not be forgotten that these are less tested techniques. Robotic instruments give extra dexterity and visualisation, and instruments that are better than our own hands may prove to be advantageous in the challenging field of pelvic surgery, albeit at considerable financial cost.

Issues to consider

The important issues in deciding the best treatment for a patient can be divided into tumour, prostate, local and patient factors. Radical open prostatectomy by an experienced and skilled surgeon is still considered the gold standard for young men with

Table 4. Raised PSA levels and referral

Question	Answer	Why?
What, other than cancer, can make the PSA level go up?	Ejaculation, cycling, prostatic massage within three days of the test, benign prostatic enlargement, prostatitis, urinary tract infection	PSA is prostate specific but not cancer specific
Is one raised PSA level enough for referral?	Not if it is only slightly raised. Two PSA tests six weeks apart is more accurate	Ornstein et al showed that normal volunteers have a PSA level fluctuation of about 15% when measured three times over six weeks.[20] Eastham et al showed that about half of men with an abnormal PSA level returned to the normal range if the test was repeated in six weeks[21]
When should a patient being followed up after a negative biopsy be referred?	If the PSA rises by more than 0.75 ng/mL per year in two consecutive years – the increase may be due to cancer If the free:total PSA continues to decrease to less than 25%	10 to 20% of patients with a negative biopsy will have prostate cancer that the biopsy failed to pick up



PHOTOGRAPH COURTESY OF DEVICE TECHNOLOGIES AUSTRALIA

Figure 1. Robotic radical prostatectomy allows the surgeon to operate from a console away from the patient. The instruments allow extra dexterity and visualisation but lack tactile sensation.

localised prostate cancer. The radiation therapies, however, have a distinct role in young men with more aggressive disease, older men and those in whom there is evidence that the tumour is slow growing.

Tumour factors

If the cancer has already spread significantly beyond the capsule then the possible side effects of surgery (erectile dysfunction and incontinence) are not justified because a cure is less likely with surgery alone. Five predictors of likelihood that the disease is beyond the capsule are the PSA level, Gleason grading, the extent of the cancer on DRE or imaging, the number of positive biopsies and the presence of extensive perineural invasion on biopsies. The higher the PSA level (above 10 ng/mL), the Gleason score (above 7) or the number the positive biopsies (more than 50%), the worse the outcome. The Kattan nomograms are often useful in this regard.[25]

Prostate factors

Prostates greater than 50 cm^3 in size are usually not suitable for low dose rate (seed) brachytherapy. Similarly, neither are men with urinary obstructive symptoms, as the treatment risks causing retention. Patients with very irritable bladders have a higher chance of incontinence if subjected to surgery.

Local factors

Obese patients or patients with a very narrow pelvis may be better candidates for radiotherapy than surgery, although previous radiotherapy of the area rules out this treatment option. It is wise to avoid surgery in men who have had a previous pelvic fracture.

Patient factors

A patient's personality type often influences the choice of treatment. Patients who are worried about their PSA levels are bad candidates for active surveillance and tend to want the problem 'removed'. The radiation treatments leave the patient not knowing whether the cancer has been cured, and although a PSA level below 0.5 ng/mL is reassuring it can never be as reassuring as the negative margin, lymph node-negative and PSA unmeasurable outcome achieved by surgery. If a patient considers the risk of erectile dysfunction too high a price to pay, seed brachytherapy may be a better option than surgery.

'Ideal' patients for each treatment group

Each patient has a complex mix of the above four factors. It is helpful to consider the 'ideal cases' for each treatment as this

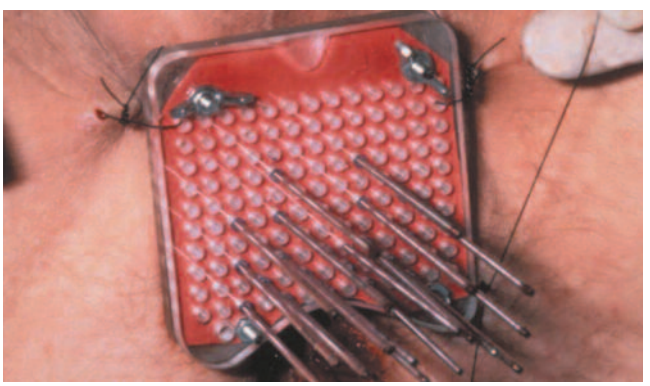


Figure 2. High dose brachytherapy. Very high doses of radiotherapy are accurately placed in the prostate by iridium directed through hollow needles.

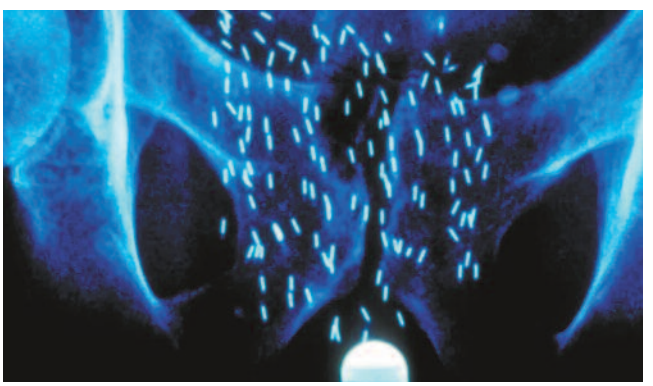


Figure 3. Low dose rate brachytherapy. Radioactive seeds are implanted into the prostate and deliver a targeted radiation dose over several months.

can guide the patient to the best treatment for their particular prostate cancer and personality profile.

Nerve sparing radical prostatectomy

Patients particularly suited to nerve sparing radical prostatectomy are less than 65 years old and have low volume non-palpable disease, a Gleason score of 6 and above, and a PSA level less than 10 ng/mL. If the PSA level is between 10 and 20 ng/mL or high volume disease is present, nerve sparing surgery risks leaving cancer behind. In such cases, complete removal of the nerve bundle on the side of the cancer is recommended and the nerve can be grafted using a sural nerve graft. The risk of incontinence with this surgery increases in patients older than 65 years.

High dose rate brachytherapy

Ideal patients for high dose rate brachytherapy include those of any age who are not keen on surgery and have minimal prostatic obstructive symptoms, a prostate smaller than 60 cm^3, PSA level above 10 ng/mL, Gleason score above 7 and palpable disease (Figure 2). This treatment, in which prostatic wires combined with external beam radiotherapy deliver high doses to the gland and immediate surrounding tissue, is showing promising results in those patients in whom surgery would probably have left behind cancer. It appears to cause less morbidity than the traditional approach of post-prostatectomy radiotherapy for a positive margin.

Seed brachytherapy

Men aged 60 to 70 years who are not keen on surgery and have no prostatic obstructive symptoms, a prostate smaller than 50 cm^3, PSA level below 10 ng/mL, Gleason score below 7 and impalpable small volume disease are ideal patients for seed brachytherapy. In this treatment, permanently implanted radioactive seeds have a localised radiation effect over several months (Figure 3). Erection failure at five years of follow up is probably less severe than after surgery and incontinence is not a significant risk.

Intensity modulated conformal external beam

Ideal patients for intensity modulated conformal external beam are aged above 65 years and have a Gleason score of 6 or above and a life expectancy of more than 10 years. This treatment is especially useful for those patients who do not want surgery or have other health problems.

Active surveillance

Active surveillance, or watchful waiting, is not meant to apply to patients who are unlikely to live more than 10 years since under the Urology Society of Australasia recommendation these patients should not have been screened in the first place.

Active surveillance is appropriate for patients who have low volume, low grade (Gleason score of 6 or below), low PSA level (below 10 ng/mL) disease. For example, a man diagnosed with a Gleason 6 cancer at the age of 65 years who opts for no treatment has about a 25% chance of dying of prostate cancer in the next 20 years. The reason he may opt for no treatment is that he has a 50% chance of dying of another condition first and a 25% chance of still being alive with prostate cancer.[26] If the patient's PSA level were to increase or repeat biopsies were to suggest progression, then the patient could be transferred to a treatment arm.

Austalian information sources

Prostate cancer
www.prostate.com.au

Prostate Cancer Foundation of Australia
www.prostate.org.au

Lions Australian Prostate Cancer Website
www.prostatehealth.org.au

Your prostate questions answered,
by P. Rashid and G. Watters. Published by the authors,1999. Available from the Prostate Cancer Foundation of Australia

Localised prostate cancer: a guide for men and their families,
by the Australian Prostate Cancer Collaboration for the Australian Cancer Network. 2003. Available from the Cancer Helpline, telephone 13 11 20, or online at www.prostatehealth.org.au

Conclusion

The choice of therapy for localised prostate cancer is complex and often requires lengthy discussion with the patient. Patients should be encouraged to talk to cancer help groups and to seek second opinions from radiation oncologists and other urologists. It is important to direct patients towards reputable and useful websites and books (see the box on this page). There is usually no turning back once the treatment has been given so it is imperative to get it right first time. MT

A list of references is available on request to the editorial office.

DECLARATION OF INTEREST: None.

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