Early prostate cancer diagnosis and management leads to improved prognosis

Prostate cancer is curable if it is detected early enough. The earlier the diagnosis, therefore, the greater the treatment options and the better the prognosis. In this article, the first in our special oncology sections this year, Netty Wood explains the common diagnostic techniques available, the spectrum of prostate cancers and how a range of pharmacotherapy regimens are used for managing these.

Introduction

Prostate cancer is a widespread disease. It is the most common cancer in men in the UK and second most common cancer in men worldwide. Mortality rates are relatively low and 70% of patients are alive at five years.[1] This article will explore the diagnosis and management of prostate cancer, highlighting the controversial role of screening and treatments in this group of patients.

Epidemiology

Worldwide statistics for prostate cancer new diagnoses are staggering. For example,

- In 2002, more than 670,000 men worldwide were diagnosed with prostate cancer.[1]
- It is the second most common cancer after lung cancer in men.[1]
- Three-quarters of all new cases are diagnosed in the developed world with the highest rates occurring in North America (specifically the USA where they have frequent use of prostate-specific antigen — or PSA — testing).[1]

In the UK prostate cancer is the most common cancer in men, but their chances of surviving for five years after diagnosis has increased during the last 20 years[1]:

- Of all new male cancer diagnoses 24% are prostate cancer.[1]
- In 2005 nearly 34,500 men were diagnosed with prostate cancer.[1]
- The five-year relative survival rate for men diagnosed in England in 2000–01 was 71%, compared with only 31% for men diagnosed in 1971–75.[1]

Many men die with, rather than from, prostate cancer. The risk of dying of prostate cancer is approximately 3.8%. It is estimated that 215,000 men are living in the UK with a diagnosis of prostate cancer.[1] and although the incidence is increasing there is no increase in mortality rates. This may be partially influenced by the introduction of transurethral prostatectomy (TURP) a minimally invasive surgical procedure for removing prostate tissue and PSA testing (see below), which has led to the detection of a greater proportion of latent, earlier, slow growing tumours.[1]

Risk factors

Age is the strongest known risk factor for prostate cancer and it is quite rare in men under 50 years.[1] The older the man, the higher the risk, with three-quarters of prostate cancer diagnoses occurring in men aged more than 65 years.

Another strong risk factor for prostate cancer is family history. Men who have a first-degree relative affected with early prostate cancer have twice the risk of developing it. The risk increases with the number of first-degree relatives affected with the condition. For example, men with two or more first-degree relatives affected with early prostate cancer, have approximately a seven- to eightfold increased risk of developing it compared with the general population.[2,3]

The variation of incidence rates across the world has lead to the suggestion that prostate cancer risk is affected by ethnicity. African American men are 61% more likely to develop prostate cancer compared with Caucasian men and are nearly 2.5 times as likely to die from the disease. Asian men generally have a lower risk. It is uncertain whether these differences in risk are the result of genetic susceptibility or exposure to causative environmental factors. There is evidence that both may play a causative role.[3]

Molecular biology studies have suggested that genetic changes, directly related to androgen metabolism, may affect the risk of prostate cancer. Furthermore, androgen levels in certain populations reflect the known ethnic risks of getting prostate cancer (For example, African American men have relatively high androgen levels and Asian men have relatively low androgen levels).[3]

Less established modifiers of prostate cancer risk, include the daily use of non-steroidal antiinflammatory drugs (NSAIDs), such as aspirin and ibuprofen, or the use of statins, which may decrease prostate cancer risks.[4,5] Observational studies have suggested that diets high in saturated fats and red meats, and low in fruits, vegetables, tomato products and fish can increase the risk of prostate cancer.[3] People following these diets tend to be associated with being overweight

Prostate cancer is incurable when diagnosed at a late stage and so there is potential benefit to detecting early stage disease.

and obesity has also been suggested as a risk factor for prostate cancer.[6] More frequent ejaculation may reduce the risk of prostate cancer, though this has not been confirmed in larger controlled studies.[3,7,8] The presence of the sexually transmitted infections Chlamydia, gonorrhoea, or syphilis has also been suggested to increase the risk of prostate cancer.[9]

Screening

Prostate cancer is incurable when diagnosed at a late stage and so there is potential benefit to detecting early stage disease. This has lead to the development of three tests that are used to detect the presence of cancer at an early, curable stage (Table 1).

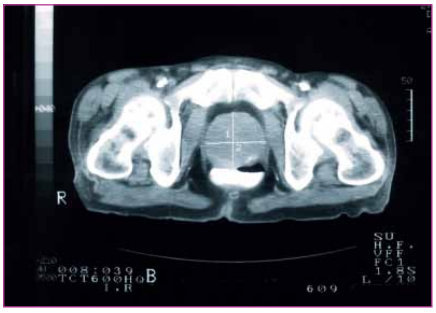
In the USA, all men over 50 years (or 45 years if considered at high risk) are offered routine PSA testing. In the UK, however, there is no current screening programme for asymptomatic men. This is a potentially controversial issue, but the decision not to screen the UK population is evidence based. Prostate cancer receives a lot of attention from patient support groups in the UK and NHS public health with the aim of raising awareness and encouraging men to talk about and think about the possibility of prostate cancer.

Why do we not screen in the UK?

1. Lack of test sensitivity. Men with prostate cancer may not have a raised PSA level.
2. Lack of test specificity: two-thirds of men with an elevated PSA level do not have prostate cancer, and this could result in many men being subjected to unnecessary investigations.
3. Lack of consensus about the best treatment for early stage prostate cancer.
4. No evidence that screening reduces mortality. There are currently two large international trials looking into prostate cancer screening.

Presentation and diagnosis

Early prostate cancer is usually detected via a routine digital rectal examination (DRE) and/or PSA test, leading to a biopsy. Local symptoms from prostate cancer usually do not manifest until there is invasion of the surrounding tissue. Symptoms are urinary hesitancy, nocturia, incomplete emptying and a diminished urinary stream, which is also a sign of benign prostatic hypertrophy. Presenting with symptoms of metastatic disease, such as bone pain and anaemia is less common.



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Diagnosis of prostate cancer is done using a transrectal ultrasound (TRUS) biopsy. The aim of this biopsy is to detect prostate cancers with the potential for causing patient morbidity or mortality.[10] CT or MRI scans are only recommended for patients who have high risk cancer and are considering radical treatment.[10]

Staging of prostate cancer

Staging of prostate cancer comprises of the Gleason score, the PSA test and the TNM system. These are described as follows:

The Gleason score

This is based upon the microscopic appearance of the biopsy tissue. Cancers with a higher Gleason score are more aggressive and have a worse prognosis. The Gleason score ranges from 2 to 10.

The PSA test

Normal age-adjusted levels are considered to be:

- <3.0ng/ml for men aged 50–59 years
- <4.0ng/ml for men aged 60–69 years
- <5.0ng/ml for men aged 70+ years.

TNM system

This is a tumour grading system based on tumour size, lymph node involvement and metastases as follows:

- Tumour size, T, is graded 1–4, where 1 is the smallest tumour.
- Lymph node involvement, N, graded 1–3, where 0 is no involvement.
- Presence of secondary cancer or metastases, M, graded 0–1, where 0 is no tumour found outside the pelvic area.

Overview of treatment options

The primary goal of treatment is to prevent mortality and morbidity while minimising the side-effects of treatment. There is a lack of good clinical evidence concerning when to use which treatments, and few adequately powered randomised trials comparing the relative effectiveness between the treatments. However, in February 2008, NICE published clinical guidance on the treatment of prostate cancer and the following section focuses on this guidance.[10] There are five main treatment options for prostate cancer. These are:

Table 1. Common tests to screen for the presence of prostate cancer

Screening Tests for prostate cancer	What is it?
Digital rectal examination (DRE)	Internal examination of the rectum by the clinician
Prostate specific antigen (PSA) measurement	An enzyme produced by the prostate, which can be measured in the blood
Transrectal ultrasound (TRUS) biopsy	Sound waves produced by a probe inserted into the rectum to create an image of the prostate to allow a biopsy to be taken

Table 2. NICE risk stratification according to risk of recurrence for men with localised prostate cancer[10]

	PSA		Gleason score		Clinical stage
Low risk	< 10ng/ml	and	≤ 6	and	T1–T2a
Intermediate risk	10–20 ng/ml	or	7	or	T2b–T2c
High risk	> 20ng/ml	or	8–10	or	T3–T4

- watchful waiting/ active surveillance
- surgery
- radiotherapy
- androgen deprivation therapy
- chemotherapy.

Most patients will receive a combination of one or more of these options as their disease progresses.

Treatment of localised prostate cancer (contained within the prostate)

NICE guidance recommends that 'Urological cancer MDTs (Multidisciplinary Team Meetings) should assign a risk category to all newly diagnosed men with localised prostate cancer'. This is based on a patient's PSA level, Gleason score and clinical stage of the condition (see Table 2).[10] This risk is then used to guide the treatment options.

The choice of treatment should always focus on balancing the goals of therapy with the risks of lifestyle alterations, and should be made together with the patient. For many, the relative risks of loss of sexual function and ongoing continence problems are important considerations in determining the choice of therapy. Table 3 shows the NICE recommended treatment options according to risk.[10] These options are described more fully in Table 4.

Patients who biochemically relapse (ie have raised PSA) after radical treatment, should be offered hormonal therapy if they have one of the following:

- symptomatic local disease progression
- any proven metastases
- a PSA doubling time of <3 months.

Treatment of metastatic or advanced prostate cancer (spread to other parts of the body)

NICE guidance recommends the following treatment options for cases of metastatic or advanced prostate cancer:[10]

- Surgery — bilateral orchidectomy (surgical castration) as an alternative to continuous androgen deprivation therapy (Figure 1).
- Androgen deprivation therapy (medical castration). It is important to ensure patient is informed that there is no long-term evidence of its effectiveness.
- Anti-androgen therapy.

Table 3. Treatment options according to risk stratification[10]

Risk level	Recommended action
Low risk	Watchful waiting
Intermediate risk	Watchful waiting, radical prostatectomy, brachytherapy or radical radiotherapy
High risk	If there is a prospect of long-term disease control then: radical prostatectomy or radical radiotherapy (with a minimum of 2 years of adjuvant hormonal therapy)
High risk — locally advanced cancer (spread to tissues surrounding prostate)	Radical radiotherapy (with neoadjuvant and concurrent hormonal therapy for three to six months)

The primary goal of treatment is to prevent mortality and morbidity while minimising the side-effects of treatment.

Treatment of hormone-refractory advanced prostate cancer

Unfortunately many patients will eventually become refractory to androgen depravation therapy and will progress. When this happens the patient should be discussed by the urological cancer MDT with a view to seeking an oncologist and/or specialist palliative care opinion, as appropriate. Treatment options suggested by NICE are:

- dexamethasone 0.5mg daily for palliation of symptoms
- radiotherapy for painful bone metastases

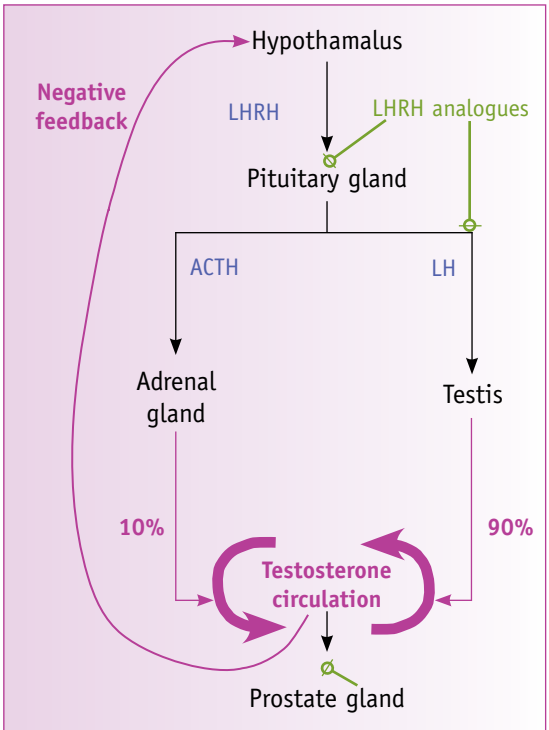

Figure 1. Mechanism of action of androgen deprivation therapy

Table 4. Types of treatment available

Watchful waiting (active surveillance)
An active plan to monitor and observe the patient closely for disease progression without invasive treatment. This treatment option is used when an early stage, slow-growing prostate cancer is suspected, or when the risks of invasive treatment outweigh the possible benefits.

Surgery
Radical prostatectomy (RP). Surgical removal of the prostate gland though an incision in the abdomen wall (retropubic prostatectomy) or the perineum (perineal prostatectomy). Laparoscopic prostatectomy, removal of the prostate gland through small incisions, is used to try and reduce nerve damage. This option is used for tumours that have not spread beyond the prostate. Side-effects include loss of urinary control, impotence, infertility, and impaired erection/ejaculation.
Orchiectomy. Surgical removal of the testicles to decrease circulating androgens.

Radiotherapy
Radiotherapy can be used instead of, or after, surgery in early stage prostate cancer. It is also used to treat painful bone metastases in advanced, metastatic prostate cancer. Radiation treatments can be combined with hormonal therapy for intermediate-risk patients. Side-effects include diarrhoea, mild rectal bleeding, urinary incontinence and impotence. Symptoms tend to improve over time.
External beam radiotherapy (EBRT) or intensity modulated radiation therapy (IMRT). This is given daily via a linac over several weeks.
Brachytherapy. The permanent implant of 100 small rods containing radioactive material through the skin of the perineum directly into the tumour.

Androgen deprivation therapy by medication
The therapeutic effect of castration was demonstrated in the 1940s, and is still the mainstay of systemic treatment today.[11]

Luteinizing-hormone releasing hormone (LHRH) agonists / Gonadotropin-releasing hormone (GnRH) agonists
These treatments have been in clinical practice since 1985. LHRH analogues mimic LHRH, and the first treatment can cause a surge in testosterone through activation of pituitary gland LHRH receptors. However, the LHRH analogue binds irreversibly to the receptor and therefore prevents further activation. The testosterone surge lasts for about 1–2 weeks and can cause a tumour 'flare'. This can manifest as spinal cord compression, ureter obstruction (leading to renal failure) or increased bone pain. Concomitant use of an antiandrogen, started 3 days before starting the LHRH analogue and continuing for 3 weeks, is recommended to prevent this 'flare'. If there is a gap in treatment with an LHRH analogue (eg missed dose) the receptors become unoccupied and the patient is at risk of a further surge in testosterone when treatment is resumed.

Buserelin, goserelin, leuprorelin, or triptorelin are synthetic analogues of LHRH with various potencies compared to natural LHRH. Side-effects include sexual dysfunction, gynaecomastia or changes in breast size and hot flushes. Treatment of hot flushes should include synthetic progestogens.

Antiandrogens
Antiandrogens compete with testosterone for the androgen receptor on the prostate and can inhibit the tumour 'flare' that may occur after starting LHRH analogue therapy. They are also licensed for monotherapy in metastatic prostate cancer refractory to LHRH analogue therapy.

Cyproterone acetate and flutamide side-effects include reduced sexual drive and potency and inhibited gonadal function. Patients who are treated with bicalutamide monotherapy need to be informed about the adverse impact on overall survival and gynaecomastia, but told that they may retain sexual function. For patients who do not maintain satisfactory sexual function bicalutamide should be stopped and androgen withdrawal started. If starting long-term monotherapy patients should receive prophylactic radiotherapy to both breast buds within the first month of treatment. If radiotherapy is unsuccessful in preventing gynaecomastia, weekly tamoxifen can be considered.

- ☐ bisphosphonates for painful bone metastases when other treatments have failed
- ☐ Strontium-89 for painful bone metastases (This a beta-emitting radioactive isotope which is given intravenously and is taken up preferentially in bone metastases.)
- ☐ Chemotherapy.

Chemotherapy

Chemotherapy is only used in advanced hormonal refractory disease. The aim of treatment is to improve symptoms, prolong life and slow progression of the disease. All patients with advanced prostate cancer should be encouraged to participate in local clinical trials if available. Chemotherapy regimens that have been used to treat the cancer include those based on mitoxantrone, estramustine and docetaxel (see Table 5).[12,13,15] Docetaxel has become the gold standard chemotherapy regimen.

The TAX 327 clinical trial compared two docetaxel schedules to mitoxantrone and prednisone (the previous standard chemotherapy regimen). The trial showed the median survival for the three-weekly docetaxel was 18.9 months compared to 16.5 months in the mitoxantrone arm and 17.4 months in the weekly administered docetaxel.

The SWOG 99[16] clinical trial compared docetaxel plus estramustine to mitoxantrone plus prednisone. Median survival for the docetaxel arm was 17.5 months compared to 15.6 months in the mitoxantrone arm. The median time to progression was 6.3 months in the docetaxel and estramustine arm and 3.2 months in the mitoxantrone and prednisone arm.[13]

In 2006 NICE recommended that docetaxel, within its licensed indications, is recommended as a treatment option for men with hormone-refractory prostate cancer within specified restrictions.[14] Hypersensitivity may occur as a response to docetaxel itself or more commonly to its polysorbate 80 vehicle. Pre-medication with steroids is extremely important to prevent hypersensitivity and dexamethasone is given before each dose of docetaxel.

Other chemotherapy regimens are not recommended by NICE for prostate cancer. However, mitoxantrone can be used for patients who cannot tolerate Docetaxel or who fall outside NICE guidance and it is generally used as the standard arm in many trials (Table 5). Mitoxantrone with prednisone improves quality of life in men

Table 5. Chemotherapy regimens

- ☐ Mitoxantrone 12mg/m^2 IV day 1 given every three weeks and prednisone 5mg orally given twice daily continuously[13,15]
- ☐ Docetaxel 60mg/m^2 day 2 plus estramustine 280mg three times per day on days 1 to 5, dexamethasone 60mg in three divided doses before docetaxel[13]
- ☐ Docetaxel 75mg/m^2 in combination with prednisone or prednisone 5mg orally twice daily continuously[12]

with advanced, hormone-refractory prostate cancer, but it does not improve survival.[15]

Side-effects of treatments

There is a potential loss of ejaculation and fertility and sperm storage should be offered. For erectile dysfunction, the patient should be offered phosphodiesterase type 5 (PDE5) inhibitors. If these fail or are contraindicated the patient can be offered vacuum devices, intraurethral inserts or penile injections, or penile prostheses. If urinary function is compromised then access to specialist continence services should be sought.

Bisphosphonates

Bone metastasis in prostate cancer affects more than 80% of patients with advanced disease. Bisphosphonates can be used for the palliation of symptoms such as pain relief and skeletal events. However, they do not influence disease progression or patient survival and there are some questions over the cost-effectiveness of their use.[10,16]

Conclusions

Prostate cancer is a common disease that affects many but has a low mortality rate. More research comparing the different treatment options in each stage of the disease is required to determine a more defined treatment strategy.

With the increased understanding of the mechanisms responsible for prostate cancer and the development of hormone resistant prostate cancer,[18] I imagine that the development of targeted therapies will soon follow, leading to a change of focus for the treatment of prostate cancer. ✣

Declarations of interest

The author has no interests to declare.

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Patient web-based information sources

www.prostatecancerfoundation.org
www.prostate-cancer.org.uk
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