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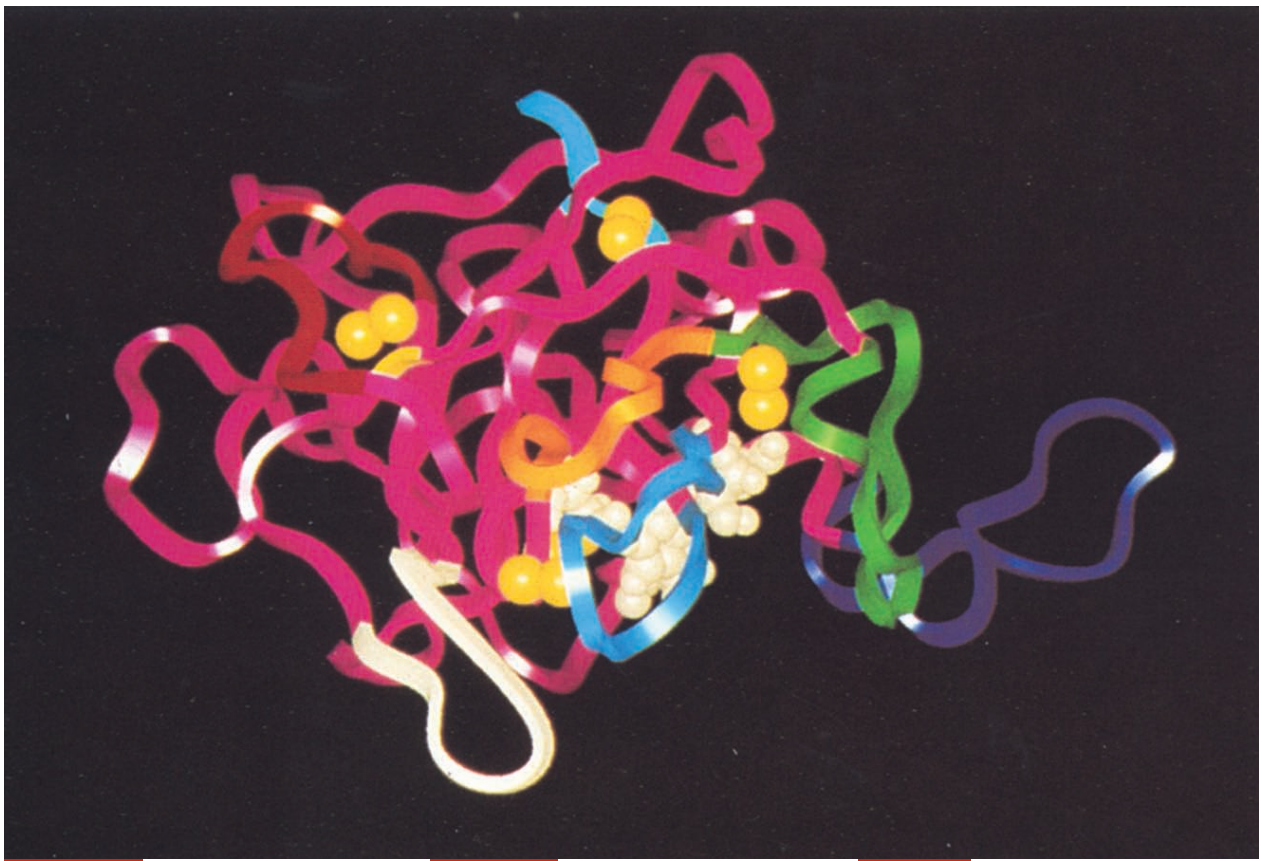
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What is the role of PSA testing?

PROSTATE CANCER IS THE MOST COMMON CANCER IN MEN. MORE THAN 35,000 NEW cases are diagnosed annually and almost 10,000 men die each year in the UK from this disease.

In general, the earlier prostate cancer is detected, the better the outlook for the patient in terms of cure or arresting cancer progression. Now an increasing majority of patients present with an isolated increase in prostate specific antigen (PSA).

In the USA, where PSA testing is widely adopted, the death rate from prostate cancer is falling four times faster than in the UK.[1] Trials are ongoing to try to establish whether universal screening would reduce mortality, but there is no firm evidence yet.

Does staging influence treatment?

EARLY DETECTION

PSA is a glycoprotein responsible for liquefying semen. PSA measurement is currently the most effective single screening test for early detection of prostate cancer. Approximately 25% of men with PSA levels above the normal range (≥ 4 ng/ml) have prostate cancer, and the risk increases to more than 60% in men with PSA levels above 10 ng/ml. The other common cause of a raised PSA is benign prostatic hyperplasia (BPH), but urinary infection and retention can also cause a transient increase.

A particularly difficult clinical situation occurs when the PSA continues to rise in spite of a previous negative biopsy. A new molecular marker, known as PCA3, has been shown to be useful in this respect.

The PCA3 is an adjunct to the PSA measurement. The test measures the expression of the PCA3 gene on »

How is early disease managed?

prostatic epithelial cells passed in the urine immediately after a prostate massage. Prostate cancer cells over-express PCA3 by around 60 times more than benign prostatic epithelial cells. A urine sample taken immediately after a prostatic massage is analysed. A value of greater than 35 indicates that there is an increased risk that the prostate harbours a malignancy.

Furthermore, this new marker may be useful in differentiating men with clinically significant tumours from those with low-risk cancers which can be managed conservatively.[2]

Transrectal ultrasonography (TRUS) is the most commonly used modality to image the prostate gland and also to direct the prostate biopsy needle. Antibiotic treatment, usually with a quinolone, such as ciprofloxacin, is given before and after the procedure to reduce the risk of infection, which is currently estimated at around 2%. Usually 8–14 TRUS-guided biopsies are taken from different regions of the prostate with an 18-gauge needle. This procedure is now routinely performed on an outpatient basis, preferably after infiltration with local anaesthesia.

Histological analysis confirms the presence or absence of cancer and provides a Gleason score for each core. Firm evidence exists to confirm that the higher the Gleason score, the greater the risk of prostate cancer progression and metastasis (see table 1, below).

TUMOUR STAGING

MRI is increasingly used to stage prostate cancer locally and to diagnose or exclude lymph node metastases. Promising results have been reported with the use of ultra-small super-paramagnetic iron oxide particles as an aid to evaluating nodal metastasis by MRI. The addition of MR spectroscopy (evaluation of chemical metabolites in a small volume of interest by MR technology) has also improved the accuracy of MR staging.

Radionuclide bone scanning is generally performed as a baseline assessment at the time of the initial diagnosis of prostate cancer. Bone metastases usually show up as "hot spots" affecting the vertebrae, pelvis or long bones. If the PSA value is < 10 ng/ml and Gleason score is below 8, it may be permissible to omit this test, as it is rarely positive in such circumstances. The use of this technique in routine follow-up has declined as PSA measurements have been shown to be the most accurate and cost-effective means of monitoring bony metastases.

Table 1

Prediction of tumour risk[7]

- Low risk: PSA value equal to or lower than 10 ng/ml, Gleason score equal to or lower than six, and clinical stage T1c or T2a.
- Intermediate risk: PSA > 10-20ng/ml, Gleason score seven, or clinical stage T2b.
- High risk: PSA > 20ng/ml, Gleason score eight to 10, or clinical stage T2c.

'In the USA, where PSA testing is widely adopted, the death rate from prostate cancer is falling four times faster than in the UK'

TREATMENT

The aim of active treatment in patients with localised prostate cancer is usually cure – whether eliminating the tumour or preventing death from prostate cancer (as opposed to death with prostate cancer). As men with localised disease often do not experience significant disease-related morbidity for several years after diagnosis, and curative treatment itself may result in some morbidity, those with a shorter life expectancy are likely to benefit least from radical treatment. Recent guidelines for the management of localised prostate cancer have been issued by NICE.[3]

Radical prostatectomy involves surgically removing the entire prostate, the seminal vesicles and a variable amount of adjacent tissue. It is most appropriate for cases where it is believed the tumour can be removed completely by surgery and in patients with no comorbidity. The procedure is most commonly performed via the retropubic route, though the perineal approach can also be used.

The major advantage of radical prostatectomy is that it excises all prostatic tissue and provides precise histological information and definitive cure in patients in whom the tumour is confined to the specimen. Thus, the patient's anxiety is relieved during the postoperative period. Given that prostate cancer has a long natural history, this is an important consideration in terms of the patient's quality of life. Long-term studies have shown normal life expectancies in those with complete excision of specimen-confined disease. Ten-year survival for men with clinically localised disease treated by radical prostatectomy is 98%, 91% and 76% for Gleason scores 2–4, 5–7 and 8–10, respectively. Moreover, the procedure also offers definitive treatment of concomitant BPH.

The principal adverse events associated with radical prostatectomy are persistent stress urinary incontinence (< 2–3%) and erectile dysfunction (> 50%); the latter is age related, tends to improve with time and can be minimised by nerve-sparing approaches. Moreover, erectile dysfunction after surgery can now be treated effectively.

Radical prostatectomy, by whichever means achieved, is believed by many urologists to offer the best opportunity for cure in patients with localised prostate cancer. A randomised study from Sweden showed that at a median 8.2 years' follow-up, radical prostatectomy reduced prostate cancer related mortality by 44% and overall death by 26%.[4] Recently, laparoscopic radical prostatectomy has been developed. The minimally invasive approach decreases blood loss and postoperative pain. It can be facilitated by robotic assistance with the da Vinci device which provides 3D vision and 10 times magnification.[5]

External beam radiotherapy is widely used in the treatment of localised prostate cancer; it offers a particular advantage in patients who are unsuitable for surgery either because of comorbidity or evidence of extraprostatic extension of cancer. The treatment generally involves a seven-week course of radiotherapy. Ten-year survival of patients undergoing external beam radiation for clinically localised, prostate cancer with Gleason score 2–4, 5–7 and 8–10 is reported to be approximately 89%, »

74% and 52%, respectively. The principal side-effects are caused by damage to the bladder, urethra and rectum from the radiation scatter. Urinary frequency and urgency are common. In its severe form, urinary bleeding and pain may occur in 2–3% of patients. Rectal side-effects consist of urgency, frequency and tenesmus. If severe, rectal bleeding, pain or fistula may very occasionally require a colostomy. Erectile dysfunction resulting from damage to the neurovascular supply to the corpora cavernosa can also occur, typically over a 6–18-month period.

Low-dose seed brachytherapy involves placing either iodine^{125} or palladium^{103} seeds into the prostate via the transperineal route, using a template and TRUS guidance. The results of seed brachytherapy in low-risk men (PSA < 10 ng/ml, Gleason score < 7 and ≤ cT2b) is equivalent to radical prostatectomy at 10 years, but they are highly dependent on the quality of seed placement. The results in patients with intermediate risk are worse, however, with freedom from recurrence approximately 66% at 10 years.

'Erectile dysfunction after surgery can now be treated effectively'

The method is popular, particularly in the USA, because of its low morbidity – the side-effects include lower urinary tract symptoms which are a direct result of the seeds. Rectal symptoms and incontinence are unusual, but erectile dysfunction may develop over time and disease recurrence may occur.

Active surveillance

This is usually reserved for men with small volume and low-to-moderate grade prostate cancer, who have a low risk of death from the disease. These men would be eligible for curative therapy, but this option is deferred until objective signs of progression are observed.[6] This approach means the majority of men are spared the side-effects of curative therapy when they do not require it.

During active surveillance, men are followed closely with repeated PSA measurements and DREs, and repeat prostate biopsies. A PSA test can be taken immediately after a DRE. (A gentle DRE will not result in a PSA rise. However, a more thorough massage, as for a PCA test will).

If the cancer appears to progress significantly, curative therapy is initiated before the cancer becomes incurable. The cancer-specific survival in men who fit the criteria for active surveillance is 99% at 8 years' follow up.[7] While men who undergo active surveillance avoid the physical side-effects of cancer treatment, they have to live with the psychological effects of having an untreated cancer which may progress.

Metastatic disease

Although there is a marked trend towards earlier detection of prostate cancer, many patients still present with metastatic disease. In contrast to localised or locally advanced disease, metastatic prostate cancer is associated with high mortality – approximately 70% within five years.

Androgen deprivation can be achieved by orchidectomy, treatment with a luteinising hormone releasing hormone (LHRH) analogue or an antiandrogen. In most cases, advanced prostate cancers treated with any form of androgen deprivation eventually begin to progress, a phenomenon known as 'hormone-refractory' or 'androgen-independent' disease.

Chemotherapy with docetaxel has recently been tested in a randomised trial against mitoxantrone and prednisone in men with androgen-independent prostate cancer. The results of this study (TAX-327) showed that docetaxel, given in a 3-week schedule, was superior to mitoxantrone and prednisone in terms of decreasing disease progression, PSA response and improving pain.[8] In addition, docetaxel significantly improved survival from a median of 16.4 months for mitoxantrone and prednisone to 18.9 months for 3-weekly docetaxol, which correlates to a 24% relative reduction in mortality. The side-effects associated with docetaxel include neutropenia, skin reactions and gastrointestinal problems.

key points

SELECTED BY
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Prostate cancer is the most common cancer in men with more than 35,000 new cases diagnosed annually and almost 10, 000 deaths from the disease. In general, the earlier prostate cancer is detected, the better the outlook for the patient in terms of cure or arresting cancer progression.

PSA measurement is currently the most effective single screening test for early detection of prostate cancer. Approximately 25% of men with PSA levels above the normal range (≥ 4 ng/ml) have prostate cancer, and the risk increases to more than 60% in men with PSA levels above 10 ng/ml.

The PCA3 is an adjunct to the PSA measurement. A PCA3 value of greater than 35 indicates an increased risk that the prostate harbours a malignancy. This marker may also be useful in differentiating men with clinically significant tumours from those with low-risk cancers which can be managed conservatively.

Transrectal ultrasonography is used to image the prostate gland and direct the biopsy needle. A total of 8-14 biopsies are taken from different regions under local anaesthesia and with antibiotic cover. Histological analysis provides a Gleason score for each core. The higher the Gleason score, the greater the risk of prostate cancer progression and metastasis.

MRI is widely used to stage prostate cancer locally and to diagnose or exclude lymph node metastases. Radionuclide bone scanning is usually performed as a baseline assessment at the time of the initial diagnosis of prostate cancer with bone metastases showing up as "hot spots" affecting the vertebrae, pelvis or long bones.

The aim of active treatment in patients with localised prostate cancer is usually cure – whether eliminating the tumour or preventing death from prostate cancer (as opposed to death with prostate cancer).

Radical prostatectomy is most appropriate for cases where it is believed the tumour can be removed completely by surgery and in patients with no comorbidity. Long-term studies have shown normal life expectancy in those with complete excision of specimen-confined disease. Radiotherapy offers a particular advantage in patients who are unsuitable for surgery because of comorbidity or evidence of extraprostatic extension of cancer.

Active surveillance is usually reserved for men with small volume and low-to-moderate grade prostate cancer, who have a low risk of death from the disease. Careful follow-up and repeat biopsy is essential to assess possible progression of cancer.

Although many conundrums surround the diagnosis and management of prostate cancer considerable progress is now being made. The results of a number of landmark studies of screening, chemoprevention and treatment options for localised prostate cancer will be available soon and should provide a sounder evidence base for the diagnosis and management of this most prevalent cancer in men.

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Useful information

The Prostate Charity UK provides useful information on all prostate conditions for patients and clinicians **(www.prostate-uk.org)**

UK Prostate Link provides links to other websites, with an assessment of the reliability of the information **(www.prostate-link.org.uk)**

Men's Health Forum is a registered charity providing information on all aspects of men's health **(www.menshealthforum.org.uk)**

The Prostate Cancer Charity offers information and support for patients and healthcare professionals **tel: 0800 074 8383 (www.prostate-cancer.org.uk)**

Cancer Backup offers information on all types of cancer for patients and healthcare professionals **tel: 0808 800 1234 (www.cancerbackup.org.uk)**