Prostate cancer

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Abstract

Prostate cancer is the most common male cancer in the UK. The disease and treatment options are wide ranging, from indolent disease requiring surveillance only to an aggressive malignancy requiring active treatment. This can prove to be challenging for both the doctor and patient deciding on the best management option. Ongoing research is revolutionizing the diagnostics, risk stratification 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 (PC) is the most common, non-cutaneous male cancer in the UK. There were approximately 47,700 new cases in the UK in 2015,[1] which accounted for 13% of all new cancer cases. It is the second most common cause of male cancer-related death (13%) in the UK. Overall, it is estimated that the lifetime risk of a man being diagnosed with PC is between 1 in 8 and 1 in 10.

Over the last 30 years, there has been a dramatic increase (almost 150%) in the UK incidence of PC. This is partly a result of increased detection; firstly, due to *ad hoc* serum prostate specific antigen (PSA) testing and secondly, the development of transurethral surgery for enlarged prostates (causing obstructive lower urinary tract symptoms, LUTS), which results in incidental detection of PC in the resected tissue. In addition, there is a true increase in PC incidence, principally due to the ageing population.[2] More than one-third of PC cases are diagnosed in men over the age of 75 and it is rare in those under 40 years old. Despite the increasing incidence, mortality from PC in the UK has been in decline for the last 10–15 years.

The development of PC is thought to be multifactorial, involving complex interplay of genetic and environmental factors. Age, ethnicity and a positive family history are the best-established risk factors,[3] and there is also evidence to suggest that obesity and dietary factors may have a role in PC development. Hormonal factors are thought to be important in the onset of PC. It has been observed that the peak age of PC onset coincides with the age at which serum testosterone levels decline, while serum oestrogen levels remain constant. This results in a change in the serum testosterone to oestrogen ratio, which is hypothesized to be an important determinant of PC risk. This is also relevant when considering ethnicity as a risk factor. It is well established that Afro-Caribbean men are at greatest risk of PC, followed by Caucasian men, followed by Japanese men. While there are no significant differences in the levels of circulating testosterone and other androgens between these groups, serum oestrogen levels are highest in Afro-Caribbeans, resulting in a more profound change in the androgen:oestrogen ratio.[4] It has been suggested that this decrease in androgen levels is an initiating event in prostate carcinogenesis; as androgen levels fall, production of its receptor (androgen receptor – AR) increases in an attempt to maintain normal AR-dependent signaling. This increased production of AR, however, results in DNA damage and production of abnormal genes, which subsequently drive the development of invasive cancer.

The decreased incidence of PC in Japanese men is also thought be due to the traditional Japanese diet, which is very rich in plant-derived phytoestrogens. These are believed to be protective against PC development through preferential stimulation of the tumour suppressor oestrogen receptor beta.[4] Interestingly, however, it has been shown that the incidence of PC in Japanese men born in the United States approaches that of the native population, suggesting a strong influence of environmental factors in PC development.[5] Greater consumption of animal protein and milk in the Western diet containing high levels of animal-derived oestrogens (that preferentially stimulate oestrogen receptor alpha, which mediates the harmful effects of oestrogen) may be partly responsible for this. Other dietary and lifestyle factors have been studied and were previously thought to affect PC risk (such as vitamin E and selenium). Conclusive evidence is however lacking.

A man with a first degree relative with PC has double the risk of developing the disease than if none of his relatives are affected. If more than two first-degree relatives are affected, the risk increases fourfold to fivefold.[6] Overall, approximately 9% of prostate cancers are believed to be inherited. There is evidence to show a link between an increased risk of PC in patients in whom there is a family history of breast or ovarian cancer.[7] Some of this may be due to germ-line mutations of *BRCA1* and *BRCA2* genes, which if present, increases the risk of PC three-fold compared to the general population.

In the past, there was some debate as to whether 5α reductase inhibitors (5αRI) such as finasteride affected PC risk. Finasteride is used commonly in the treatment of male LUTS to reduce the size of the prostate and relieve obstructive symptoms. The Prostate Cancer Prevention Trial (PCPT) randomized 18,000 men to finasteride 5 mg OD or placebo. Results suggested that finasteride reduced the risk of developing PC by 25%, but also increased the risk of higher grade (and therefore clinically significant) cancers.[8] These results have been much debated since, with most urologists now believing that the observed increase in high-grade cancers in those taking Finasteride was artefactual, due to a preferential decrease in the volume of benign over malignant prostate tissue, which resulted in increased detection of high-grade cancer by needle biopsy. 5αRIs are therefore not recommended for use as a chemo-preventative agent for PC.

Pathology of prostate cancer

The vast majority of PC (over 95%) is adenocarcinoma, arising from glandular structures of epithelial tissue. Initial proliferation

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of malignant cells occurs within the glandular epithelium (prostate intraepithelial neoplasia, PIN), then subsequently progresses to cross the epithelial basement membrane and become invasive adenocarcinoma. PIN is identified in approximately 5% of initial prostate biopsies. It is defined as 'architecturally benign glands lined by cytologically atypical cells.' It is subdivided into low- and high-grade PIN depending on the prominence of nucleoli. It is associated with similar molecular changes to those seen in PC, but is not associated with an increase in the PSA value. A finding of multifocal high-grade PIN is an indication for repeat biopsy, as the subsequent yield of PC on repeat biopsy is approximately 40%.

Another histological finding, atypical small acinar proliferation (ASAP) 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 PC on 40% of subsequent prostate biopsies.

Other histological types of PC include urothelial cell carcinoma (arising either from the urothelial lining of the prostatic urethra or local spread from the bladder), intraductal carcinomas (arising from prostatic ducts), sarcomas, neuroendocrine and small cell carcinomas. Metastases to the prostate from other primary sites are rare and tend to be aggressive with poor prognosis.

Anatomically, the prostate is often described according to its zonal anatomy (so-called McNeil's zones). Seventy per cent of PC arises in the peripheral zone, 25% in the transitional zone and 5% in 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, distal ureter, pelvic side wall and the rectum. Nodal metastases most commonly occur in the obturator and iliac nodes. There is no defined sentinel lymph node in PC (as seen in other cancers such as penis or breast), so when undertaken, lymph node dissection is performed according to a pre-defined anatomical template. Metastatic disease characteristically occurs to the bone with the axial skeleton commonly affected (especially the spine). These lesions are typically described as sclerotic on imaging. Metastasis to other sites, such as the liver, lung and brain, are much less common.

Gleason grading

The Gleason system was described in the 1960s to grade prostate adenocarcinoma. It is graded from 1 to 5 according to the degree of glandular de-differentiation from normal tissue architecture seen under microscopy. The higher the grade, the more different the cancer tissue is from normal, benign tissue and therefore, the more aggressive the cancer. Two grades are assigned to represent the two most dominant patterns seen (or a single grade is doubled if only one pattern is identified). The result is the Gleason sum score, which gives a score of between 2 and 10. For example, if the most dominant pattern is Gleason 4 with smaller quantity of Gleason 3, then the prostate biopsy would be reported as: Gleason 7 (4 + 3). The Gleason score is an important determinant of disease prognosis and the treatment options available to the patient as it is one of the three elements used in PC risk stratification, and is the most important indicator of prognosis after radical, curative treatment of PC. In contemporary practice, Gleason patterns 1 and 2 are no longer regarded as being cancerous. Therefore, the lowest possible grade of PC is Gleason 6 (3 + 3), and the highest is Gleason 10 (5 + 5).

International society of urological pathology (ISUP) grading

In 2016, ISUP introduced a new 5-point grading system for PC[9] with the purpose of simplifying the grading and making it more straightforward for patients to understand. This was prompted by the realization that it is much easier for patients to recognize that a score of '1 out of 5' represents the least aggressive form of PC, as opposed to a score of '6 out of 10'. Furthermore, the ISUP system removes some of the confusion (for patients and clinicians not familiar with PC) surrounding the Gleason 7 category; as this includes both patients with Gleason 3 + 4 and Gleason 4 + 3 disease. It is well established that the prognosis for these two patient groups is significantly different and it is therefore logical that a grading system should clearly reflect this. Gleason sum scores translate to ISUP grades as follows:

- ISUP grade group 1: Gleason score 6 (3 + 3)
- ISUP grade group 2:Gleason score 7 (3 + 4)
- ISUP grade group 3: Gleason score 7 (4 + 3)
- ISUP grade group 4: Gleason score 8 (4 + 4 or 5 + 3 or 3 + 5)
- ISUP grade group 5: Gleason score 9 (4 + 5 or 5 + 4) or Gleason score 10 (5 + 5)

Prostate cancer diagnosis

The majority of men with localized PC do not have symptoms arising as a direct result of the cancer itself. It is often diagnosed when men present to their family doctor with LUTS, and subsequent rectal examination reveals a suspicious feeling prostate or an elevated serum PSA level (see section below), which then prompts referral to a urologist. Patients are then seen in an urgent 2-week wait clinic for full assessment, including a consultation and repeat examination of the prostate along with a number of simple investigations in the clinic. Important points in the history are those of LUTS, family history, recent urinary infection or instrumentation (as this may artefactually increase serum PSA levels) and symptoms of back pain, leg swelling, peripheral neurological symptoms or new-onset erectile dysfunction which may suggest advanced disease. Patients may also be diagnosed with PC following the histological analysis of prostatic tissue removed during bladder outlet surgery for LUTS (such as transurethral resection of prostate (TURP) or holmium laser enucleation of prostate (HoLEP)).

An isolated raised PSA in itself, in the presence of a normal-feeling prostate need not automatically lead to a prostate biopsy, but should prompt a discussion between patient and clinician of the potential risks and benefits of the procedure.[10] Patients should be adequately counselled to ensure that they understand the implications of the potential outcomes of the biopsy; namely that a negative biopsy does not exclude PC (with a false-negative rate of 30%) and that even if diagnosed, not all PC requires active treatment. At the other end of the spectrum, in an elderly patient with a very high PSA level (e.g. over 100) and very suspicious digital rectal examination (DRE) then a clinical

diagnosis of prostate cancer can be made. In this setting, a prostate biopsy may not be needed (thus avoiding the potential associated risks) unless, for example, a patient is likely to be eligible for systemic chemotherapy or a histological diagnosis is needed for entry into a clinical trial.

The manner in which PC is diagnosed is evolving rapidly, and prostate diagnostics has become a subspecialty discipline in its own right. Traditionally, patients would undergo a transrectal ultrasound (TRUS)-guided prostate biopsy. This involves a short local anaesthetic procedure where 12 cores are taken from the prostate via an ultrasound 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, clopidogrel and factor Xa inhibitors such as rivaroxaban must be stopped before the procedure. Aspirin does not need to be stopped. TRUS biopsy carries an estimated false negative rate of around 30%, and is therefore not a reliable test for excluding PC. Men with a negative biopsy result, with ongoing suspicion of PC (on the basis of abnormal examination or elevated PSA level) are therefore candidates for further investigation such as MRI scanning or repeat biopsies.

In contemporary practice, however, the use of multiparametric MRI (mpMRI) scanning prior to prostate biopsy has rapidly become commonplace, with two important research studies demonstrating its value. Firstly, the PROMIS study[11] demonstrated that mpMRI had a false negative rate of just 15%; half that of TRUS biopsy, with a sensitivity of 93% for the detection of clinically significant PC. Secondly, the PRECISION study[12] showed that the combination of mpMRI with a targeted biopsy technique resulted in a cancer detection rate of 38% (c.f. 26% for TRUS biopsy). In recently published draft guidance, NICE now recommends that mpMRI is the first-line investigation of choice for men with a suspected diagnosis of localized PC.[13]

A second important development in prostate diagnostics lies with the use of the transperineal approach to biopsy the prostate (Figure 1). In this technique the prostate is biopsied by passing a needle through the skin of the perineum (thus avoiding the rectum altogether) to approach the prostate from below, rather than behind. This approach can be combined with MRI/US fusion, whereby real-time, intraoperative US is merged with the pre-biopsy mpMRI scan to enable precise targeting of suspicious lesions. It is estimated that this technique yields an extra 38% diagnosis of PC.[14] It is recommended by NICE in men with an initial negative TRUS biopsy due to the additional cancer yield over a repeat TRUS biopsy.[10] The principle advantage of the transperineal biopsy approach, rather than the transrectal approach is in the reduced risk of UTI and sepsis. A number of large series, involving thousands of men have been published with no episodes of post biopsy sepsis. In the era of antibiotic resistance, this benefit is of increasing importance. The majority of transperineal biopsies are currently performed under general anaesthetic, however a number of centres have now adopted local anaesthetic, clinic-based transperineal biopsy.

Prostate specific antigen

PSA is a glycoprotein serine protease enzyme produced by prostate epithelial cells. Physiologically, it liquefies seminal fluid. Testing for serum PSA levels was developed in the late 1980s. While it is prostate specific it is not cancer specific, and is therefore not a diagnostic test in its own right. Rather, it should be considered an indicator of risk. It may be significantly elevated due to benign causes such as infection, prostatitis, BPH or recent instrumentation of the urinary tract and indeed it may be normal in patients with significant prostate cancer. While a DRE can cause minor elevations in PSA values, this is not clinically significant. There is no PSA level at which PC can be completely excluded; however, accepted normal PSA values based on the patient's age are shown in Table 1.

Notwithstanding the pitfalls of using PSA as a screening or diagnostic tool, PSA is an important part of PC risk stratification, and is extremely useful in the follow-up of patients with PC. It is used in active surveillance protocols to monitor for signs of disease progression, with an increase in PSA levels being one of the triggers to instigate active treatment. PSA monitoring is used after radical treatment (radical prostatectomy or radiotherapy) to monitor for evidence of disease recurrence. When the PSA level rises over defined levels (termed 'biochemical recurrence'), it is an indication that further salvage treatment may be needed.

Prostate cancer screening

PSA screening remains a controversial topic and is not currently undertaken in the UK. As a screening tool, PSA testing does not satisfy the WHO criteria for an adequate screening test. A number of large PSA-screening trials have been published over the years. The European Randomized trial of Screening for Prostate Cancer (ERSPC) trial[15] concluded that the number of men needed to screen to save one life was 27. In contrast, the CaP trial[16] involving almost 420,000 men showed no improvement in PC-specific mortality using a single PSA-screening test. As clear evidence to support a PSA-based screening programme is not currently available, it is not recommended by NICE. Instead, 'opportunistic screening' can be offered to well-informed men, and those thought to be at elevated risk of PC due to a positive family history or other relevant risk factors.

Risk stratification and staging

Once a man has been diagnosed with PC, his case will be discussed at a multidisciplinary team (MDT) meeting where a team of specialists including urologists, oncologists, radiologists and pathologists as well as cancer nurse specialists are present to review histology and imaging, and detail a management plan for the patient. The three broad categories of PC that are important to distinguish are localized disease (T1/2 N– M–), locally advanced (T1/2 N+ M– or T3/4 N–/+ M–) and metastatic disease (Any T/N M+). Localized and locally advanced PC are further risk-stratified into one of three risk groups; low-, intermediate- or high-risk groups as developed by D'Amico et al.,[17] which have now been adopted by NICE (Table 2). These groups inform prognostication, and discussions with the patient about the appropriate treatment options.

One element of this risk stratification is disease staging. Like all solid-organ cancers, PC is staged according to the TNM classification[18] (Table 3) with the T stage being either 'c' clinical (i.e. findings in DRE and imaging) or 'p' pathological (i.e. findings on a prostatectomy specimen). In addition to its developing use as a

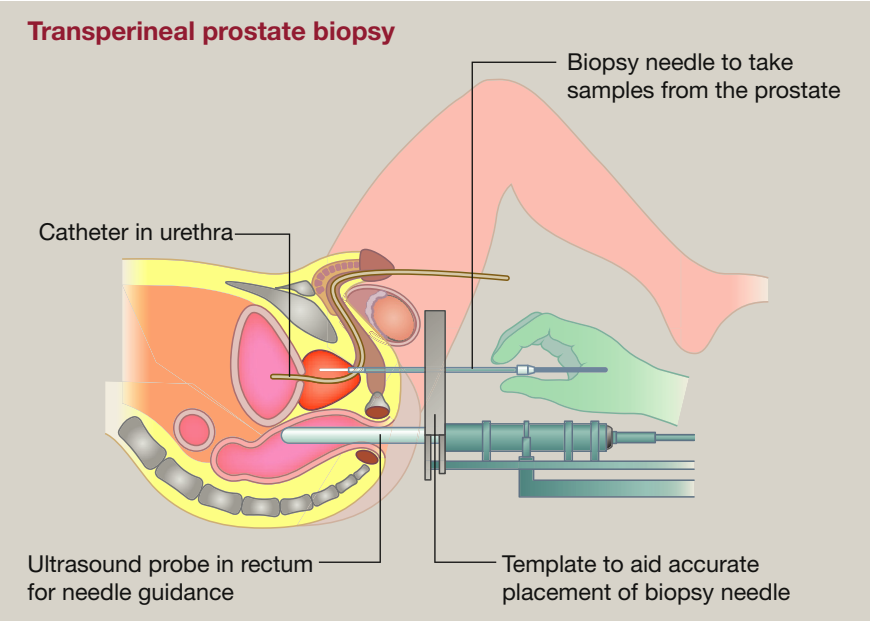

Figure 1

Age related normal PSA values

Age	Normal PSA range (ng/ml)
All ages	<4.0
40-49	<2.5
50-59	<3.5
60-69	<4.5
>70	<6.5

Table 1

diagnostic tool, mpMRI is used to determine local disease staging. These MRI scans incorporate T1, T2, dynamic contrast-enhanced and diffusion-weighted imaging modalities to identify and characterize lesions in the prostate. In those patients who decide to undergo surgery to remove the prostate (radical prostatectomy), the mpMRI is used in surgical planning to guide nerve sparing (i.e. if unilateral disease is seen close to or breaching the capsule, then nerve sparing on the contralateral side at the time of radical prostatectomy may be performed in an attempt to preserve erectile function). If an MRI is contra-indicated, a CT scan can instead be performed to assess for nodal disease.

D'Amico risk categories for prostate cancer

Risk	PSA (ng/ml)	Gleason score	Clinical stage (DRE)
Low	<10	≤6	T1-T2a
Intermediate	10–20	7	T2b
High	>20	8–10	≥T2c

Table 2

The management of prostate cancer

Following the MDT, the patient is seen in clinic to discuss the results and the relevant treatment options. Increasingly, these are joint clinics with both urologists and oncologists present as well as a dedicated uro-oncology nurse specialist. For each risk group of PC there are a number of suitable treatments available, which vary hugely in their application and potential side effects. This can make treatment decisions very challenging for men newly diagnosed with PC. It is essential therefore that time is given for detailed discussion of the different treatments available, including the outcomes, mode of delivery and side effects associated with them. Management options should be tailored to the individual patient and take account of their disease risk stratification, priorities, lifestyle factors and life expectancy.

Broadly, PC treatment is divided into the management of localized, locally advanced and metastatic disease. High-risk localized disease is often considered in the same group as locally advanced disease. An important initial consideration following the diagnosis of PC lies with trying to determine whether radical (curative) treatment is expected to be beneficial to the patient. Long-term studies of large numbers of men have shown that in order to benefit (in terms of overall survival) from radical treatment, a patient needs to have a life expectancy of at least 10 years from the time of treatment delivery.[19] It is therefore reasonable not to offer radical treatment to very elderly men, or those with advanced comorbidities, as they are more likely to die from causes not related to PC and would therefore only be exposed to the potential side effects, rather than the potential benefits of radical treatment.

Having determined this in discussion with the patient, the following treatment options can be considered:

- Localized prostate cancer
  - active surveillance
  - watchful waiting

TNM staging classification of Prostate Cancer[18]

T – Primary tumour
Tx Primary tumour cannot be assessed
T0 No evidence of primary tumour
T1 Clinically unapparent tumour, not palpable or visible by imaging
  T1a Incidental histological finding; ≤5% of tissue resected during TURP
  T1b Incidental histological finding; >5% of tissue resected during TURP
  T1c Tumour identified by needle biopsy
T2 Tumour confined within the prostate
  T2a Tumour involves half of one lobe or less
  T2b Tumour involves more than one half of one lobe but not both lobes
  T2c Tumour involves both lobes
T3 Tumour extends through the prostate capsule but has not spread to other organs
  T3a Extracapsular extension (unilateral or bilateral) including microscopic bladder neck involvement
  T3b Tumour invades seminal vesicle(s)
T4 Tumour is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles and/or is fixed to pelvic wall
N Regional lymph nodes
NX Regional lymph nodes cannot be assessed
N0 No regional lymph nodes metastasis
N1 Regional lymph node metastasis
M Distant Metastasis
MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1a Non-regional lymph node(s)
M1b Bone(s)
M1c Metastasis at other site(s)

Table 3

    - radical prostatectomy
    - radical radiotherapy
    - brachytherapy
- locally advanced (non-metastatic) prostate cancer (including high-risk localized)
    - radical radiotherapy + hormonal therapy
    - radical prostatectomy
    - cytotoxic chemotherapy
    - hormonal/androgen deprivation therapy (ADT)
    - watchful waiting
- metastatic prostate cancer
    - hormonal/androgen deprivation therapy (ADT)
    - cytotoxic chemotherapy
    - palliation.

Watching waiting

This involves a conscious decision to avoid any treatment until it is required for the purposes of symptom relief. It is an option for all risk categories of PC and is generally used for elderly or co-morbid men with a life expectancy of less than 10 years, i.e. in those for whom radical treatment is not appropriate. PSA monitoring should be infrequent and repeat biopsies are not recommended. Treatment is commenced with the development of symptomatic disease or marked PSA progression. The aim of treatment for these men is therefore palliative rather than curative (radical).

Active surveillance

This is a management option for men with potentially curable PC who wish to avoid or defer treatment until it is deemed to be necessary. It may be thought of as 'delayed radical treatment,' and is therefore only suitable for men eligible for radical treatment. The aim of active surveillance (AS) is to avoid over-treatment of small, localized, low-risk tumours, many of which will not progress to cause the patient any harm during their lifetime. According to NICE guidelines,[10] it is the preferred treatment option for men with low-risk disease (i.e. T1c-T2a, Gleason ≤6, PSA <10) and may be considered for selected, well-informed men with intermediate risk disease. In contrast to watchful waiting, it is an active management process, which mandates regular PSA measurement and re-biopsy (+/− repeated local re-staging with MRI) at 12 months from initial diagnosis. AS requires a high level of patient counselling, motivation and compliance. Indications for switching to radical treatment include patient choice, rising PSA, upgrading on repeat biopsy or upstaging on imaging. The risk with AS is that once there is evidence of disease progression and the decision is made to instigate radical treatment, the disease is no longer curable. However, outcomes from AS are excellent, with numerous studies demonstrating 100% cancer-specific survival after 10 years. The ProtecT study,[20] which randomized men with low- and intermediate-risk disease to AS, prostatectomy or

radiotherapy has been hugely important in understanding the outcomes of AS, and will be discussed below.

Brachytherapy

Brachytherapy refers to the implantation of radioactive seeds under US guidance (transperineal route) directly into the prostate. The procedure requires a short general anaesthetic and is generally done as a daycase. The most commonly used radioactive isotype is ^{125}Iodine which has a half-life of 60 days and delivers a dose of 145Gy. It is most suitable for low-risk localized PC, although certain cases of intermediate-risk disease may be considered. It can also be used in combination with external beam radiotherapy. Equal efficacy to radiotherapy for low-risk disease has been reported. Side effects include worsening LUTS or urinary retention (both occur as a result of prostatic oedema), urinary incontinence (low), perineal haematoma, erectile dysfunction and seed migration. Contraindications are moderate to severe LUTS (because of the risk of these deteriorating or urinary retention developing), prostate size >50 cc, previous TURP (because of the significantly increased risk of post procedure incontinence) and previous pelvic irradiation.

Radical radiotherapy

Radiotherapy for PC is suitable for localized and the preferred treatment for locally advanced disease. It is delivered under the supervision of a clinical oncologist and takes place 5 days per week (Monday to Friday with a break over the weekend) for a period of 7 1/2 weeks (37 fractions). Up to 2Gy is delivered per treatment with a minimum total dose of 74Gy delivered over the treatment period. Technological developments of 3D conformal and intensity-modulated radiotherapy have led to more accurate and precise delivery of the radiation, thus limiting the toxicity to adjacent organs (such as the rectum), hence shorter treatments over 4 weeks (20 fractions) each with a higher dose has emerged without increase in side effects. Common side effects include radiation cystitis and haematuria, LUTS including urinary incontinence, radiation proctitis and erectile dysfunction. There is also the risk of the development of a secondary cancer after radiotherapy which has been estimated at up to 1/70 in long-term survivors. Contraindications are severe LUTS, previous pelvic radiotherapy and patients with bowel problems such as inflammatory bowel disease or severe proctitis. Bilateral hip replacement may also preclude radiotherapy for PC. Radiotherapy is given in combination with ADT for intermediate- and high-risk prostate cancer. The duration of adjuvant treatment depends on the risk stratification of the disease. This has been shown to significantly improve both disease-free and overall survival compared to radiotherapy alone in localized and locally advanced disease.[21]

Follow up after radiotherapy relies on PSA monitoring. Disease recurrence following radiotherapy (defined as a PSA rise of 2 over the nadir PSA value, i.e. the lowest PSA value achieved: Phoenix criteria) may be treated by salvage prostatectomy, cytotoxic chemotherapy or ADT depending on patient and disease characteristics.

Radical prostatectomy

This involves surgical removal of the entire prostate and seminal vesicles followed by an anastomosis (join) of the bladder neck to the urethra. Robotic-assisted radical prostatectomy is now widely established, although laparoscopic and open approaches are still in use. The operation may be combined with a bilateral pelvic lymph node dissection depending on the disease risk stratification. It is a suitable treatment option for low-risk localized prostate cancer (particularly if AS is declined), intermediate- and high-risk disease.[10] Patients undergoing robotic-assisted or laparoscopic surgery are typically in hospital for 1 or 2 nights and are discharged with a urethral catheter in situ for 7–10 days. Common side effects are urinary incontinence and erectile dysfunction. Uncommon (<5%) side effects include thrombosis, urethral and bladder neck stricture, inguinal hernia or lymphocoele formation (if lymph node dissection is performed). Rectal or ureteric injury are rare complications. At present, open, laparoscopic and robotic-assisted techniques are regarded as equivalent with respect to oncological outcomes. Laparoscopic and robotic-assisted surgery are beneficial in terms of intraoperative blood loss and length of hospital stay, and there is some evidence (though not randomized data) to suggest that functional outcomes (continence and erectile function) are better with robotic-assisted surgery. However, it is the experience of the operating surgeon, rather than the technique used, which is the most likely determinant of outcome. Following radical prostatectomy, it is expected that the PSA falls to an undetectable level. A rise in PSA (generally regarded as PSA >0.2ng/ml) termed 'biochemical recurrence' is an indication for salvage treatment with radiotherapy and/or hormonal therapy or cytotoxic chemotherapy depending on patient and disease characteristics.

The ProtecT study: To date, the ProtecT study (Prostate testing for cancer and Treatment) is the only randomized study comparing treatment modalities in PC.[20] A UK multicentre study, it randomized 1643 men with PSA screening-detected low- and intermediate-risk PC to either AS, radical prostatectomy or radical radiotherapy. Importantly, there were no differences in either PC-specific or overall survival between the three groups, with low mortality rates (1% at 10 years follow up) regardless of the treatment received. However, AS was associated with a two-fold increase in the risk of metastatic disease, and by the end of the study period approximately half of men initially randomized to AS had undergone radical treatment. While at first glance this would appear to be concerning, it must be remembered that these men were recruited between 1999 and 2009, when the standard diagnostic test for PC was a simple TRUS biopsy. Transperineal biopsy and MRI were rarely used. Furthermore, these men were not followed with contemporary AS protocols and therefore did not undergo re-biopsy/re-staging MRI scan at 12 months. It is therefore likely that a number of men diagnosed with low- or intermediate-risk disease included in the study did, in fact have more aggressive or advanced disease undetected at the time of enrolment. The ProtecT findings, in combination with the recent advances in prostate diagnostics, should give patients diagnosed nowadays with low-risk disease confidence that AS is a safe treatment option, which avoids for many men the potential side-effects of radical surgery or radiotherapy.

Hormonal therapy

Hormonal/androgen deprivation therapy (ADT) is commonly used to treat advanced and metastatic PC, and disease relapse

after radical treatment. The aim of ADT is to control the disease by reducing circulating levels of testosterone, upon which PC cells are reliant. There are a number of different forms of ADT in current use:

- leuteinizing hormone releasing hormone (LHRH) agonists (e.g. goserelin)
- LHRH antagonists (e.g. degarelix)
- anti-androgens (e.g. bicalutamide)
- surgical castration (i.e. bilateral subcapsular orchidectomy).

Most commonly used are the LHRH agonists. Overstimulation of the anterior pituitary gland by LHRH agonists leads to a down-regulation of the receptor resulting in decreased levels of LH release and, in turn, lower levels of testosterone secretion from the Leydig cells of the testes (positive feedback inhibition). An important consideration when starting a LHRH agonist is that it results in an initial rise in the serum testosterone level – termed 'tumour-flare,' this occurs in the first 2 weeks after treatment is started. Tumour-flare is particularly concerning in men with extensive spinal metastases, as it may result in spinal cord compression/cauda equina syndrome or pathological fractures. To counter this effect, an anti-androgen is given alongside the LHRH agonist for the first 2 weeks of treatment. One of the benefits of the LHRH antagonist degarelix is that there is no risk of tumour flare as it is a direct antagonist of the LHRH receptor. Anti-androgens work by blocking the AR directly and are often used in the treatment of advanced, non-metastatic prostate cancer or in combination with an LHRH agonist – so-called maximum androgen blockade.

Surgical castration in the form of bilateral subcapsular orchidectomy was the mainstay of treatment prior to the development of pharmacotherapy and achieves rapid castrate levels of testosterone. It is still a treatment option for men who do not wish to have regular injections, or who have severe cardiovascular risk factors, which may be exacerbated by ADT pharmacotherapy.

All of the above treatments share a common and significant side-effect profile related to the lowering of the testosterone level. These include erectile dysfunction and loss of libido, weight gain, fatigue, gynaecomastia, depression, cognitive changes and osteoporosis with an increased risk of bone fracture. Current NICE guidance states that men should be offered a DEXA scan to assess bone mineral density prior to commencing ADT, and if appropriate, should then receive treatment if osteoporosis is identified.

Combination therapy: hormone therapy with docetaxel chemotherapy (STAMPEDE trial)

Recently, a multicentre study – STAMPEDE[22] has reported clinically and statistically significant improvement in survival in men with locally advanced and metastatic PC at diagnosis when hormone therapy was combined with docetaxel compared to hormone therapy alone. The addition of docetaxel increased median survival by 10 months; this is now regarded as the standard of care for newly diagnosed metastatic/locally advanced PC. The multi-arm, multi-stage platform design of the STAMPEDE study means that new treatments and treatment combinations are continually under evaluation, so it is likely that further results from the study will change the standard of care again in the near future.

Castrate-resistant prostate cancer

Castrate-resistant prostate cancer (CRPC) develops in virtually all men treated with ADT as a result of 'selection pressure' arising from loss of normal androgen receptor activity. CRPC carries a poor prognosis, with median survival of 18 months from diagnosis[23] and is diagnosed when PSA levels rise despite castrate levels of serum testosterone. In chemotherapy-naïve men, docetaxel is commonly used for first-line treatment. In those who develop docetaxel resistance, or those who have already had docetaxel earlier in their treatment prior to the onset of CRPC, abiraterone and enzalutamide have been shown to improve overall survival by a mean of 3 months. Abiraterone inhibits the enzyme responsible for the production of androgens from the adrenal gland, whereas enzalutamide blocks the AR from entering the cell nucleus to activate DNA. As part of the STAMPEDE study, abiraterone has been shown to improve overall survival in hormone-sensitive disease as compared with standard ADT alone.

Management of the complications of advanced and metastatic prostate cancer

Two important complications of locally advanced and metastatic disease require urgent management and are considered urological emergencies. Other important complications are sepsis, hypercalcaemia, anaemia, urinary retention and pathological fractures. Bone pain from metastases may be treated with palliative radiotherapy.

Ureteric obstruction

As PC advances locally, it can cause bilateral ureteric obstruction. It is an important cause of bilateral hydronephrosis and does not improve with catheterization unlike in patients with high pressure urinary retention. Patients may present with acute kidney injury (AKI) and symptoms of renal failure with or without hyperkalaemia. Emergency management is treatment of life-threatening hyperkalaemia, if present, and the involvement of nephrology colleagues where appropriate. Definitive treatment is with decompression of the obstructed kidneys by insertion of bilateral nephrostomies with or without antegrade stent insertion, or retrograde ureteric stent insertion via cystoscopy. Careful discussion with the patient about the appropriateness of these interventions is essential, in what is an advanced stage of the disease process.

Malignant spinal cord compression

This most commonly occurs in the thoracic and upper lumbar regions of the spinal cord secondary to vertebral collapse (related to a bone metastasis) or by direct tumour growth into the spinal cord. Prompt diagnosis and management is essential to prevent long-term neurological deficit. Patients usually present with back pain with peripheral neurological symptoms and evidence of neurological dysfunction such as urinary or bowel incontinence or weakness of the lower limbs. The patient may or may not have a known history of metastatic PC. Clinicians must have a high index of suspicion for cord compression, and must be mindful to examine the prostate and check a PSA level in men who present with sudden onset of this clinical picture. Following a complete neurological examination, definitive diagnosis is with MRI scan.

Definitive management is with high dose steroids followed by either neurosurgical decompression or radiotherapy.

Summary

Prostate cancer is a common disease affecting large numbers of men. It is a complex condition to diagnose and treat, with a number of treatment options available at each stage of the disease process. With a number of high-profile cases of PC in the recent UK press, family doctors, urologists, oncologists and specialist nurses alike must be prepared to discuss much of the information presented in this article with increasing numbers of concerned or affected men. ◆

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