Prostate cancer

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Abstract

Prostate cancer is a major health problem. In the UK, it is the commonest male cancer and the second commonest cause of male cancer death. Increasing age is its strongest predeterminant. Virtually all cancers are adenocarcinomas, the grade being indicated by the Gleason score. There are often no presenting symptoms. Investigations such as serum prostate-specific antigen, digital rectal examination, biopsy and, increasingly, magnetic resonance imaging (MRI) are required for diagnosis. Local staging consists of MRI, with computed tomography, bone scanning and, increasingly, positron emission tomography for detecting metastases. Management depends on disease stage, the patient's fitness and their wishes regarding treatment. Active surveillance is increasingly used for low-volume and low-grade cancers. For localized prostate cancer, radical prostatectomy can offer a cure. Curative treatment can be given as external-beam radiotherapy or brachytherapy. The survival rate at 10 years may be as high as 90% for a well-differentiated, localized prostate cancer. Hormonal therapy, which lowers or blocks testosterone, is used in locally advanced and metastatic disease. Hormonal therapy slows but does not cure metastatic disease. Cytotoxic chemotherapy is increasingly used for castrate-refractory prostate cancer and has recently been shown to significantly improve overall survival in hormone-naive patients with metastatic prostate cancer.

Keywords Chemotherapy; Gleason score; hormonal therapy; prostate cancer; prostate-specific antigen; prostatectomy; radiotherapy

What's new?

- The role of magnetic resonance imaging in diagnosis and treatment planning is evolving
- Studies have shown improved survival in intermediate and high-risk localized prostate cancer with the use of a combination of radiotherapy and hormonal therapy
- New hormone therapies including abiraterone and enzalutamide have shown a significant survival benefit in metastatic disease
- Cytotoxic chemotherapy is increasingly being used for castrate-refractory prostate cancer and has recently been shown to significantly improve overall survival in hormone-naive patients with metastatic prostate cancer

Epidemiology

Prostate cancer is a significant international health problem and the second leading cause of cancer death in men in the UK.[1] For men in developed countries, the lifetime risk of developing microscopic prostate cancer is 30%,[2] and of developing clinical disease is 13%.[1]

In 2012, 43,436 men in the UK were diagnosed with prostate cancer.[1] The incidence is increasing; this is thought to be a result of greater disease awareness and increased detection due to the prostate-specific antigen (PSA) serum test. Prostate cancer accounted for 10,837 deaths in the UK in 2012.[1] The disease is highly heterogeneous, varying from low-grade, low-volume disease that can be managed with surveillance, through to high-volume metastatic disease that is almost always lethal. There is significant variation in incidence worldwide, from relatively high in Western Europe and North America to low in Eastern and South Central Asia.

Aetiology and risk factors

Several risk factors have been implicated. The most important are age, ethnicity and genetic factors.

Age: this is the strongest predetermining factor for the development of prostate cancer, which is increasingly common with advancing age. In the UK between 2009 and 2011, only 1% of cases were diagnosed in men under 50 years of age, with 36% of cases diagnosed in men aged 75 years and over.[1]

Ethnicity: the highest incidences are found in African−American men and the lowest in Chinese men.

Familial: several studies have shown the prevalence of prostate cancer within certain families. This hereditary form of prostate cancer starts 6−7 years before the sporadic type. No single gene has been implicated.

Genetic: mutations in the *BRCA1* and *BRCA2* genes contribute to the development of certain prostate cancers. In particular, *BRCA2* mutations are associated with a higher Gleason score, rapid progression and poorer overall survival.[3]

Other risk factors: the amount of dietary fat consumed appears to be a risk factor for the development of prostate cancer. Studies have shown a small but significant association between obesity and prostate cancer, and a modest association between cigarette smoking and fatal disease.

Pathology

Over 95% of prostate cancers are adenocarcinomas; other less common types include sarcomas and neuroendocrine tumours. The majority (90%) of adenocarcinomas are acinar, with ductal carcinomas being less common. Characteristic prostate adenocarcinoma cells have hyperchromatic, enlarged nuclei with

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prominent nucleoli and abundant cytoplasm. The basal cell layer is absent in prostate cancer. Prostate cancer is often multifocal. About 70% of cancers are found in the peripheral zone, 20% in the transition zone and 10% in the central zone.

Prostatic intra-epithelial neoplasia (PIN) is the precursor of prostate cancer. Cells show similar characteristics to prostate cancer cells, but the basal cell layer is present. PIN is often found adjacent to areas of prostate cancer, and its identification on biopsy in the absence of cancer warrants further investigation to exclude co-existing invasive carcinoma.

Grading and staging

Prostate cancer is graded using the Gleason system, which is based on the microscopic appearance of the glandular architecture of the prostate. A grade between 1 and 5 is given first to the most dominant pattern, and then to the second commonest pattern. The two grades are added together to give the Gleason score, which ranges from 2 to 10. The grade indicates the degree of glandular differentiation: grade 1 indicates a well-differentiated tumour, whereas grade 5 is a poorly differentiated tumour. The Gleason score gives an indication of prognosis and tumour progression.

Once the diagnosis is confirmed, additional investigations are necessary to determine the extent of disease and assign the patient to a risk group. The stage is assessed using a number of diagnostic tools, including digital rectal examination (DRE), magnetic resonance imaging (MRI), computed tomography (CT) and bone scintigraphy. Not all are essential in every case; the decision is guided by symptoms, PSA concentration, Gleason score, clinical stage, risk group and life expectancy.

Tumour progression

The likelihood of local extension outside the prostate capsule, invasion into the seminal vesicle, and nodal and distant metastases increases with increasing PSA, tumour volume and Gleason score. The obturator lymph node chain is the most common site for lymphatic spread. Metastatic spread usually involves bone metastases in the axial skeleton and non-regional lymphatics. Bone metastases are a characteristic feature of metastatic prostate cancer and present in 90% of metastatic cases.

Diagnosis

Early low-grade prostate cancer is usually asymptomatic, unlike locally advanced or metastatic disease, which is usually symptomatic. Local growth can cause obstructive or irritative urinary symptoms, and metastatic spread can present with bone pain and even compression of the spinal cord. Patients may also present with systemic symptoms such as anorexia, weight loss and fatigue.

The main investigations used to diagnose prostate cancer are discussed below.

Prostate-specific antigen: many cases of prostate cancer are discovered by routine measurement of PSA in serum. PSA is a glycoprotein produced only by prostate cells. Its concentration is raised in prostate cancer as well as in benign prostatic hyperplasia (BPH) and prostatitis, and more transiently following prostate biopsy and in acute urinary retention. PSA is a sensitive but non-specific test for prostate cancer.

A screening programme for prostate cancer and the routine measurement of PSA have not been adopted in the UK. The advantages would include:

- earlier detection of disease
- subsequent decrease in mortality from advanced disease.

The disadvantages would be the:

- number of false-positives, as PSA concentrations may be high due to other causes
- number of false-negatives, as serum PSA may be within the 'normal range' in the presence of cancer
- potential identification and treatment of clinically irrelevant disease
- adverse effects of treatment, especially incontinence and impotence
- healthcare resource costs.

PSA testing remains controversial and men should be adequately counselled on the pros and cons as outlined above.

Digital rectal examination: this is an essential part of the urological examination, enabling the size of the prostate gland to be assessed and nodules or lumps to be detected; clinical stage is a key prognostic factor.

Transrectal ultrasound (TRUS) and biopsy: these may be indicated if cancer is suspected but are not necessary in all cases. Where the PSA concentration is high and there is evidence of bone metastases, a biopsy is not recommended for confirmation.[4] TRUS biopsy is performed under local anaesthesia and 10–12 biopsies of the prostate are taken. Occasionally, despite a high PSA concentration, the biopsies are negative, or PIN is found. In these cases, multiparametric MRI can be used to assess whether another biopsy is needed[4] (see *Diagnostic and Therapeutic Imaging in Oncology* on pages 6–9 of this issue).

Template and targeted biopsies: transperineal template biopsies and MRI-targeted biopsies have been shown to detect more significant prostate cancers than TRUS biopsy and can be used when the initial TRUS biopsy is negative but clinical suspicion remains high.[5]

Other investigations

If a biopsy is positive for adenocarcinoma, a decision must be made regarding suitability for radical treatment before proceeding with additional investigations.

MRI: the role of MRI is evolving and MRI of the pelvic area (or CT if MRI is contraindicated) is recommended prior to treatment.[4] This gives information about the local extension of the cancer and nodal involvement, which is important if radical prostatectomy or radiotherapy is planned.

Whole-body bone scintigraphy: this is recommended for symptomatic patients and asymptomatic men with local disease at high risk of bony metastases, based on grade, stage and PSA.

PET: this is increasingly used for detection of metastases. A variety of radioactive tracers can be used.