Prostate Cancer Risk Management Programme

information for primary care

PSA testing in asymptomatic men

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Preface

The purpose of this booklet is to supply primary care teams with an easy reference to assist them in providing asymptomatic men with information on the benefits, limitations and implications of having a PSA test for prostate cancer.

Development of the original booklet, published in 2002, was informed by consultation with over 100 GPs and primary care cancer leads, as well as advice from an expert multidisciplinary group set up by the Department of Health to advise on all aspects of the Prostate Cancer Risk Management Programme (PCRMP). The pack has subsequently been evaluated; references can be found in the evidence document available at http://www.cancerscreening.nhs.uk/prostate/index.html.

In 2007, the PCRMP commissioned a review of this booklet, its summary sheet and the accompanying patient information leaflet. This second edition, published in 2009, incorporates information from recent research developments and the recommendations of the National Institute for Health and Clinical Excellence (NICE) in the *Prostate cancer: diagnosis and treatment guidelines*, published in February 2008. This booklet was reviewed by GPs and members of the PCRMP Scientific Reference Group prior to publication.

It is anticipated that this pack will be reviewed in 3 years' time, unless major significant breakthroughs are made within that time frame.

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1 Introduction

Prostate cancer is now the second most common cause of cancer deaths in men in the UK [1]. There has been considerable media focus on the disease, along with calls for the introduction of a national prostate cancer screening programme. The prostate-specific antigen (PSA) test is currently the best available and can lead to the diagnosis of localised prostate cancer for which potentially curative treatment can be offered. However, there are a number of uncertainties surrounding the PSA test and the diagnosis and treatment of prostate cancer. Currently, there is no evidence that the benefits of a PSA-based screening programme would outweigh the harms.

The Prostate Cancer Risk Management Programme and informed choice

The Prostate Cancer Risk Management Programme aims to help the primary care team give clear and balanced information to men who request details about testing for prostate cancer.

Any man over the age of 50 who asks for a PSA test after careful consideration of the implications should be given one.

In response to growing public concern about the risks of prostate cancer, the government launched the Prostate Cancer Risk Management Programme in 2002 [2,3]. One of the main aims of the programme is to ensure that men who are concerned about the risk of prostate cancer receive clear and balanced information about the advantages and disadvantages of the PSA test, biopsy and treatments for prostate cancer. This will enable men to make informed decisions about whether or not to have a PSA test. Many men have inaccurate or incomplete knowledge about the PSA test, gained either from the media or through friends and relatives. There may be advantages to a man knowing his PSA level and in finding cancer at an 'early' stage; however, there may also be disadvantages to being tested. The patient's personal preferences should be an important factor in the decision. The following factors will vary between individuals and affect their decision about whether or not to have a PSA test:

- fear of cancer;
- the consequences of the diagnosis of disease which is unlikely to become symptomatic (e.g. anxiety);
- the potential impact of treatment complications on quality of life; and
- the importance placed upon the current lack of scientific proof [4].

This booklet provides background information about the diagnosis and treatment of prostate cancer and outlines the issues surrounding the use of the PSA test. This booklet is part of an information pack, which also contains a summary card and patient information sheets [5].

2 Prostate cancer background information

2.1 Incidence and mortality

Prostate cancer is the most common cancer and the second most common cause of cancer-related deaths in men in the UK. In 2005, a total of 34,302 men were diagnosed with prostate cancer, and, in 2006, 10,038 men died from the disease [1]. The most common cause of cancer-related deaths is lung cancer, which was diagnosed in 22,259 men in 2005 and which claimed the lives of 19,600 men in 2006 [1].

Prostate cancer is largely a disease of older men, and diagnosis is less common below the age of 50 (Figure 1). The average age at diagnosis is 70–74 years and the average age at mortality is 80–84 years. The numbers of deaths by age in 2006 are shown in Figure 2.

Ninety-three per cent of prostate cancer deaths occur in the 65 and over age group. By the age of 80, approximately 80% of men will have some cancer cells in their prostate (Table 1) [6]. However, in contrast, around 1 in 26 men (3.8%) in England and Wales will die from prostate cancer [7]. By comparison, 1 in 2 men will die from cardiovascular disease and 1 in 53 from colon cancer [7].

The number of prostate cancer cases has risen steadily since 1975 [1]. Part of the increase is a result of an ageing population. However, improved ascertainment by cancer registries, improved diagnostic accuracy and additional methods of detecting prostate cancer have also contributed to the increase in age-specific incidence. Initially, this came from the use

Figure 1
Number of new cases of prostate cancer in the UK, 2005.

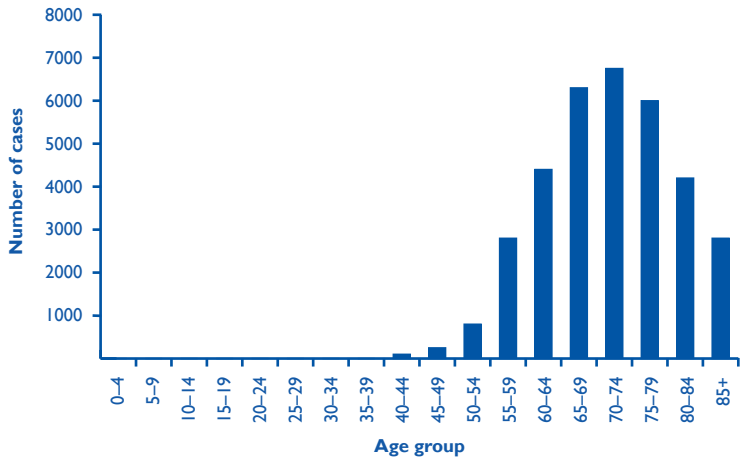
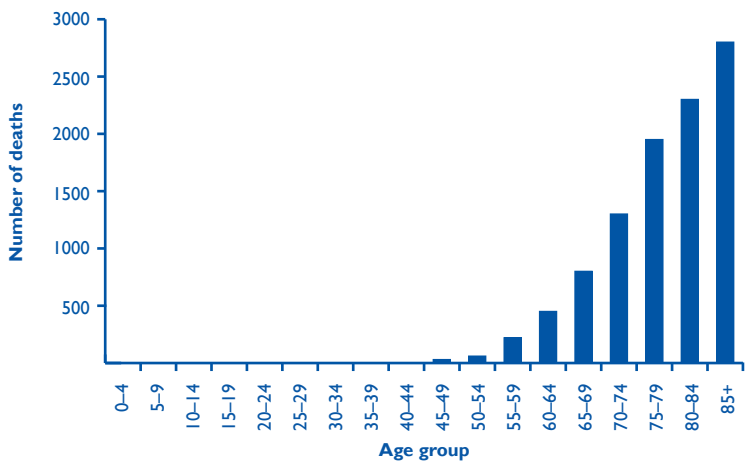


Figure 2
Number of deaths from prostate cancer in the UK, 2006.



of transurethral resection of the prostate (TURP) as therapy for benign disease, with mandatory histological examination of chips removed during TURP. Subsequently, there has been a widespread increase in the use of the PSA test and ultrasound-guided biopsies in men with raised PSA levels. These tests have led to the diagnosis of many cancers, some of which would not have presented clinically within the man's lifetime [8].

As with other cancers, prostate cancer can cause premature death in the UK and reduce life expectancy. Early detection and treatment may reduce the impact of this cancer. A study of differing mortality rates in the USA and the UK has noted that a striking decline in prostate cancer mortality in the USA coincided with the increasing use of PSA screening. However, the authors noted that the differences may be attributable to different treatment approaches between the two countries or differing recording of cause of death as well as any effect of screening [9].

2.2 Natural history of prostate cancer

The natural history of prostate cancer is not fully understood. Prostate cancer is not a single disease entity but more a spectrum of diseases, ranging from slow-growing tumours, which may not cause any symptoms or shorten life, to very aggressive tumours (see section 3.4 for staging procedures). Some tumours can change from being low risk to high risk. Many men with slow-growing tumours die with their cancer rather than of it.

Table 1
Presence of prostate cancer determined at autopsy

Age	20–29	30–39	40–49	50–59	60–69	70–79
Percentage of men in whom prostate cancer was detected at autopsy	8	28	39	53	66	80

2.3 Risk factors for prostate cancer

There is often increased anxiety amongst men with risk factors, particularly those with a family history of prostate cancer. If these men present in primary care, it is important that they receive the best available information and support to assist them in the decision of whether or not to have a PSA test.

The causes of prostate cancer are not known. A recent review of 18 studies showed that sex hormones do not alter the risk of prostate cancer [10]. The risk factors for incidence (listed below) may be different from the risk factors for mortality (e.g. family history) [11].

The strongest risk factor is age (see Table 1), but many other factors also play a part:

Family history

Prostate cancer may cluster in families, and approximately 5–10% of cases are thought to have a substantial inherited component [12]. It has been estimated that a strong predisposing gene could be responsible for 43% of cases by age 55 [13] and research is currently under way to identify prostate cancer predisposition markers [14]. A link between prostate cancer and a family history of breast cancer has been established, believed to be due to the *BRCA1* and *BRCA2* genes [15,16].

The relative risk to a patient increases with increasing numbers of first-degree relatives diagnosed (Table 2). The father-to-son relative risk is increased 2.5-fold whilst the relative risk between brothers is increased 3.4-fold [17].

At present, there are no definitive guidelines for prostate cancer screening in high-risk families in the UK because of the uncertainties around the effectiveness of testing and treatment.

Ethnicity

Black men (irrespective of black-African or black-Caribbean origin) have a 3-fold higher risk of developing prostate cancer than white men [18] whilst Asian and Oriental men have the lowest incidence [19,20]. South Asian men living in England have a lower incidence of prostate cancer than their white counterparts (0.8:1) [21].

Table 2
Effect of family history on the relative risk of prostate cancer

Number of first-degree relatives diagnosed	Increase in relative risk
1	2.5-fold, increasing to 4.3-fold if the relative was under 60 years of age at diagnosis
2	3.5-fold

Diet

Much of the research investigating a link between diet and prostate cancer is, at present, inconclusive [1]. Studies have suggested that lycopenes [22,23] and possibly selenium [24] may have a protective effect. The evidence for red meat is equivocal [1]. However, a diet high in protein or calcium from dairy products may increase the risk of developing prostate cancer [25]. For a more comprehensive list of dietary risk factors, please see the Cancer Research UK *Prostate CancerStats* sheets which accompany this booklet [1]. Obesity has also been linked to prostate cancer, with risk of high-grade disease increasing with body mass index (BMI) [26].

2.4 Clinical features

2.4.1 Localised prostate cancer

Localised prostate cancer (confined within the capsule) is usually asymptomatic. Prostate cancers, unlike benign prostatic enlargement (BPE), tend to develop in the outer part of the prostate gland. It is unusual for these early cancers to cause any symptoms, but they may be palpable by digital rectal examination (DRE).

Localised cancers range from just a few cells to more extensive disease that is considered 'clinically important'.

2.4.2 Locally advanced prostate cancer

These cancers have extended outside the prostatic capsule and are also frequently asymptomatic.

2.4.3 Metastatic prostate cancer

Metastases may be the first sign of prostate cancer, which frequently metastasises to the bones, causing pain. Appearance on x-ray is usually as a sclerotic lesion. It has been estimated that, in 1992, 34% of men diagnosed with prostate cancer in the Thames Valley presented with metastatic disease [8] and in 1999 the UK figure was approximately 22% [27]. However, information about staging is not always available with incidence reports and these data are also difficult to collect as metastatic disease can present very late after diagnosis. Although the majority of men with metastatic prostate cancer die from the disease, it does respond well to hormonal therapy, which often keeps it controlled for several years. The 5-year survival rate of men who present with metastatic disease is approximately 30% [28].

2.5 Lower urinary tract symptoms and prostate cancer

Lower urinary tract symptoms (LUTS) are common in older men. It is important to realise that early prostate cancer itself will not usually produce symptoms and that LUTS (frequency, urgency, hesitancy, terminal dribbling and/or overactive bladder) are usually related to the presence of BPE rather than prostate cancer [29]. Between 70% and 80% of prostate tumours originate in the peripheral zone of the gland distant from the urethra [30]. As a consequence, by the time prostate cancer itself causes LUTS, it may have reached an advanced and incurable stage.

Due to the high coincidence of BPE and prostate cancer in the older age group, some men will have a benign pathology and a co-existing early prostate cancer [31]. When a man seeks advice about LUTS this can lead to investigations which diagnose what is a coincidental prostate cancer.

3 Assessment of prostate cancers

There are currently several ways of determining the presence and/or extent of prostate cancers:

- the prostate-specific antigen (PSA) test;
- digital rectal examination (DRE);
- transrectal ultrasound (TRUS);
- TRUS-guided prostate biopsy and histology; and
- imaging techniques (magnetic resonance imaging [MRI], computerised tomography [CT] scan, x-ray, bone scan).

3.1 The PSA test

> The PSA test should not be added to a list of investigations without a careful explanation of why the test is being performed and its implications.

Prostate-specific antigen (PSA) is a glycoprotein responsible for liquefying semen and allowing sperm to swim freely. It is expressed in both benign and malignant processes involving epithelial cells of the prostate. Due to an alteration in the architecture of the prostate in conditions such as prostatitis and BPE as well as prostate cancer, PSA leaks out, leading to increased levels in the bloodstream.

The incidence of prostate cancer varies up to 4-fold between different European countries, being higher in those countries where PSA testing is more common [32]. Men who have a PSA test increase their chance of a prostate cancer diagnosis. The PSA test provides the opportunity; where clinically relevant prostate cancer does exist, it will be diagnosed at a stage when treatment options and outcome may be improved. However, the PSA test may lead to investigations which can diagnose clinically insignificant cancers which would not have become evident in a man's lifetime.

The most commonly used PSA test measures the total amount of prostate-specific antigen (both free and protein bound) in the blood. An alternative recent test calculates the ratio of free:total PSA to give an indication of whether prostate cancer is present; free PSA is associated with benign conditions and bound PSA with malignancy, so a low ratio (<25%) may be indicative of cancer [33]. A lower significant ratio than 25% may be quoted by the local laboratory based on their specific assay method [34].

The PSA test is currently the best method of identifying an increased risk of localised prostate cancer. However, since PSA is an enzyme also found in men without prostate cancer, and PSA values tend to rise with age due to BPE, the difficulty in using this marker comes in defining the 'normal' range and knowing when referral and biopsy are appropriate. Recent research has indicated that PSA levels are diluted in obese men [35]; however, there is currently no specific guidance on how obesity should affect PSA values for referral, so the PCRMP recommends that the values given (see Table 3) should be used for all men, regardless of their weight.

3.1.1 Test benefits

- The PSA test may lead to the detection of cancer before symptoms develop.
- The PSA test may lead to the detection of cancer at an early stage when the cancer could be cured or treatment could extend life.
- Repeat PSA tests may provide valuable information, aiding in a prostate cancer diagnosis.

3.1.2 Test limitations

- The PSA test is not diagnostic: those with an elevated PSA level may require further investigation, possibly a TRUS-guided prostate biopsy (see section 3.4) and histology to confirm the presence of prostate cancer.
- PSA is not tumour specific in the prostate [36]. Therefore, other conditions, such as benign enlargement of the prostate, prostatitis and lower urinary tract infections, can also cause an elevated PSA. About two-thirds of men with an elevated PSA[1] do **not** have prostate cancer detectable at biopsy [37,38], but this will vary from centre to centre.
- The PSA test result may not be elevated and provide false reassurance. One study has shown that approximately 15% of all men with a 'normal' PSA level may have prostate cancer, and 2% will have

[1] This publication classed an abnormal PSA level as >4 ng/ml.

high-grade cancer,[2] although it is not known how many of these would have become clinically evident in a man's lifetime [39]. This is due to the poor sensitivity and specificity of the PSA test [38]. A one-off test is therefore not reliable enough to provide reassurance.

- The PSA test may lead to the identification of prostate cancers which might not have become clinically evident in the man's lifetime.
- A single PSA test will not distinguish between aggressive tumours which are at an early stage but will develop quickly and those which are not, but further tests may provide valuable information.

3.1.3 Test practicalities

Before having a PSA test men should **not** have:

- an active urinary infection (PSA may remain raised for many months);
- ejaculated in the previous 48 hours;
- exercised vigorously in the previous 48 hours;
- had a prostate biopsy in the previous 6 weeks; or
- had a DRE within the previous week.

Prior to performing a PSA test, the conditions listed in the box above should be met in order to ensure that, where possible, a raised PSA result is the result of prostate cancer, not a confounding physical condition [40].

Evidence indicates that PSA is stable in whole blood for up to 16 hours at room temperature. When taking blood you should ensure that the specimen will reach the laboratory and be separated within this time frame. The quality of PSA testing can vary between laboratories, depending on the type of PSA test employed. To reduce the effects of this variation, samples should be sent only to laboratories which employ a method for PSA assay which is equimolar (measures free and complexed PSA equally) and has calibration traceable to the World Health Organization international standard [41]. Such laboratories should also participate in the UK National External Quality Assessment Service (UK NEQAS) for PSA testing. In addition, samples from each individual patient should always be sent to the same laboratory.

3.1.4 Referral guidance

The serum PSA level alone should not automatically lead to a prostate biopsy.

Other factors that should be considered in conjunction with the PSA level are prostate size, DRE findings, age, ethnicity, co-morbidities, history of any previous negative biopsy and any previous PSA history.

The patient should be involved in any decision about referral to another healthcare provider.

The Prostate Cancer Risk Management Programme recognises that, currently, there is a wide range of referral practice around the country. Further work is being done to consider the evidence in this area, with the aim of standardising the test itself and the referral values used.

The Prostate Cancer Risk Management Programme recommends that age-related referral values are used as detailed in Table 3. The PCRMP will be piloting a recent finding from the ProtecT study, which showed that two PSA tests performed 7

Table 3
Age-related referral values for total PSA levels recommended by the Prostate Cancer Risk Management Programme [43]

Age	PSA referral value (ng/ml)
50–59	≥3.0
60–69	≥4.0
70 and over	>5.0

[2] This publication classed an abnormal PSA level as ≥4 ng/ml.

weeks apart allowed more accurate risk prediction and may assist in decision-making as to whether or not to proceed with referral [42].

Although age-related referral values have traditionally been used, it is now also recognised that PSA levels are a continuum, as demonstrated by the Prostate Cancer Prevention Trial [38]. Whereas a very high PSA reading is strongly suggestive of cancer, the situation is less clear when the PSA is mildly elevated, because of the contribution of BPE. Specialist advice should be sought on abnormal results.

There are additional factors which should be considered in conjunction with the PSA level: prostate size, DRE findings, age, ethnicity, co-morbidities, history of a previous negative biopsy and the man's own view [44].

The following are associated with high-grade cancer:

- smaller prostate volume (as determined by TRUS) [45–47];
- abnormal DRE findings (if the prostate gland is enlarged, tender, nodular, hard or immobile due to adhesion to surrounding tissue) [45,48,49];
- increasing age [45,49,50]; and
- black-African and black-Caribbean ethnicity [45,49].

Previous negative prostate biopsy results are associated with a reduced risk of finding high-grade cancer.

3.2 Digital rectal examination of the prostate

DRE is a useful diagnostic test for men with lower urinary tract symptoms.

DRE is not recommended as a screening test in asymptomatic men.

The digital rectal examination (DRE) is a useful diagnostic test for men with lower urinary tract symptoms or symptoms suggestive of metastatic disease. It allows assessment of the prostate for signs of prostate cancer (a hard gland, sometimes with palpable nodules) or benign enlargement (smooth, firm, enlarged gland). However, a gland which feels normal does not exclude a tumour. Cancer of the prostate may produce changes detected on a DRE, but these are not specific and many early prostate cancers will not be detected by DRE [51].

3.3 Transrectal ultrasound

Transrectal ultrasound (TRUS) can be used to examine the prostate and determine its size accurately but its main value is in enabling precise needle placement in the prostate during systematic prostate biopsy. It is not sufficiently reliable to exclude prostate cancer and should not be used to screen asymptomatic men.

3.4 TRUS-guided prostate biopsy and Gleason score

Approximately two-thirds of men undergoing TRUS biopsy because of an elevated PSA level are found not to have cancer.

The best management for those with a persistently elevated PSA level but negative biopsies is unclear. These men may face prolonged periods of follow-up and may experience considerable anxiety.

A TRUS biopsy involves taking 10 to 12 cores of prostatic tissue through the rectum under ultrasound guidance [52]. A series of biopsies are taken in a systematic manner and additional biopsies may be taken if a lesion is seen. If a tumour is detected, histological examination reveals how well differentiated the tumour is. Tumour differentiation is graded by a Gleason score, by analysing the most common and second most common tumour patterns. Each tumour pattern is assigned a grade (1 to 5) and these grades are combined to produce the Gleason score (2 to 10). The lower the score, the more well differentiated the tumour, the less likely the tumour is to progress and the better the prognosis. Tumours can be classified into three categories on the basis of their Gleason score: low grade (≤ 6), intermediate grade ($=7$) and high grade (8 to 10).

At the recommended PSA referral values, the following should also be taken into account: co-morbidities, ethnicity, family history and abnormal DRE findings. Biopsy may be carried out prior to treatment, unless there is a high clinical suspicion of prostate cancer because of a high PSA level and evidence of multiple bone metastases (positive isotope bone scan or sclerotic metastases on plain radiographs) [44].

As with other medical procedures, the biopsy procedure can cause significant anxiety. Most men describe the biopsy as an embarrassing, uncomfortable experience, and some describe it as painful (although this should be alleviated by use of local anaesthetic) [52].

3.4.1 Biopsy benefits

- A biopsy can find cancer before symptoms develop.
- A biopsy can identify cancerous tissue and identify the grade of tumour.
- A negative biopsy result can relieve anxiety about prostate cancer, although a second biopsy may be necessary if recommended by the multidisciplinary team, particularly if the PSA level remains elevated.
- The diagnosing capability of the biopsy procedure increases with the number of cores taken.

3.4.2 Biopsy limitations

- Post-biopsy complications include bleeding and infection, but antibiotics should be given, so infection is rare (see Appendix 1 for full details).
- Up to 20% of tumours are missed at biopsy (false negatives) [53], although the number of tumours missed at biopsy decreases with the number of cores taken.
- Diagnosis of prostate cancer which is not clinically significant may have a significant impact on the patient. The patient may experience increased psychological burden and problems gaining (more costly) insurance cover [54].
- Management of men with a negative biopsy but a persistently elevated PSA level is very difficult. Prolonged periods of follow-up, with the possibility of re-biopsy, may cause considerable anxiety.

3.5 Imaging techniques

Imaging techniques such as magnetic resonance imaging (MRI), computerised tomography (CT) scans and radioisotope bone scans can be used to assess the extent of cancer and whether it has, or how far it may have, spread. No imaging test is sufficiently reliable to exclude prostate cancer or to screen asymptomatic men.

3.6 The future of prostate cancer detection

The PSA test is the best currently available for prostate cancer, but there are concerns about its accuracy. There has been much debate about how it can be improved to provide a more reliable detection procedure for prostate cancer, as well as a method of differentiating between indolent and aggressive cancers. Studies are currently under way to investigate aspects of PSA levels, such as proportions of free and complexed PSA, PSA density, PSA velocity and PSA doubling time (reviewed in [55]). The proportion of free PSA is higher in benign conditions and the proportion of complexed PSA is higher in malignant conditions, so a low free to complexed PSA value can be indicative of prostate cancer. High PSA levels from a small prostate volume (prostate density; PSA level divided by the TRUS estimated prostate volume) may raise the suspicion of prostate cancer. PSA levels tend to increase with the progression of prostate cancer; calculating the rate of increase in PSA and the time taken for a PSA level to double can be useful diagnostic tools, although the best method of calculation, ideal number of time measurements and optimum time intervals between measurements are unknown at present [56].

Research is also under way to find alternatives to the PSA test, such as prostate cancer 3 (PCA3) [57], human kallikrein 2 (HK2) [58] and early prostate cancer antigen 2 (EPCA-2) [59]. In addition, genetic markers such as 2+Edel, which can potentially distinguish between aggressive and non-aggressive cancers, are being investigated [60].

4 Management of prostate cancer

The management of localised prostate cancer is central to the controversy surrounding screening. Men considering a PSA test should understand that:

- early detection and treatment of prostate cancer may be beneficial;
- at present, there remains uncertainty about how to identify those men at greatest risk of prostate cancer and likely to benefit from further investigations and treatment;
- there is, at present, no strong evidence to indicate which treatment option is most suitable for which man; and
- active treatments have significant side-effects, although improvements to treatment regimes and their side-effects are being made.

4.1 Management options for localised prostate cancer

To date, there are no data from randomised controlled trials giving clear evidence about the *optimum treatment* for localised prostate cancer.

There are several different management options:

- watchful waiting;
- active surveillance or active monitoring;
- radical prostatectomy (open, laparoscopic or robotic);
- radiotherapy (external beam radiotherapy [EBRT] or brachytherapy);
- high-intensity focused ultrasound (HIFU);
- cryotherapy; and
- adjuvant therapy.

There is continuing debate regarding the appropriate identification of patients for the different treatment options. Comparisons of efficacy between treatment options are difficult because of differences in case mix, staging and treatment techniques but, generally, surgery is more likely to cause urinary and sexual dysfunction and radiotherapy is more likely to cause bowel and rectal injury [61]. Randomised controlled trials such as the ProtecT study (http://www.epi.bris.ac.uk/protect/index.htm) are under way. This is a large UK trial comparing radical prostatectomy, radical radiotherapy and active monitoring. The study recruited men between 2001 and 2008 and the primary outcome is 10-year survival, with the initial results expected in 2015. Additional UK-based treatment trials (http://www.cancerhelp.org.uk/trials/trials/default.asp for more details) are currently recruiting patients.

Men with localised low-risk prostate cancer (as defined by Gleason grading, PSA level and T-stage) who are considered suitable for radical treatment should also be offered active surveillance after appropriate counselling. Full NICE guidance on treatment options is available at http://www.nice.org.uk/guidance/index.jsp?action=byID&o=11924.

Men and their partners should be advised that infertility arising from sexual dysfunction may be a significant side-effect of radical treatment.

Before choosing a treatment regime, men should be appropriately counselled about the important quality of life differences between the options. Research to find the optimal treatment regime is ongoing and a treatment decision aid will soon be available [62].

4.1.1 Watchful waiting

During watchful waiting the patient is followed up regularly in primary care. The approach is non-invasive and avoids unpleasant side-effects. Watchful waiting is offered to men who, on the grounds of their age or co-morbidity or on the basis of having slowly progressing tumours, are likely to die from other causes and will not suffer significant morbidity from their prostate cancer. These men will be offered palliative treatment only if and when symptoms of prostate cancer develop. Such treatment will not be curative, but will aim to slow the cancer growth sufficiently to prevent the man dying from it.

4.1.2 Active surveillance and active monitoring

During active surveillance or monitoring the patient is followed up regularly by an oncologist or urologist. Active surveillance or monitoring is offered to men who are generally younger and fitter and who wish to avoid the possibility of unnecessary treatment of indolent cancers. The downside is that disease may spread locally and advanced disease, which may be more difficult to treat, may develop. The aim is to monitor those with stable disease and to identify where radical treatment may

be appropriate for those whose cancer progresses. Men on active monitoring will be monitored by serial PSA tests. Men on active surveillance will be monitored by serial PSA tests and repeat prostate biopsies. Radical treatment with curative intent is offered if there are signs of disease progression.

4.1.3 Radical prostatectomy (open, laparoscopic and robotic)

The aim of radical prostatectomy is to remove the entire prostate gland and to cure the disease; however, complete tumour clearance is not always achieved and approximately 20% of men go on to develop biochemical or clinical recurrence of the disease [63]. Recurrence does not, however, necessarily equate with death from prostate cancer. Complications of surgery include operative mortality, sexual dysfunction and urinary problems (see Appendix 2 for more details). This treatment is uncommon in men over 70 years of age [44].

4.1.4 Radiotherapy (external beam and brachytherapy)

Radiotherapy aims to cure the disease. See Appendix 3 for more details on complication rates for external beam radiotherapy (EBRT) and brachytherapy.

EBRT involves an external source of radiation targeted at the tumour. Short-term side-effects relate mainly to bowel and bladder problems from the radiation. Longer-term complications include sexual dysfunction and urinary problems. This treatment is not usually recommended for men with less than 10 years' life expectancy.

Brachytherapy may be given by two very different techniques. Low dose rate (LDR) brachytherapy involves the permanent implantation of tiny radioactive seeds into the prostate to deliver a high radiation dose into the gland. High dose rate (HDR) brachytherapy requires fine catheters to be inserted into the prostate, through which a radioactive source is temporarily passed. Although the isotope used has a higher dose rate, the overall dose is lower than that given by LDR brachytherapy so it is usually given in conjunction with EBRT. This latter technique is much more recent, with limited clinical data, and is usually reserved for patients with high-risk disease. Possible side-effects include urinary symptoms and sexual dysfunction.

4.1.5 High-intensity focused ultrasound and cryotherapy

High-intensity focused ultrasound (HIFU) and cryotherapy are newer radical therapies for the treatment of localised prostate cancer undergoing assessment through clinical trials. At present, there is insufficient knowledge about the benefit and harm of these therapies for their routine use. HIFU aims to cure the disease by heating the prostate gland using ultrasound waves. Cryotherapy aims to cure the disease by freezing the prostate gland.

4.1.6 Adjuvant therapy

Adjuvant hormone therapy is being used increasingly in conjunction with radiotherapy for apparently localised disease [64]. Hormone therapies (luteinising hormone-releasing hormone [LHRH] analogues or anti-androgens) attempt to suppress growth of the cancer by reducing circulating androgen levels. They can be used as adjuvant treatments to those outlined above and are also widely used in the control of metastatic disease. Side-effects include sexual dysfunction, loss of libido, breast swelling, hot flushes and osteoporosis (see Appendix 4 for more details). Men on the watchful waiting regimen who develop symptoms of progressive disease are usually managed with hormone therapy.

4.2 Locally advanced and metastatic prostate cancer

Clinically advanced localised cancer cannot normally be eradicated by surgery alone. The rate of progression of the disease varies considerably. Patients with locally advanced disease mainly receive radiotherapy or hormone therapy. Some men live for many years with few symptoms, whilst others develop extensive disease quite rapidly.

4.3 Monitoring effectiveness of treatment with PSA

PSA levels are used to monitor disease activity in those with established prostate cancer, giving an indication of response to treatments. It may also give an early indication of the progression of a cancer either after treatment or as part of an active surveillance or monitoring protocol.

5 Population screening for prostate cancer

To date there are no UK data from randomised controlled trials to show the benefit to harm ratio of using the PSA test for prostate cancer screening. However, there is evidence from Europe to show that the PSA test can save lives from prostate cancer, but it is unknown how many cases would be diagnosed and subsequently overtreated.

There have been calls for a national screening programme for prostate cancer, just as there are for breast and cervical cancers. Three trials are currently under way in the UK, Europe and the USA. The UK-based Prostate testing for cancer and Treatment (ProtecT) (http://www.epi.bris.ac.uk/protect/index.htm) study was open for recruitment until December 2008, with follow-up due to continue for a further 10 years. The ProtecT study includes a randomised controlled trial looking at the potential impact of prostate cancer screening. Recruitment has also ended for the European Randomised Study of Screening for Prostate Cancer (ERSPC) (http://www.erspc.org/) and the American Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial (http://prevention.cancer.gov/programs-resources/groups/ed/programs/plco/about). Further information from these trials will be available in 2015, 2010 and 2014 respectively, but results from the ERSPC [65] and interim findings from the PLCO [66] have resulted in more controversy around PSA-based prostate cancer screening [67]. After a median follow-up of 9 years, the ERSPC concluded that PSA-based screening resulted in a statistically significant reduction in the rate of death from prostate cancer by 20% in men aged 55 to 69 years. However, this was associated with a high risk of overdiagnosis and therefore overtreatment (1410 men would need to be screened and 48 additional cases of prostate cancer would need to be treated to prevent one death). After studying the ERSPC data, the European Association of Urology concluded that current published data are insufficient to recommend the adoption of population screening for prostate cancer as a public health policy due to the large overtreatment effect [68]. After 7 to 10 years of follow-up, the PLCO concluded that the rate of death from prostate cancer was very low in men aged 55 to 74 years and did not differ significantly between the screening and control groups. Both studies revealed levels of screening that had taken place before the trials began and screening outside the study by men in the control arm of the PLCO may have led to a reduction in size of the difference in prostate cancer mortality between the screening and control arms. Neither of these studies used data from a UK population or UK-comparable screening protocols, nor have the impacts on men's symptoms and quality of life or costs been published for either study, so care must be exercised in applying these results to any decisions about a screening programme in this country.

When considering population screening programmes, the benefits and harms should be assessed, and the benefits should always outweigh the harms. For prostate cancer the benefits of a population screening programme are not yet known because of our poor understanding of the natural history of different types of prostate cancer and an optimal treatment regime [69].

There are significant gaps in our knowledge about the PSA test, prostate cancer and treatment options. The potentially harmful effects of prostate screening are particularly significant. Whilst some early cancers would be detected and lives saved, the introduction of a PSA-based screening programme at this stage would undoubtedly lead to some men with indolent disease unnecessarily experiencing the side-effects of radical treatment, including sexual dysfunction, urinary problems and, in extreme cases, death.

For these reasons, the National Screening Committee has recommended that a prostate cancer screening programme should **not** be introduced in the UK at this time. Instead, the Prostate Cancer Risk Management Programme was introduced so that men who ask about a PSA test can make an informed choice, based on good quality information, about the advantages and disadvantages of having the test. To aid men in making a decision which is right for them, a decision aid was developed and is available at http://www.prosdex.com/index_content.htm.

6 Conclusions

Prostate cancer is a significant health problem, mainly affecting older men. There are problems surrounding the early diagnosis and treatment options for the disease, and to date there is no evidence to say whether the introduction of a population screening programme would reduce mortality in the UK without significant numbers of men being overtreated. Due to the uncertainties surrounding PSA testing and treatments for prostate cancer, it is imperative that men who request a PSA test receive balanced information about the pros and cons to assist them in making an informed shared decision about being tested.

7 Resources for further information on prostate cancer

Organisation	Website address	Telephone number
Prostate Cancer Risk Management Programme	http://www.cancerscreening.nhs.uk/prostate/index.html	
NHS Direct	http://www.nhsdirect.nhs.uk/	0845 4647
NHS Choices	http://www.nhs.uk/Pages/homepage.aspx	
Health Talk Online	http://healthtalkonline.org/	
UK Prostate Link	http://www.prostate-link.org.uk/	
Cancer Research UK	http://www.cancerresearchuk.org/	0808 800 4040
Cancerbackup	http://www.cancerbackup.org.uk/home	0808 800 1234
The Prostate Cancer Charity	http://www.prostate-cancer.org.uk/	0800 074 8383
Prostate UK	http://www.prostateuk.org	020 8877 5840
Prostate Cancer Support Federation	http://www.prostatecancerfederation.org.uk	0845 601 0766

8 Appendices

Appendix 1: Complications of TRUS biopsy

Two large studies of 5,957 and 5,802 prostate biopsies showed that minor complications were relatively common (haematospermia, 36.3–50.4%; haematuria, 14.5–22.6%; rectal bleeding which subsided without intervention, 1.3–2.3%) whilst major complications were relatively rare (prostatitis, 0.9%; fever, 0.8–3.5%; epididymitis, 0.07–0.7%; rectal bleeding for longer than 2 days, 0.6%; urinary retention, 0.2–0.4%) [70,71]. Re-admission to hospital as a result of prostate biopsy was required in 0.4% of cases [71].

In a recent UK-based analysis of 750 men (within the ProtecT study) who underwent TRUS-guided biopsy, reported side-effects included haematospermia (83.6%), haematuria (64.9%) and rectal bleeding (33.1%) [72].

Appendix 2: Complications of radical prostatectomy

Two large studies of 4,165 and 11,010 men undergoing radical prostatectomy show that the surgical risk of mortality within 30 days is less than 0.5%, but that the risk increases with age [73,74].

Several factors have been shown to influence post-operative sexual function (e.g. age, clinical and pathological stage and surgical technique). Erectile dysfunction has been reported by up to 82.1% of men at 2 years and 79.3% of men 5 years post-operatively [75] and climacturia (leakage of urine at climax) in 38% 9 months after surgery [76].

Incontinence is a significant problem for some patients after radical prostatectomy. It is difficult to quantify and there are wide variations in the definitions and assessment of incontinence between studies. It has been reported that 15.3% of men are incontinent 5 years after surgery [77].

Nineteen per cent of men report bowel urgency and 10% of men report painful haemorrhoids 5 years after surgery [78].

Appendix 3: Complications of radiotherapy

External beam radiotherapy

Urinary problems are reported by 4.1% of men, 29% report bowel urgency and 20% report painful haemorrhoids at 5 years post-operatively [75]. Levels of erectile dysfunction decrease from 63.5% 2 years post-operatively to 50.3% 5 years post-operatively [75]. Approximately 33% of men experience moderate episodes of rectal bleeding 3 years after treatment [77].

Brachytherapy

Between 1% and 2% of men report urinary problems 1 year after treatment [78,79]. Reports of urinary retention in the literature range from 2.2% to 13% [80,81]. A UK-based study has reported a 7% retention rate [82]. Potency was maintained in 83% of patients 2 years after brachytherapy, with only 17% reporting erectile dysfunction [83].

Appendix 4: Complications of adjuvant therapy

Reports of erectile dysfunction range from 50% to 100% [84], and 54% of men report a loss of libido after 1 year [85]. Up to 80% of men report experiencing hot flushes [86]. Reports of gynaecomastia (breast swelling) range from 13% to 70%, depending on the therapy drug used [84]. Twenty-three per cent of patients developed osteoporosis within 66 months [87], and this reduction in bone mineral density has been linked to a 7% increased risk of bone fractures [88].

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