Patient management – brief overview of prostate cancer: diagnosis and management

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Brief Overview of Prostate Cancer: Diagnosis and Management

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Abstract

Prostate cancer is the most common cancer in men in the United Kingdom (UK). The disease is becoming increasingly common with rising age. An increasing awareness of the disease as well as improved diagnostic modalities such as multi-parametric magnetic resonance imaging (MRI) have also contributed to the increase in the prostate cancer detection rates. The increased incidence has led to numerous changes in diagnosis and treatment over the past few years. As there are a variety of modalities for diagnosing and managing the disease, it can be poorly understood because some prostate cancers are slow-growing and may not require treatment, while other cancers can be aggressive and metastasise. Foundation year doctors will come across many patients with prostate cancer and its complications during their training as the diagnosis is on the increase. This article focuses on providing junior doctors with the basic knowledge about prostate cancer, its diagnosis and the multi-disciplinary approach to its management.

What is the prostate?

The prostate gland is a walnut-shaped structure that is located just anterior to the rectum and inferior to the bladder. The urethra runs through the centre of the prostate. Its main function is to secrete a slightly alkaline fluid that forms part of the seminal fluid. This is the fluid that nourishes and carries sperm. During orgasm, the muscular glands of the prostate help to propel the prostatic fluid, in addition to sperm that was made in the testicles, into the urethra. The semen then leaves the body out through the tip of the penis during ejaculation. (1).

Prostate Cancer

Prostate cancer is the most commonly diagnosed male cancer in the United Kingdom (UK). Its diagnosis is on the increase, probably as a result of increasing use of serum prostate-specific antigen (PSA) for both symptomatic and asymptomatic men. Almost all prostate cancers are adenocarcinomas and arise within the gland in a multifocal distribution. While it is the most common male cancer, it is not responsible for the most deaths as the majority are slow-growing and present later in life. There were 47,300 new cases of prostate cancer diagnosed in 2013 which

equates to 130 cases per day. It accounted for 11,287 deaths in 2014, making it second behind lung cancer as a cause of male cancer mortality (2).

Risk Factors

There are many risk factors for prostate cancer. Age is an important risk factor for the development of prostate cancer, the disease being rare below the age of 40 and becoming increasingly common with rising age. The disease is also more common in western nations, making an environmental aetiology important. Ethnicity is also a risk factor and black men are at greatest risk. Family history can play an important role with 5% of prostate cancers believed to be inherited. Genetic abnormalities and mutations of the BRCA2 gene have also been reported. The risk is doubled if there is one affected first-degree relative. A healthy diet and regular exercise may help to lower the risk of developing prostate cancer (3).

Role of Androgen Receptor

The androgen receptor is an important target in oncological therapy because it plays a role in cell-to-cell signalling, cell growth and even in the ability of cancer cells to invade and subsequently spread to distant sites.

As the cancer progresses, the cells bear less of a resemblance to their tissue of origin and eventually can divide and grow in the absence of androgen, which then leads to the so-called 'androgen escape' seen in the later stages of the disease (4). The utilisation of exogenous androgen as a therapy for prostate cancer will be discussed in more detail later in this review.

Prostate Cancer Presentation

Since the introduction of serum PSA testing in the late 1980s, the majority of new patients have non-metastatic disease at presentation. In cases of localised prostate cancer, patients can be asymptomatic and the disease is only detected with an elevated or rising serum PSA or incidental abnormal digital rectal examination (DRE). There may also be symptoms of bladder outflow obstruction, haematospermia, haematuria or perineal discomfort, probably due to coexisting prostatitis. Locally advanced non-metastatic prostate cancers can present with similar symptoms as well as symptoms of renal failure due to ureteric obstruction. Malignant priapism and rectal obstruction are rare presentations. Metastatic disease can be asymptomatic or it can present with anorexia, weight loss, bone pain, pathological fractures, lower limb swelling due to lymphatic obstruction as well as neurological signs and symptoms in the lower limbs. Spinal cord compression

can also be an important presentation. It is an oncological emergency which needs prompt diagnosis and treatment.

Prostate Cancer Diagnosis

The early detection of prostate cancer in asymptomatic men can be very challenging. A thorough history and examination to elicit the above-mentioned signs and symptoms are important. Diagnosis is usually first made by a raised suspicion of disease and an elevated serum PSA or abnormal DRE. Since most prostate cancers arise peripherally in the peripheral, posterior part of the prostate, they should be palpable on DRE. An abnormal DRE is defined by asymmetry, a nodule or a fixed craggy mass.

Prostate Specific Antigen

Prostate specific antigen (PSA) was first measured quantitatively in 1980 (5). Since then it has become instrumental in the screening and monitoring of prostate cancer. It is a protein secreted by all prostate glands and is thought, physiologically, to provide some of the liquid quality to semen, thereby increasing sperm motility (6). It is raised in cases of benign prostatic hyperplasia as well as in cases of prostate cancer. Its levels increase physiologically with age as the prostate gland becomes larger and therefore has a greater capacity to secrete PSA. It is for this reason that PSA results must be interpreted in the context of a patient's age and digital rectal examination findings. It can also be raised in cases of urinary tract infections (UTI), vigorous exercise, ejaculation and even a DRE having been performed in the preceding week (7). These features make PSA a sensitive, but not particularly specific, screening test.

Table 1 shows the age-specific ranges for serum PSA levels (8).

Age Range (Years)	Asians	Africans	Caucasians
40 to 49	0 to 2.0 ng/mL	0 to 2.0 ng/mL	0 to 2.5 ng/mL
50 to 59	0 to 3.0 ng/mL	0 to 4.0 ng/mL	0 to 3.5 ng/mL
60 to 69	0 to 4.0 ng/mL	0 to 4.5 ng/mL	0 to 4.5 ng/mL
70 to 79	0 to 5.0 ng/mL	0 to 5.5 ng/mL	0 to 6.5 ng/mL

Table 1. Age-specific PSA ranges

Prostate Cancer Investigation

A raised serum PSA or an abnormal DRE will lead to further investigations to confirm or exclude the diagnosis of prostate cancer. This will include prostate biopsy and imaging in the form of magnetic resonance imaging (MRI). Traditionally, biopsies were obtained prior to imaging. However, post-biopsy bleeding causes artefact on scans and makes interpretation difficult. This means MRI scans have to be delayed for around 6 weeks which then slows down the pathway to diagnosis and treatment. This is the reason why pre-biopsy imaging is being further evaluated. There is ongoing research into the use of MRI scans before biopsy, in order to more accurately target suspicious regions of the gland. Multi-parametric MRI techniques are being increasingly used for diagnosis and image-guided targeted biopsy. Other imaging modalities such as computed tomography (CT) and bone scanning are also used to establish whether the disease is metastatic once the diagnosis of prostate cancer has been made.

The prostate imaging reporting and data system (PI-RADS) refers to a structured reporting scheme for evaluating the prostate for cancer. The PI-RADS score is assessed on prostate MRI. The scale is based on a score from 1 to 5 given to each lesion on the scan, with one being most probably benign and 5 being highly suspicious of malignancy.

Prostate biopsy is usually achieved, at least in the initial instance, under trans-rectal ultrasound guidance (TRUS-guided prostate biopsy). An ultrasound probe is placed inside the rectum at the level of the prostate gland and is used to identify the structures of the prostate to enable systematic targeting of different anatomical areas of the gland. This approach is essential to the diagnosis of prostate cancer as the disease develops in a multifocal distribution, arising in potentially many areas of the gland. It is hoped that by taking ten to twelve cores of prostatic tissue, one will target any suspicious areas. It is said that as many as 20% of small cancers will be missed by this method (9). If a patient has a raised PSA and TRUS-guided biopsies are negative, then a transperineal template biopsy can be made using the information from the MRI scan which can then accurately target the suspicious areas. It has the advantage of not going through the rectum and therefore has lower rates of post-biopsy sepsis. The transperineal method can also target anterior lesions. One disadvantage is that it should be performed under general anaesthesia and there is a higher risk of urinary retention as more biopsies are taken compared to the TRUS-guided prostate biopsy. The procedure however has a lower infection rate as the needles are going through the skin rather than the rectum.

Prostate Cancer Grading

Prostate cancers are graded by pathologists using the Gleason scoring system of 1-5 based on the differentiation of cells under the microscope and therefore their similarity to the tissue of origin. If the sample has features of malignancy but the cells still resemble prostatic cells, then they are assigned grade 1 and if there is extremely poor differentiation, they receive a grade of 5, with differing levels available in between. Since multiple cores are obtained and prostate cancer often has differing grades in different samples, the pathologist will consider the two areas that comprise the greatest amount of disease. The score is given as two numbers, for instance Gleason 3 + 4 = 7. The first number refers to the fact that the majority of disease is cells of grade 3 severity and the second number refers to disease that is grade 4 but makes up a lower proportion than grade 3 disease. Therefore, Gleason 4 + 3 = 7 confers a more aggressive disease than 3 + 4.

Gleason scores of 6 are said to be well differentiated cancers. Scores of 7 are said to be moderately differentiated and scores between 8 and 10 are said to be poorly differentiated. The Gleason score is extremely important in predicting the likely behaviour of the cancer. It is used in assigning patients to different prognostic risk groups but is not used alone. It must be interpreted in conjunction with patient factors and DRE findings when informing management decisions.

It may be that a patient has had a biopsy, the indication for which was a rise in PSA, which shows only inflammation. This is commonly seen at multi-disciplinary team (MDT) meetings and is a good example of how PSA can be non-specific. Patients with prostatitis commonly have a raised PSA and are subsequently found to have no malignancy at biopsy. Careful counselling of patients at the time of PSA testing and in subsequent interpretation is important to minimise anxiety.

Risk Stratification and the Multi-Disciplinary Team

The management of prostate cancer relies on careful risk stratification in order to identify patients with cancers at risk of progression. Categorising patients into different groups remains very challenging. Various clinical parameters such as the Gleason score, clinical stage and pre-treatment PSA are used to stratify patients in the different groups and estimate the long-term disease progression.

Table 2 below shows some of the different criteria used by the National Institute for Health and Care Excellence (NICE) to stratify prostate cancer (10).

Level of risk	PSA	Gleason score	Clinical stage

Low risk	<10 ng/ml	and	≤6	and	T1–T2a
Intermediate risk	10–20 ng/ml	or	7	or	T2b
High risk	>20 ng/ml	or	8–10	or	≥T2c

Table 2. NICE prostate cancer risk stratification

Prostate Cancer Treatment

Treatment is usually started in the secondary care setting. It is based upon the decisions of the multi-disciplinary team. At the MDT meeting, the patient's presenting complaint, DRE findings, blood test results including PSA, family history and medical co-morbidities including WHO performance status score, are presented to the team. A pathologist will then present the histopathological findings from the core biopsies sent and will assign a Gleason score to the disease. A radiologist with specialist knowledge in urological cancer will then present the findings from the MRI and other imaging modalities before assigning a TNM score to the disease. It is then for the consultant urological surgeon and oncologist to decide on the management pathway best suited to the patient in question.

Management of Prostate Cancer

NICE guidelines outline the range of treatment options available for men who are diagnosed with prostatic cancer. Options for men diagnosed with localised disease include active surveillance, external beam radiotherapy, brachytherapy and the gold standard radical prostatectomy. Other management options, which are not available in all centres throughout the UK include high-intensity focused ultrasound and cryotherapy. The mainstay of advanced disease remains hormone therapy.

1. Active Surveillance and Watchful Waiting

Active surveillance (AS) involves serial PSA measurements at frequent intervals and regular outpatient appointments where DRE will be performed to identify any change. Patients will also have repeat prostate biopsies. The key difference between watchful waiting and active surveillance is that performing repeat biopsies and correlating the PSA with the histopathology from the biopsies, allows the patient's prognostic risk to be closely monitored to detect any disease progression. It aims to reduce the number of patients being subjected to the morbidity of treatment, whilst also identifying those at risk of progression, requiring active intervention. If a man's risk increases, he should be offered radical therapy. The modality of treatment is dependent on the co-morbidities and patient's preferences. Active surveillance is only reserved for men who are fit for radical treatment, but prefer to defer treatment until it is necessary. It is also an option

for intermediate-risk groups, but is not appropriate for those in the high-risk category as outlined in Table 2.

Watchful waiting on the other hand is an option in any prognostic risk group but is more likely to be employed in those with very low risk disease or in elderly people with multiple co-morbidities in whom it is unlikely that treatment will improve their overall outcome or survival. It involves PSA testing at pre-determined intervals and regular clinical assessments. It does not include repeated DRE or serial prostate biopsies. If the clinical picture changes, for instance if the PSA starts to rise rapidly, or patients become symptomatic with bony pain or bladder outflow obstruction, then their case will be re-assessed and may be re-referred to the MDT for further decision making. They might be started on hormonal treatment at that point.

2. Radical Prostatectomy

This involves the surgical removal of the entire prostate gland and seminal vesicles. It has traditionally been performed via the open perineal or retropubic approach. However, minimally-invasive techniques are becoming increasingly popular. These include laparoscopic and robot-assisted prostatectomy. Radical prostatectomy is an option in those with localised disease who are fit for surgery and is generally reserved for younger patients. It is rare that it is offered to those over the age of 70. It remains an option for patients in all prognostic risk groups including low-risk patients and is offered to those with a chance of cure or long-term disease control.

Salvage radical prostatectomy is also an option in those who have had a so-called biochemical relapse following radical radiotherapy. A man is said to have had a biochemical relapse when he has undergone radical radiotherapy to his prostate gland and on subsequent follow-up, is found to have a rising PSA. When radical prostatectomy is performed in this setting, the co-morbidities of surgery are higher when compared to primary radical surgery. There is also a significantly increased risk of damage to the rectum due to ongoing radiation proctitis.

Radical prostatectomy can be performed in those with locally-advanced high-risk disease. However, the presence of T3 disease or higher is usually a contraindication to radical surgical approach.

Specific side-effects of radical prostatectomy include erectile dysfunction, affecting 60-90% of patients. Spontaneous erections can return up to 3-year post-operatively. The use of nerve-sparing techniques has however improved outcomes. Urinary incontinence (stress type) is another

complication of radical surgery. Most patients do recover their continence after pelvic floor exercises. Implantation of an artificial urinary sphincter is rarely necessary.

3. External beam radiotherapy

This technique involves irradiating the prostate gland from a source outside the body. The source of radiation is often x-rays and can lead to similar side-effects to surgery. Erectile dysfunction and urinary problems are also an issue. It carries with it the additional risk of bowel dysfunction, such as bleeding and diarrhoea, due to inflammation of the mucosa caused by radiation.

It is delivered over 4-8 weeks of daily therapy. Attempts are made to accurately direct the radiation to the prostate gland to minimise collateral damage to surrounding structures. Due to the significant potential for morbidity with this treatment, it is not offered to those in the low prognostic risk group. It is instead reserved for the intermediate and high-risk populations. If a man is receiving radical external beam radiotherapy and has a Gleason score of 8 or more, he will be offered at least 2 years of hormone therapy as an adjuvant to the radiation.

External beam radiotherapy is also used in those with biochemical relapse after radical prostatectomy, with radiation being delivered to the prostatic bed following surgery. This is only offered if the man is radiologically demonstrated to have no metastases.

In locally-advanced disease, external beam radiotherapy can be combined with brachytherapy.

4. Brachytherapy

This is where the source of radiation is actually implanted within the prostate gland itself. It shares the complications of its external beam cousin, but these are often markedly reduced due to the more locally directed nature of the therapy. It can be used for localised disease in men who are in the low or intermediate-risk group, but is not used alone in those in the high-risk group.

For those with locally advanced disease, it can be combined with external beam therapy to increase the dose of radiation given to the prostate.

5. High intensity focused ultrasound (HIFU):

This causes destruction of prostatic tissue by heating. It is currently only offered as part of clinical trials, where it is compared to the standard treatments already described above. It may be

appropriate for all three categories: localised disease, locally-advanced disease and relapse of cancer following radiotherapy.

6. Cryotherapy

This causes tissue destruction by freezing, as the name suggests. Like HIFU, it is only offered as part of clinical trials.

Non-Curative and Adjuvant Treatments

Metastatic disease is the cause of nearly all prostate cancer-related death. Currently incurable, the 5-year survival is about 35%. The gold standard treatment is hormone therapy, with chemotherapy reserved for progressive disease.

1. Hormone Therapy

Prostatic cells grow in response to androgens, so manipulation of the androgen receptor on prostatic cells is a useful tool in disease management.

Androgen withdrawal (castration): This can be achieved via chemical means with gonadotrophin-releasing hormone agonists (Goserelin, Leuprorelin and Triptorelin) or antagonists (Degarelix). It can also be achieved surgically with bilateral orchidectomy. In practice, this latter option is rarely offered due to the associated psychological side effects.

Androgen blockade: This is achieved with drugs that bind to the hormone receptors of prostatic cancer cells and therefore block them from the action of endogenous androgens, thereby removing the growth stimulus. Examples include bicalutamide, flutamide and cyproterone acetate. These drugs can be used prior to the initiation of androgen withdrawal drugs as the latter can cause a temporary surge in testosterone as the testes respond paradoxically to the withdrawal of stimulus. This flare of androgen causes a temporary worsening of symptoms and is to be avoided.

Hormonal therapy is useful in an array of situations in prostate cancer. It can be used in the neo-adjuvant setting for some months before the initiation of radical therapy, or can be given concurrently alongside radiotherapy. It can also be given as adjuvant therapy in the aftermath of external beam radiotherapy and is sometimes offered after radical prostatectomy but only in the case of biochemical relapse and metastasis.

The side effects of hormone therapy depend on the mechanism. Androgen withdrawal commonly results in symptoms similar to those experienced by women during the menopause. They include hot flushes and loss of libido, osteoporosis and increase in cardiovascular risk. Androgen blockade has fewer of these side-effects, with the main problems being gynaecomastia and mastalgia.

2. Chemotherapy

This can be given to men with advanced disease who become castrate-resistant. Castrate-resistance is defined by two consecutive PSA rises from its nadir or symptomatic progression despite a favourable biochemical response following hormone therapy. Its use is weighed against the patient's preferences, symptoms and quality of life. Common chemotherapy agents include docetaxel and cabazitaxel. Novel therapies include Abiraterone which is administered orally with prednisolone and Enzalutamide which is an orally bioavailable androgen receptor antagonist more potent than Bicalutamide.

3. Palliative Care

Multidisciplinary involvement of the oncologist, urologist and palliative care team is often necessary for patients in the terminal phase of the disease, where the aim is to optimise their comfort and quality of life. Adequate pain management is needed to treat bone pain. Bladder outflow surgery may be required to treat persistent voiding symptoms. A long-term urethral or suprapubic catheter is an alternative for patients not fit for major surgery. Ureteric obstruction causing renal failure may require percutaneous nephrostomies or ureteric stents

Summary

Prostate cancer is extremely common in the United Kingdom today. It is a field of significant ongoing research and we are now seeing it being managed as a chronic disease for many people in whom it will, in all likelihood, not be the process that kills them. It is increasing in incidence largely due to increased life expectancy, better awareness and the success of PSA screening. A multidisciplinary team approach involving general practitioners, urologists, oncologists, radiologists, cancer nurse specialists and palliative care is essential in managing this complex disease.

SBA Questions

Q1. You are a GP working in a busy East London practice. A 65-year-old man presents complaining of nocturia of up to 4 times a night. His urine dipstick test is positive for nitrites and leukocytes. What is the most appropriate management?

1. Perform a random PSA test to exclude prostate cancer
2. Perform a DRE and ask him to see the practice nurse afterwards for a PSA
3. Perform a bladder scan and administer antibiotics for his UTI
4. Perform a bladder scan and DRE, administer antibiotics and ask him to attend for a PSA check in 2 weeks, meanwhile refer to a urologist for further evaluation
5. Send a urine culture, administer empirical antibiotics, perform a bladder scan and DRE and ask him to return for a PSA in 6 weeks

Answer: 5

The most likely cause for UTI is incomplete bladder emptying, which in this age group is most likely due to prostatic enlargement. It is essential to exclude malignancy as a cause for this enlargement which the DRE and PSA will help to do. If the PSA is raised or the DRE suspicious, he will need referral. It is essential to send a urine culture prior to antibiotic therapy in order to prevent resistance and the overuse of broad spectrum antibiotics. The bladder scan will give you an idea of whether this man is retaining urine or not. DRE or UTI can falsely raise PSA so the blood test should not be performed within 6 weeks of a urinary tract infection or physical gland examination.

Q2. A 60-year-old man is shown to have Gleason 4 + 3 =7 disease. His MRI shows anterior gland disease that is confined to the prostate. CT shows some reactive lymph nodes and no metastases. This man is suffering from frequency and nocturia with poor flow. What is the most appropriate management?

1. Watchful waiting
2. Brachytherapy
3. Transurethral resection of prostate
4. Radical prostatectomy
5. Active surveillance

Answer: 4

Young, fit patients with localised disease should be treated with curative intent if they opt for radical treatment. Radical prostatectomy is the most appropriate option. Brachytherapy would have been an option were it not for the bladder outflow obstruction. Brachytherapy can make this problem worse. This makes option 4 the most appropriate.

Q3. An 80-year-old man with recurrent UTIs and intermittent haematuria presents to clinic. His CT urogram is normal but flexible cystoscopy reveals a significantly inflamed bladder with friable mucosa and contact bleeding. His past medical history includes radical external beam radiotherapy to his prostate when he was in his sixties. His PSA is within range. What is the most likely cause for his symptoms?

1. Transitional cell carcinoma of the bladder.
2. Radiation cystitis.
3. Post-BCG instillation to the bladder.
4. Infection with coliform bacteria.
5. Recurrence of his prostate cancer.

Answer: 2

The damaging effects of ionising radiation on tissues surrounding the malignant target are often debilitating and hard to treat. BCG would be an option but there is nothing in his history to suggest he has had BCG immunotherapy.

Q4. A 50-year-old man is noted by his GP to have a PSA of 5. DRE reveals a firm, normal sized prostate. He is referred for TRUS-guided prostate biopsy and is not found to have any areas of disease. His MRI shows an area of suspicion anteriorly. What is the most appropriate management?

1. Discharge back to the GP for watchful waiting
2. Active surveillance
3. Transperineal template biopsy of the prostate
4. Hormone therapy as his PSA is high
5. TURP

Answer: 3

The MRI has demonstrated an area of interest which the TRUS biopsy may have missed. Transperineal template biopsies allow more focused targeting of suspicious areas anteriorly. Transperineal template biopsy is therefore the best way of making a definitive diagnosis.

Q5. A 79-year-old man with hormone refractory prostate cancer attends A&E complaining of pins and needles and numbness in both feet. What is the single most important clinical examination you must perform in this patient?

1. Neurological assessment of lower limbs
2. Cranial nerve examination
3. Plantar reflex assessment
4. DRE
5. Cardiovascular examination

Answer: 4

All other examinations listed are important in assessing someone with these symptoms but the DRE will allow assessment of anal sphincter tone and perineal sensation. These findings will inform how urgently this man requires MRI of his spine to exclude cauda equina syndrome. Prostate cancer is one of the malignancies that classically spread to bones and therefore can compromise the spinal canal. Other symptoms include retention of urine and faecal incontinence. Other cancers that commonly spread to bone are breast, lung, thyroid and kidney.

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