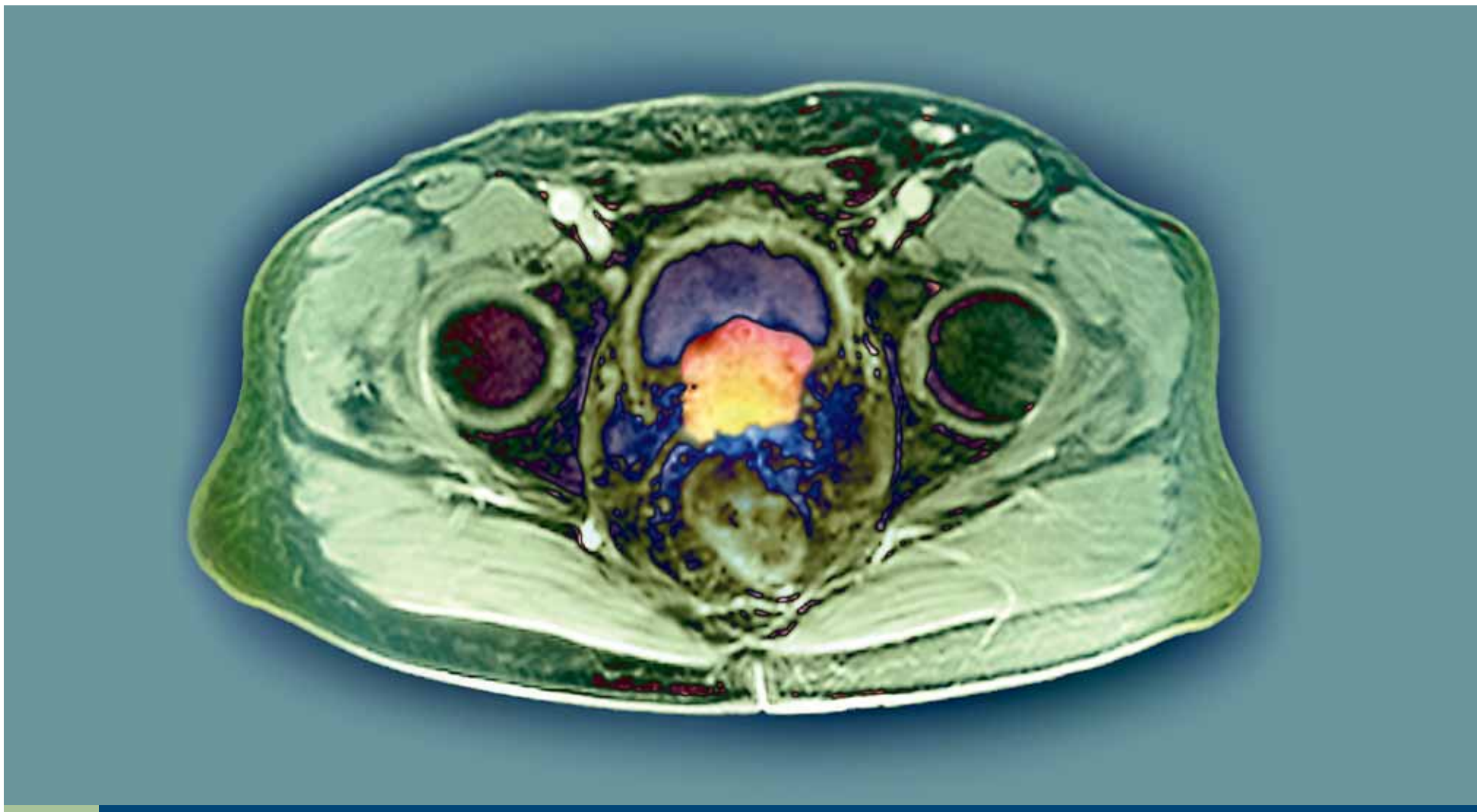


PART 1

Treatment options for prostate cancer

Prostate cancer treatments are now many and varied. A detailed knowledge of the different options will help GPs advise their patients.

ASSOCIATE PROFESSOR PHILLIP STRICKER

PROSTATE cancer continues to be in a stage of rapid evolution. It is the most commonly diagnosed cancer in men and the second most common cause of male cancer deaths.

Over 18,000 Australians are diagnosed annually and over 3000 men die of prostate cancer each year. What makes prostate cancer different from most other cancers is the lack of symptoms of 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 its detection when it is still contained within the prostate and potentially curable.

The variable natural history of the condition means that some patients with screen-detected cancers may have a relatively indolent cancer. At present, we have no perfect marker to differentiate the natural course of each individual cancer.

There are a number of different and effective treatments for localised prostate cancer. 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.

GPs need to be able to assist patients in making an informed decision, not only about the tests but also about the investigations and treatment.

PATHOLOGY

Prostate cancer occurs when the tissue of the prostate gland changes. When a cancer develops, the gland cells multiply and change their architectural pattern. This range of patterns are an indication of how aggressive the tumour is and are classified under the Gleason grading system named after the pathologist who first designed the system.

Gleason grade and score

The Gleason score is the sum of the two most predominant grades of prostate cancer cell patterns, as assessed by the pathologist examining the biopsy specimens.

The Gleason grading system originally recognised five grades of cancer cell patterns (1-5) based on the degree of cell differentiation. However, the system now only recognises three (3-5) grades. The pattern of any one cancer can be mixed and the two most common or dominant grades are recorded and then added to give the Gleason score (see table below).

As early prostate cancer has no symptoms, only active testing will lead to its detection.

The Gleason score is used as an indicator of prognosis. Gleason 6 has a good prognosis while Gleason 8-10 has a poor prognosis. Whichever pattern is the most dominant (written first) also affects prognosis — within the Gleason 7 category, a Gleason 4+3 tumour is a worse tumour than a Gleason 3+4 tumour.

Cancer stage

As well as the grade, the extent of cancer felt on digital rectal examination is also important in determining a prognosis. The extent of cancer is referred to as the cancer stage. Stage 1 (T1) cannot be felt. Stage 2 (T2) can be felt but still is felt to be within the prostate. Stage 3 (T3) is felt to have extended outside the prostate. Stage 4 (T4) is felt to be well outside the prostate, invading other organs such as the bladder or pelvic wall.

Each of these stages are further categorised depending on the spread of cancer within that category. For example, a T2a tumour involves one lobe of the prostate, whereas a T2b tumour involves both.

Gleason grading system for prostate cancer

Gleason score	Growth rate	Prognosis
6 (3+3)	Very slow	Good
7 (3+4)	Slow	Good
7 (4+3)	Faster	Intermediate
8-10 (3+5, 4+4, 5+3, 3+5, 5+4, 5+5)	More rapid	Poorer

TREATMENT

There are many new treatments available for localised prostate cancer.

Options include radical prostatectomy in all its forms, including nerve-sparing and non-nerve-sparing techniques performed by a retropubic open approach, laparoscopic approach, robot-assisted laparoscopic approach or perineal approach.

It also includes radiotherapy in all its forms, including external beam radiotherapy, low-dose brachytherapy, high-dose rate brachytherapy, conformal radiotherapy, image modulated conformal radiotherapy techniques, Cyberknife, and proton therapy. Further options include active surveillance, hormone

cont'd next page

PART 1 TREATMENT OPTIONS FOR PROSTATE CANCER

from previous page

therapy, high-intensity focused ultrasound, and cryotherapy.

Surgery

Radical prostatectomy involves the complete surgical removal of the prostate along with the seminal vesicles and often some pelvic lymph nodes for cancer-staging purposes. Radical prostatectomy remains the gold standard of management of localised prostate cancer, particularly in young men with a life expectancy of greater than 15 years.

Radical prostatectomy can be performed by the open (retropubic) route, or by laparoscopy, (or, more recently, robot-assisted laparoscopic techniques), or — to a lesser extent — via the perineal technique.

The cure rate for localised disease is in the order of 40 to 95%. Open radical prostatectomy is the traditional approach and has proven efficacy.

The main complications include urinary incontinence and erectile dysfunction. The incidence of urinary incontinence varies between 2% and 40% but in recent series and in experienced hands is less than 10%, with severe incontinence occurring in less than 2%.

a. Nerve-sparing surgery

Nerve-sparing surgery aims to protect the nerves needed for erectile function. With modern surgical techniques it is increasingly possible to protect the vast majority of these nerves while still eradicating the cancer.

The extent of the cancer does, however, influence the degree to which these nerves can be spared.

Potency rates as high as 90% can be achieved in young patients who have early cancers. Overall, however, the likelihood of erectile recovery is extremely variable ranging from only 5% to 90%, depending on factors including the patient's age and pre-operative potency.

The recovery rate of erectile functioning is also variable, often taking 12-18 months for erections to recover and they often only recover 80-90%. Recovery is also dependent upon the sexual rehabilitation that occurs after surgery.

It has been shown that the use of PDE5 inhibitors and penile injection therapy used shortly after surgery may improve the chance of recovery of erectile function.

b. Laparoscopic surgery

In experienced units, these forms of minimally invasive surgery achieve the same outcomes as open surgery with the added benefit of reduced blood loss, shorter hospital stay and an earlier return to normal activities.

However, the technique is not as important as the experience of the surgeon. In the process of deciding which technique, surgeon or institution to use, it has been shown that high-volume units have better outcomes. It is preferable to find out what the results of individual surgeons are with regard to the cure, continence and potency results rather than the technology used.

Furthermore, there is some evidence that the best oncology results in high-volume aggressive cancers are achieved by the open technique, although this is surgeon specific.

In my own practice I have found many factors need to be considered before deciding on the appropriate technique for a particular patient, including the extent of the cancer, previous abdominal surgery, obesity, previous pelvic pathology and patient preference.

c. Outcomes

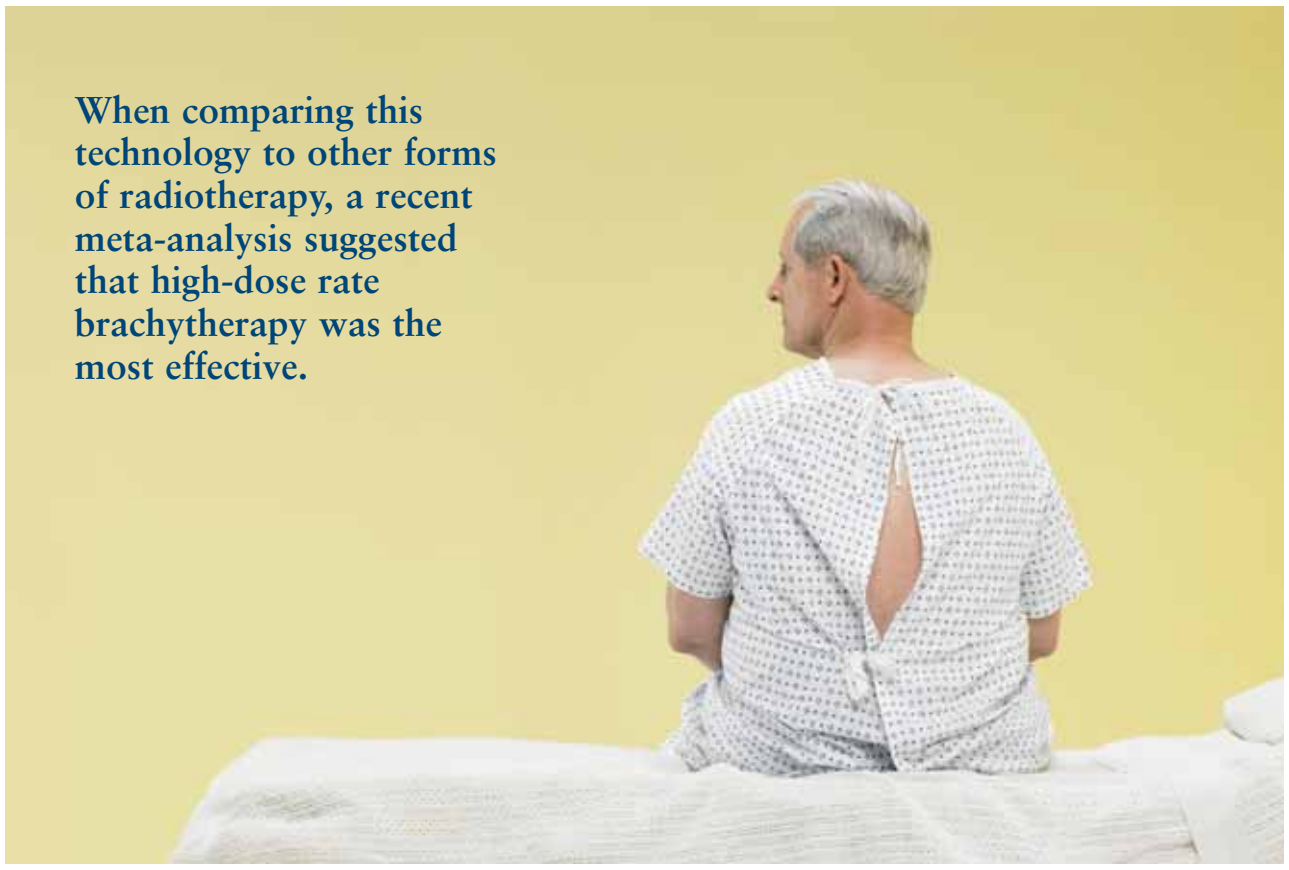
The main aim of surgery is to achieve the so-called 'trifecta' of cure, continence and potency with the minimum of complications.

A predictor of cure is the surgical margin. A pathologist, on reviewing the removed prostate, examines all the edges and if there is cancer at the edge, or a 'positive surgical margin', this increases the likelihood that there has been inadequate removal of the prostate cancer. Therefore, adjuvant or salvage external beam radiotherapy is possibly required.

If the cancer is contained, the positive margin rate should be less than 10%. If the cancer is outside of the capsule, the positive surgical margin rate is higher, varying between 20% and 50%.

Major complications of radical prostatectomy surgery are now very uncommon and occur in fewer than 2% of cases. The risk of transfusion in open series tends to be less than 10% and in minimally invasive series lower than 2%.

When comparing this technology to other forms of radiotherapy, a recent meta-analysis suggested that high-dose rate brachytherapy was the most effective.



d. Cure rates

Special tables or nomograms known as Kattan nomograms have now been developed to help predict the likely cure rates of not only surgical treatments but also radiotherapy treatments.

These can be found on the website www.nomograms@mskcc.org. Cure rates, however, are surgeon-, radiotherapist- and institution-specific. A specialist's individual results should be available to patients, as the Kattan nomograms only give the results of the institutions or surgeons contributing to that table.

External beam radiotherapy

Modern techniques of delivering external beam radiotherapy are now well established in Australia.

It has been recognised that a high dose of radiotherapy above 70Gy is usually necessary to treat prostate cancer, sometimes in association with hormone therapy. Lower doses of radiotherapy have led to very disappointing results.

As a result, conformal radiotherapy (where radiotherapy beams from a number of directions are focused on the prostate) is now standard in most units and indeed the next stage of image-modulated conformal radiotherapy (IMRT) is now widely available.

This technique allows a higher dose to be delivered more accurately to maximise the chance of curing the cancer and minimise side effects. These techniques require experience.

A newer, less-tested technology is the Cyberknife — a form of radiosurgery allowing the full course of radiotherapy to be delivered in three days as opposed to the standard 7-8 weeks. This is not yet available in Australia but should be available soon.

While long-term data on this technique are not yet available, it does appear to be safe in experienced hands.

Radiotherapy is generally suitable for slightly older men (perhaps over 60) or in patients who are unsuitable for or refuse surgery. Furthermore it is particularly appropriate in patients with very high-risk cancer, often being used in conjunction with hormone therapy.

The clear advantage of this therapy is that it is less invasive, while the disadvantages are that it can potentially aggravate obstructive urinary symptoms, it increases the risk of secondary malignancies within 10-15 years, and it makes salvage therapy difficult should it be required.

It is therefore not ideal for patients who have particularly large prostates with severe urinary symptoms or patients who suffer bowel disease, such as ulcerative colitis, or those patients who have had previous radiotherapy.

Common side effects include rectal damage and urinary problems and impotence. Disturbances of stool frequency are reported in 10-20% of men.

Modern series have reported impotence rates of between 10% and 50%, chronic proctitis in less than 2%, and urethral stricture and incontinence.

Brachytherapy

a. Low-dose rate

Low-dose rate brachytherapy is suitable for patients who have a Gleason 7 or below tumour, a PSA of less than 10ng/mL, and a prostate size of less than 40cm^3.

The therapy involves making a volume assessment of the prostate, constructing a template and preparing a plan to place the seeds correctly. It is a day-only procedure where the seeds are placed evenly through the prostate, avoiding damage to the urethra and rectum and attempting to minimise damage to the erectile nerves.

In correctly selected patients with low-risk tumours, results after 15 years of follow-up are similar between brachytherapy series and surgical series. Long-term complications include chronic dysuria and chronic voiding problems in 2-5% of patients, and erectile dysfunction — which is generally less severe — in 30-50% of patients.

Most of the patients with erectile dysfunction after brachytherapy respond to PDE5 inhibitors. Most series have reported better potency rates after low-dose rate brachytherapy than surgery.

However, there has not been a formal series comparing sexual outcomes performed by experienced nerve-sparing surgeons compared with low-dose rate brachytherapy. The risk of late secondary malignancies in the bladder and rectum is exceedingly low.

b. High-dose rate

High-dose rate brachytherapy is a more invasive treatment where high doses of radiotherapy can be accurately delivered to the prostate with iridium through surgically placed perineal wires.

This is always combined with external beam radiotherapy.

This form of therapy is suitable for more advanced cancers where the PSA is greater than 10ng/mL, the Gleason score greater than 7 and the clinical stage greater than or equal to T2b.

Two fractions of brachytherapy are delivered over a 24-hour period. This is done as an inpatient. This, in combination with the external beam radiotherapy, delivers a radiobiological equivalent dose of at least 86Gy of radiotherapy, improving the cure rate for intermediate- and high-risk cancers of the prostate.

Our 10-year follow-up comparing high-dose rate brachytherapy to surgery in high-risk tumours suggests high-dose rate brachytherapy is more advantageous. In patients with extensive cancer at locations such as the apex of the gland, high-dose rate

cont'd page 44

PART 1 TREATMENT OPTIONS FOR PROSTATE CANCER

from page 42

brachytherapy is more effective than surgery in treating the cancer.

The major advantage of this technique over standard radiotherapy techniques is that it delivers very high doses of radiotherapy to the prostate but not at the expense of rectal damage.

Complications include a 5% risk of urethral stricture, a 50% chance of impotence and a 1% chance of incontinence.

When comparing this technology to other forms of radiotherapy, a recent meta-analysis suggested that high-dose rate brachytherapy was the most effective.

High intensity focused ultrasound is an emerging therapy that uses intense heat applied through the rectum to destroy the prostate and the contained cancer.

Active surveillance

Active surveillance involves the careful monitoring of prostate cancer progression in patients with less aggressive tumours.

An increasing proportion of patients with Gleason 6 cancers, particularly in the older age group, are having their tumours monitored. This involves four-monthly PSA testing and a repeat biopsy in 12-18 months, then ongoing monitoring depending upon these results.

This management option has become increasingly popular following the realisation that many patients with prostate cancer, particularly older patients with low-grade cancer, die with the disease rather than because of it.

In appropriately selected patients, this is a safe management option, with about one in three patients ultimately requiring treatment within 10 years. It is important before embarking upon an active surveillance policy that patients have adequate biopsies of the prostate.

Depending upon circumstances, patients with low-risk tumours — even in the younger age group — can be initially monitored with these tumours.

Other treatments

a. High intensity focused ultrasound (HIFU).

HIFU is an emerging therapy that uses intense heat applied through the rectum to destroy the prostate and the contained cancer. This therapy only became available in Australia in 2005, but it has been used in Germany and France for over a decade.

Currently, there are two devices available — the Ablatherm and the Sonoblate. Most published results have been with the Ablatherm machine. Neither of these techniques is approved by the US Food and Drug Administration. Generally this technology should be reserved for older men with less extensive tumours where other more established treatments are either felt to be unsuitable or refused.

The treatment involves heating the prostate through the rectum, sometimes associated with a transurethral resection of the prostate. Most series (albeit with short follow-up) have shown a 70-80% success rate.

The risk of impotence is similar to that of radical prostatectomy and there is a 1-5% incidence of incontinence. The risk of a rectal fistula is less than 1% but higher in patients who have had radiotherapy previously. The incidence of urethral stricture has been reported to be as high as 20%.

HIFU is one of the few therapies that can be repeated if it is initially ineffective.

Salvage treatment, however, is more complicated. HIFU is sometimes used as a salvage treatment after failed radiotherapy. In this setting there is a very high incidence of incontinence (50%).

The role of HIFU as primary treatment for localised prostate cancer in men under 65 remains highly controversial.

b. Cryotherapy

Cryotherapy as a treatment for prostate cancer is not widely popular in Australia. It involves extensive training and many technical modifications to avoid severe complications. However, in experienced hands with modern techniques, this relatively minimally invasive treatment has satisfactory intermediate results.

c. Hormone therapy

Hormone therapy is generally reserved for patients with metastatic disease. It is sometimes used in association with radiotherapy in patients with locally advanced disease. In patients with localised disease it is sometimes used in older patients (over 75) who insist on treatment but have a limited life-expectancy.

Hormone therapy does increase the risk of cardiovascular problems and can severely affect quality of life due to lethargy, hot flushes, osteoporosis, depression, mood swings and decreased libido. In patients with more advanced, symptomatic and incurable cancer, it has a much more established role.

Associate Professor Stricker is chairman of the department of urology at St Vincent's Hospital, Sydney, director of the St Vincent's Prostate Cancer Centre and is an inaugural director of the Prostate Cancer Foundation of Australia.

In PART 2 of the series,
Professor Stricker will discuss how to choose between the different treatment options for prostate cancer.

Look out for the special GP edition of the DVD *So how do you choose?* on prostate cancer treatments, produced by Professor Phillip Stricker, included with next week's issue of *Australian Doctor*.