Prostate cancer

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Abstract

Prostate cancer is the most common male cancer in the UK representing approximately a quarter of all male cancer diagnosis. The disease and treatment options are wide ranging from a relatively benign disease requiring monitoring only, to an aggressive malignancy requiring active treatment. This can prove a challenge to both the doctor and patient deciding on the best management option. Ongoing research is revolutionizing both the diagnostics and treatment of the disease. This article aims to summarize the current knowledge of prostate cancer and treatment options available.

Keywords Men's health; prostate cancer; PSA; urology

Epidemiology and aetiology

Prostate cancer is the most common male cancer in the UK. There were approximately 43,400 new cases of prostate cancer in the UK in 2012[1] which accounted for 13% of all new cancer cases. Worldwide, it is estimated that 1.11 million men were estimated to have been diagnosed with prostate cancer in the same year. Overall, it is estimated that the lifetime risk of a man being diagnosed with prostate cancer is one in eight.

Over the last 30 years, there has been a sharp increase (almost 150%) in the incidence of prostate cancer in the UK which appears to be slowing in the last decade. Much of this is due to increased detection — most likely because of the increased use of the Prostate Specific Antigen test (PSA) but in part the result of an ageing population. Indeed, age is a major risk factor for prostate cancer with more than a third of cases of prostate cancer being diagnosed in men over the age of 75. It is rare below the age of 40.

Although prostate cancer survival is improving, with 85% of men diagnosed with prostate cancer in the UK surviving for five or more years, it remains the second most common cause of cancer death in the UK, after lung cancer.

The development of prostate cancer is thought to be multifactorial and a complex interplay of both genetic and (possibly) environmental factors. Whilst age, racial origin and a positive family history are established risk factors in the development of prostate cancer,[2] no modifiable risk factors have been conclusively linked with an increased risk in the development of prostate cancer. A man with a first degree relative with prostate cancer has double the relative risk of developing the disease than if none of his relatives were affected.[3] Overall, approximately 5% of prostate cancers are believed to be inherited. There is also some evidence to show a link between an increased risk of prostate cancer in patients in whom there is a family history of breast, ovarian, bladder or kidney cancer.[4] Afro-Caribbean men are at greatest risk whilst it is relatively rare in Asians. Interestingly, it has been shown that Japanese men born in the United States have a higher incidence of prostate cancer, compared to their immigrant Japanese fathers and approaches that of the native population suggesting a strong environmental component to the development of prostate cancer.[5] There have been many dietary and lifestyle factors that have been studied which were thought to affect a man's chance of developing prostate cancer (such as vitamin E and selenium). Conclusive evidence is lacking. Smoking is thought to be associated with fatal prostate cancer.

An important drug has been studied in terms of their association with prostate cancer. The 5α reductase inhibitor (5αRI) finasteride, used commonly in the treatment of male lower urinary tract symptoms (LUTS), has been suggested as a chemopreventative agent. A trial of 18,000 men (the PCPT Trial) randomized men to finasteride 5 mg OD or a placebo. Results suggested that finasteride reduced the risk of developing prostate cancer by 25%, but also increasing the risk of higher grade (and therefore clinically significant) cancers.[6] These results have been much debated since and at present there is no indication for 5αRIs to be used as a chemo-preventative strategy for prostate cancer. With the improvements in prostate cancer diagnostics and the ageing population it is likely that prostate cancer will continue to occupy a significant part of the workload of urologists, oncologists and general practitioners.

Pathology of prostate cancer

The vast majority of prostate cancers (over 95%) are adenocarcinomas. Prostate cancer arises from glandular structures in epithelial tissues. In the process of malignant transformation, the basal cell layer is lost and the basement membrane is invaded by malignant cells which lead to local invasion. Transitional cell carcinoma (reflecting local spread from the bladder urothelium), intraductal carcinomas (arising form prostatic ducts), sarcomas, small cell carcinomas and metastasis to the prostate from other primary sites are rare and tend to be aggressive forms with a poor prognosis.

Anatomically, the prostate is often described according to its zonal anatomy (so-called McNeil's zones) and 70% of prostate cancers arise from the peripheral zone. Approximately 25% of prostate cancers are derived from the so-called transitional zone. This area tends to be anterior in the gland and therefore difficult to target using traditional transrectal ultrasound (TRUS) biopsy techniques. The remaining 5% of prostate cancers arise from the central zone of the prostate which has a separate embryological origin.

Prostate cancer can develop into locally advanced disease by invading surrounding structures: penis, seminal vesicles, bladder and distal ureter and, more rarely, the rectum. Nodal metastasis most commonly occurs in the obturator and iliac nodes and this forms the basis of a lymph node dissection when done in combination with radical prostatectomy. Metastatic disease characteristically occurs to the bone with the axial skeleton commonly affected (especially the spine). These are typically described as sclerotic on imaging. Metastasis to other sites, such as the liver, lung and brain, are much less common.

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Gleason grading

Adenocarcinoma has been graded according to the Gleason grading system since its description in the 1960s. It is graded from one to five according to the degree of gland differentiation; the glandular architecture seen under microscopy. The higher the grade, the more aggressive the cancer. Two grades are given which represent the two most dominant patterns seen (or a single grade is doubled if only one pattern is identified) to give an overall score of between 2 and 10. For example, if the most dominant pattern seen on a prostate biopsy (or a radical prostatectomy specimen) is Gleason 4 with some Gleason 3 pattern also (but less commonly) seen then the prostate biopsy would be reported as follows: Gleason 7 (4 + 3). The Gleason score is crucial in deciding how to manage a man with newly diagnosed prostate cancer. It forms one of the three components of the risk stratification of prostate cancer (see later); ≤ Gleason 6 cancers would be considered well differentiated (or low risk in the stratification); Gleason 7 moderately differentiated (intermediate risk) and Gleason 8 or higher cancers poorly differentiated (high risk). The Gleason score is the most important prognostic indicator after radical, curative treatment of prostate cancer.

Prostatic intra-epithelial neoplasia (PIN)

This is a common histological finding on prostate biopsy; it is identified in approximately 5% of initial prostate biopsies. It is defined as 'architecturally benign glands lined by cytologically atypical cells.' It is further subdivided into low and high grade PIN depending on the prominence of nucleoli. It is associated with similar molecular changes to those seen in prostate cancer but is not associated with an increase in the PSA value. Overall, the chance of diagnosing prostate cancer on a repeat biopsy after high grade PIN is identified on an initial biopsy is around 25% — i.e. roughly the same as if the first biopsy had been negative. Re-biopsy is reserved for those men in whom multi-focal high grade PIN is identified where the subsequent yield of prostate cancer on repeat biopsy is higher (estimated at approximately 40%).

Atypical small acinar proliferation (ASAP)

This is another histological finding that is seen in approximately 5% of initial prostate biopsies. It is defined as 'features suggestive of, but not diagnostic of, prostate cancer.' It is associated with a formal diagnosis of prostate cancer on 40% of subsequent prostate biopsies.

Prostate cancer diagnosis

Prostate cancer is often diagnosed after a patient presents to his family doctor with lower urinary tract symptoms and a suspicious feeling prostate on rectal examination or an elevated PSA (see section below) blood test result which prompts a referral to a urologist. The urologist would then see the patient in an urgent clinic and take a history and repeat the examination of the prostate. Important points in the history are those of LUTS, family history and symptoms of back pain, leg swelling or peripheral neurological symptoms which may suggest advanced disease. Another common way in which patients are diagnosed is following the histological analysis of prostatic tissue removed during bladder outlet surgery for LUTS (such as TURP — transurethral resection of prostate or HoLEP — holmium laser enucleation of prostate). A raised PSA in itself need not automatically lead to a TRUS prostate biopsy being arranged (NICE guidelines) but should prompt a discussion between patient and clinician of the potential risks and benefits of the procedure.[7] At the other end of the scale, if an elderly patient has a very high PSA level (e.g. over 100) and very suspicious DRE then a clinical diagnosis of prostate cancer can be made. In this setting, a prostate biopsy may not be needed (and thus avoids the potential associated risks) unless, for example, histological diagnosis is needed for entry into a clinical trial.

Traditionally, the patient would then undergo a TRUS-guided prostate biopsy. This involves a short local anaesthetic procedure where 12 cores are taken from the prostate via a probe in the rectum. It is associated with a small (approximately 1%) but significant risk of sepsis as well as bleeding (haematuria, haematospermia or rectal) and urinary retention. Anticoagulant medication such as warfarin or clopidogrel must be stopped before the procedure; aspirin needn't be. The results of these biopsies would prompt further imaging investigations as needed and a treatment decision made. As well as the morbidity associated with the procedure, there is an estimated false negative rate of around 30%.

More recently, the field of prostate diagnostics is becoming a subspeciality of urology in itself. Whilst, TRUS biopsies are still commonplace, the use of multi-parametric MRI scans and transperineal prostate biopsies are being increasingly used. This is especially useful for patients in whom prostate cancer is suspected but may have had an initial negative TRUS prostate biopsy. The technique involves, under a general anaesthetic, taking between 20 and 40 prostate biopsies using a specially designed template via the transperineal route (Figure 1). It is estimated that this technique yields an extra 38% diagnosis of prostate cancer.[8]

A further technique gaining popularity is MRI fusion biopsies. In this technique, a pre-procedure MRI is obtained and any lesions can be mapped on real time US during transperineal biopsies in order that these are specifically targeted. MRI is increasingly being used and has several roles in prostate cancer diagnosis. It is recommended by NICE[7] in men who have had an initial negative TRUS prostate biopsy to determine whether further biopsies are needed. It is also used in fusion biopsies as described above and has a role in follow up for patients on active surveillance. In some institutions, it is being utilized as the initial investigation in patients being referred with suspected prostate cancer which may avoid the need for any invasive biopsy procedure. In advanced stages of the disease, MRI of the spine is used if spinal cord compression is suspected.

Nuclear medicine is also often used in the diagnostic work up of a patient with suspected metastatic prostate cancer. Whole body bone scans are used to detect evidence of bony metastasis the presence (or absence of which) has a dramatic effect on the treatment decision for the patient.

Prostate specific antigen

PSA is a glycoprotein serine protease enzyme that is produced by prostate epithelial cells. Its role is thought to be in the liquefaction of seminal fluid needed for fertilization. Its detection in a blood test has been in use since its development in the late 1980s. It is often said to be prostate specific but not prostate cancer

