



Prostate cancer

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Developments in diagnosis and therapy, such as genetic testing and brachytherapy, are improving the therapeutic options available to patients with this condition. By Professor Stephen Langley and Dr Philip Marazzi.

ABSTRACT

Prostate cancer is the most common cancer among men in the UK, usually developing in men aged over 50 years. In the early stages, the disease may have no symptoms. A new test, for prostate cancer gene 3 (PCA3) is proving a useful adjunct in diagnosis. Brachytherapy is becoming a popular alternative to radical surgery and radiotherapy.

Key words

Prostate cancer, prostate specific antigen, brachytherapy

SECTION 1: EPIDEMIOLOGY AND SCREENING

Prostate cancer is the most common cancer in men in the UK, accounting for about 25 per cent of all new male cancer diagnoses. Nearly 35,000 men are diagnosed with prostate cancer each year in the UK and about 10,000 die from the disease annually.¹

Prostate cancer develops most commonly in men over 50 years of age and estimates suggest that 15-30 per cent of men over 50 have histological evidence of prostate cancer.^{2,3} This rises to 60-70 per cent by the age of 80.

Early prostate cancer usually causes no symptoms. The disease may become symptomatic when the prostate has grown large enough to put pressure on the urethra, which can affect urination. These symptoms are not indicative of prostate cancer because the prostate naturally becomes larger with age. Early steps in diagnosis are based on digital rectal examination (DRE) and measurement of prostate specific antigen (PSA) levels.

PSA testing

PSA is a protein produced by normal and malignant prostate cells. Enlargement of the prostate tends to be associated with an increase in the levels of PSA in the blood and while levels can fluctuate, the risk of prostate cancer increases with rising PSA levels. However, benign prostatic enlargement and UTI may raise the PSA level.

The prostate enlarges with age, so there is an age-related PSA range (men in their forties, <2.5ng/ml, in their fifties, <3.5ng/ml, in their sixties, <4.5ng/ml, and in their seventies, <5.5ng/ml). The higher the level of PSA, the more likely it is to be prostate cancer. The speed at which the PSA increases over time, the PSA velocity, may also suggest malignant change. Levels above 0.75ng/ml per year suggest the development of prostate cancer. If the PSA level is very high (>200ng/ml) a diagnosis of prostate cancer can usually be made without the need for biopsy. An abnormal level or significant change in PSA level over time is, therefore, a warning sign for prostate cancer that warrants further investigation.

PCA3 testing

Other tools, such as the PCA3 test, can help to determine whether the high levels of PSA are due to prostate cancer or benign enlargement. PCA3 is a new test and not a replacement for PSA testing. It is measured in the urine following a short prostatic massage and can provide extra reassurance that prostate cancer has not been missed.

SECTION 2: DIAGNOSIS OF PROSTATE CANCER

Staging and grading

The management of prostate cancer depends on the stage of the disease, the PSA level and the pathological grade. The stage of prostate cancer reflects how far the cancer has spread. There are four TNM stages and it usually takes several years to pass from stage I to stage IV. Grading is performed on prostate tissue obtained by biopsy. The grading system used for prostate cancer is known as the Gleason scoring system. The lower the score, the less likely the cancer is to spread. To determine the Gleason score, the pathologist identifies the cancer cells in the biopsy. Having selected the largest and second largest areas of cancerous cells, a Gleason grade is assigned to each area based on histological features. Grades range from 1 to 5, with grade 1-3 tumours least likely to spread and grades 4 and 5 most likely to do so. The Gleason score is calculated by adding together the two Gleason grade numbers: the score ranges from $1 + 1 = 2$ to $5 + 5 = 10$. Prostate cancers with a Gleason score of seven or more will always contain at least some grade 4 tumour and hence have a worse prognosis.

Prostate biopsy

Not all men suspected of having prostate cancer will benefit from a prostate biopsy. **NICE guidelines**⁴ state that there is a need to identify a group at high risk not just of prostate cancer, but of significant prostate cancer.

Factors to consider include the patient's age, the PSA level and velocity, the estimated size of the prostate and DRE findings and any comorbidities or risk factors that may place the patient in a higher risk category.

Biopsies are performed with transrectal ultrasound guidance under local anaesthetic, generally in an outpatient setting. Antibiotics are given to reduce the chance of infection. Ten to 12 biopsies are typically taken and analysed for the presence of tumour cells.

If the patient's PSA level is still rising and initial biopsy results are negative, a transperineal template saturation biopsy may be performed. This technique overcomes some of the limitations of the traditional transrectal biopsy because it allows tissue to be sampled from areas of the gland inaccessible to the normal technique. MRI is the most accurate and commonly used imaging technique for determining the spread of cancer. A bone scan can determine whether the tumour has invaded bone.

Risk stratification

A risk category is assigned to all newly diagnosed men with localised prostate cancer (see box 1). The category identifies the most appropriate treatment and management options. However, factors such as the patient's age and the possible side-effects of treatment are important considerations, and the ultimate decision lies with the patient.

BOX 1: RISK STRATIFICATION			
Risk stratification criteria for men with localised prostate cancer⁴			
Risk	PSA (ng/ml)	Gleason score	Clinical stage
Low risk	<10; <i>and</i>	≤6; <i>and</i>	T1-T2a
Intermediate	10-20; <i>or</i>	7; <i>or</i>	T2b-T2c

High risk	>20; or	8–10; or	T3–T4*
*T3-T4 = locally advanced disease			

The choice of treatment should take into account quality of life for the patient and not be based solely on clinical benefit.

SECTION 3: THE ROLE OF BRACHYTHERAPY

Permanent implant or low dose-rate brachytherapy is becoming increasingly popular as an alternative to radical surgery and radiotherapy for many patients who have early, localised prostate cancer.⁵

Brachytherapy is a form of radiation therapy that involves inserting 80-120 radioactive I-125 seeds into the prostate under transrectal ultrasound guidance (figure 1). Long-term results show that brachytherapy has similar outcomes in terms of cancer eradication, but patients may favour this option because there is no need to undergo major surgery and the incidence of side-effects, such as impotence and incontinence, is lower (see box 2). Patients suited for the procedure are those whose cancer is confined to the prostate.

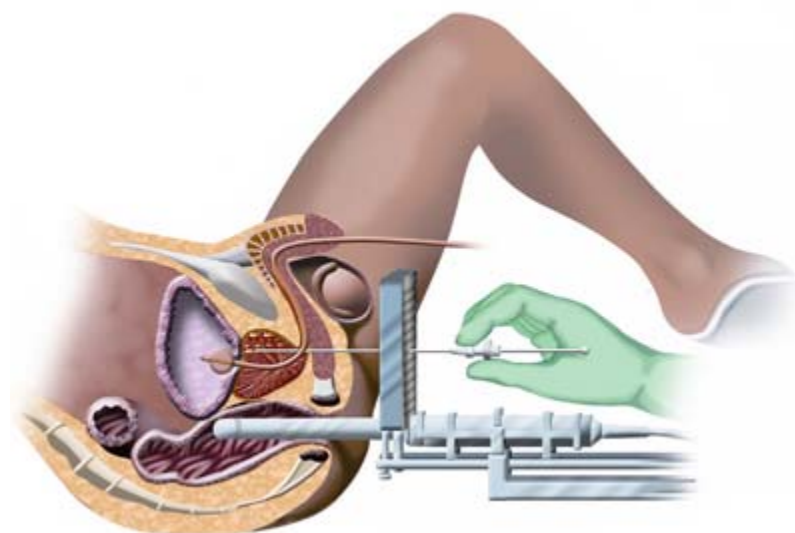


Fig 1: Diagram showing how brachytherapy implant is performed with transrectal ultrasound guidance. Image: Prostate Cancer Centre

Seeds are placed to give a high dose of radioactivity to the entire prostate, while at the same time minimising the dose of radioactivity to surrounding tissues, such as the bladder and urethra. The seeds eventually become inert and will remain permanently in the prostate.

Brachytherapy is either a single- or a two-stage process. Some centres use real-time planning, which allows the planning and implantation of seeds to take place at the same time. This single-stage process takes longer, but avoids the need for the patient to have a separate planning scan. To plan the position of seeds to give the highest dose of radioactivity to the tumour cells, a detailed transrectal ultrasound examination of the prostate is performed. The dose plan is unique to the patient and determines the position and number of seeds required.

Seed implantation

If the prostate is too large (60-80cc), a three-month course of luteinising hormone releasing hormone therapy may be required to shrink the prostate to a size that is suitable for the process of seed implantation.

The radioactive iodine seeds are preloaded into fine needles and inserted into the prostate under transrectal ultrasound guidance at their predetermined positions. This is carried out under general anaesthetic and typically takes between 30 and 45 minutes. Postoperative CT scans are used to check the placement of the seeds.

Treatment is usually carried out as a day-case procedure or overnight stay and patients should be able to drive the next day. They are also usually able to return to work after a short period of rest, normally a few days.

The implants carry no significant risk to the health of the patient's family or work colleagues. Regular PSA monitoring is used to check the progress of treatment.

SECTION 4: OUTCOME AND SIDE-EFFECTS

Brachytherapy is the only NICE-approved minimally invasive treatment option for prostate cancer and is a safe, first-line treatment choice for localised prostate cancer. It is as effective as radical prostatectomy or external beam radiotherapy in patients with low- or intermediate-risk disease. Brachytherapy alone is not suitable for patients whose cancer has spread.

The primary complication associated with the procedure is a temporary deterioration of urinary function. The symptoms peak one to two months after brachytherapy has been carried out, but improve thereafter.

These side-effects are due to the swelling of the prostate and irritation of the prostate and bladder lining caused by radiation from the implanted seeds. However, there is little chance of radiation damage to these tissues and although the seeds are radioactive, the patient is not.

Approximately 25 per cent of patients experience a transient rise in PSA, typically of less than 3ng/ml (known as a PSA bounce) one to two years after the procedure. This is quite common and the level drops again after a few months.

Less than 5 per cent of patients experience urinary retention, which may require temporary catheterisation, usually for about two weeks. Erectile dysfunction can occur in some patients following brachytherapy, but it is significantly less common than with radical prostatectomy.

BOX 2: RELATIVE COMPLICATION RATES FROM LOCAL CONTROL TREATMENTS for PROSTATE CANCER²

Site	Prostatectomy	External beam radiotherapy	Brachytherapy	External beam radiotherapy & brachytherapy
Rectal	+	+++	+	++
Sexual impotence	+++	++	+	++
Urinary incontinence	+++	+	+	+
Urinary retention	+	+	+	+

Increasing number of +s indicates increasing complication rates.

Source: Lancet 2003; 361: 1045-53

Long-term follow-up

At the **Prostate Cancer Centre** in Guildford, Professor Langley and his team started using brachytherapy in 1999 and have now successfully treated more than 1,500 patients.

The long-term, seven-year follow-up of the first 500 patients treated has shown an overall 91 per cent PSA cure rate and a 99.6 per cent prostate cancer survival rate. Less than 1 per cent of patients experienced urinary incontinence and 83 per cent of patients remained potent. After treatment, most patients are able to return to routine daily activities within a few days.

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Competing interests: None declared

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Further resources

Prostate Brachytherapy Advisory Group
Prostate Cancer Centre
PCA3 test

Tags: **Prostate cancer**, **PSA**, **Brachytherapy**