Management of prostate cancer

Prostate cancer is common, but may take an indolent course. Hospital doctors regularly encounter patients with prostate cancer who have unrelated diseases, but occasionally these patients present to different specialties with cancer-related symptoms. This article reviews the core knowledge needed for managing these patients.

Prostate cancer is diagnosed in 37 000 new patients a year, and causes 10 000 deaths each year in the UK (Cancer Research UK, 2011). Diagnoses are increasingly the result of screening using measurement of prostate-specific antigen levels. The natural history of early disease is unclear. Autopsy studies before prostate-specific antigen screening showed an actual latent prevalence (not diagnosed during life) of around 30% at the age of 50 years and 75% at the age of 80 years, and many of these demonstrated local invasion (Franks, 1954). One of the main current challenges in urology is distinguishing indolent prostate cancers from potentially lethal ones. The specificity of the prostate-specific antigen test for clinically significant disease remains disappointingly low and population screening is not encouraged (Ilic et al, 2011). However, prostate-specific antigen testing is often done in good faith, but pre-test counselling is essential. Thus, prostate-specific antigen testing should only be undertaken by the patient's GP or on the advice of a urologist.

Prostate cancer patients commonly present to other hospital specialties, most often as a result of unrelated disease. In these circumstances, prostate cancer should be viewed as a chronic disease and should rarely influence management of the presenting problem. Survival even with metastatic disease is usually measured in years, thus patients may also present as a result of symptoms or complications from metastatic disease. If there is any suggestion that the patient's symptoms are directly related to his prostate cancer or the treatment thereof, it is prudent to inform the patient's urologist or oncologist, so that the treatment can be reviewed.

Treatment of prostate cancer, especially castrate-resistant prostate cancer, has changed dramatically in recent years and is the focus of much debate among urologists and oncologists. Over 7000 English language articles on prostate cancer have been indexed with Medline in the last year alone.

Diagnosis

Prostate cancer may be diagnosed incidentally after transurethral resection of the prostate for obstructive symptoms, through screening, as a result of local symptoms or as a result of symptoms of metastatic disease (*Table 1*). Diagnoses have increased by over 50% since the advent of prostate-specific antigen testing with relatively little change in mortality (Cancer Research UK, 2011).

To date, there is no reliable imaging technique to diagnose localized prostate cancer. Once suspected, a prostate-specific antigen test and digital rectal examination are usually undertaken, if not previously performed, and the prostate-specific antigen test is often repeated to confirm a raised level. The only diagnostic test for prostate cancer is an ultrasound-guided needle biopsy of the prostate (this may be transrectal or transperineal). Possible complications of this procedure include pain or discomfort, urinary tract infection and sepsis, bleeding (in stool, urine or semen) and acute retention of urine.

Table 1. Symptoms and signs of prostate cancer

Extent of prostate cancer	Possible symptoms or signs
Localized	None
	Abnormal digital rectal exam
Locally advanced	None
	Abnormal digital rectal exam
	Lower urinary tract symptoms
	Acute or chronic urinary retention
	Haematuria, dysuria, incontinence
	Haemospermia
	Erectile dysfunction
	Perineal or suprapubic pain
	Loin pain or anuria from ureteric obstruction
	Symptoms of renal failure
	Rectal irritation, tenesmus
	Bone pain in pelvis
Metastatic	None
	Bone pain, sciatica
	Bone fracture
	Paraplegia or sphincter dysfunction from spinal cord compression
	Pain or altered function in affected organ
	General deterioration, lethargy, cachexia

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Prostate-specific antigen and screening

Measurement of prostate-specific antigen is now frequently used to 'screen' men for prostate cancer. Screening is not currently recommended in the UK, but early detection is, as per the Department of Health Prostate Cancer Risk Management Initiative (NHS Cancer Screening Programmes, 2011). Prostate-specific antigen measurement should only be requested after adequate counselling, explaining the following:

1. The shortcomings of the test itself (see below)
2. The diagnostic test in case of a raised prostate-specific antigen level (ultrasound-guided needle biopsy)
3. The significant risk of overdiagnosis and overtreatment
4. The significant morbidity of treatments for prostate cancer
5. The possibility – even in the face of a positive diagnosis – of having no increase in life expectancy compared to not being screened.

Prostate-specific antigen is indeed prostate specific, but it is not cancer specific (*Table 2*). It is a normal glycoprotein produced by the prostate and excreted into the ejaculate. There is no 'normal' cut-off value, and normal ranges are often assigned by age group, e.g. <2.5 ng/ml for age 40–49 years to <6.5 ng/ml for age 70+ years. A major difficulty of relying on prostate-specific antigen values is the high population prevalence of prostate cancer and the uncertainty around the clinical significance in a screening setting.

The natural history of early screen-detected prostate cancer is still unclear. Before the prostate-specific antigen test was available, most men with diagnosed localized prostate cancer could expect to live for 10 years or more (Johansson et al, 1992). Screening has added an uncertain lead time to this, which is now estimated to be between 5 and 12 years depending on the age of the patient and the characteristics of the cancer. Looking at current screening studies, the mortality benefit from screening starts to appear 10–15 years after screening. There is clear overdiagnosis and overtreatment, with current data showing that the number needed to screen is 1410 and the number needed to treat (with radical treatment) is 48 to prevent one death (Bul and Schröder, 2011; Heidenreich et al, 2011).

Most importantly, checking a patient's prostate-specific antigen level in an emergency situation is rarely justified. It is often requested in good faith for patients with acute retention of urine or urinary infections, and these are exactly the situations in which any patient's prostate-specific antigen level will be raised above his baseline. Many men then face a theoretical discussion about prostate cancer and a further prostate-specific antigen test at least 6 weeks later to determine whether further investigation (with ultrasound-guided needle biopsy) is justified. Therefore, if in doubt, a urologist should be consulted before requesting a prostate-specific antigen measurement.

In contrast, an elderly man found to have bone metastases from an unknown primary should have a digital rectal examination and a prostate-specific antigen test. Alternatively, for a patient with known prostate cancer and symptoms or signs suggestive of progressive disease (e.g. bilateral ureteric obstruction, new bone pain) a repeat prostate-specific antigen test is very helpful and will guide treatment.

Table 2. Causes of raised prostate-specific antigen level

Cause	Effect on prostate-specific antigen level
Prostate cancer	Permanently raised, rate of increase depends on volume and aggressiveness of cancer
Benign prostatic enlargement	Permanently raised, usually slow increase over decades
Urinary tract infection Acute or chronic prostatitis Acute or chronic retention Recent urological instrumentation (includes catheterization attempts, successful catheterization, long-term catheters, intermittent self-catheterization, prostate biopsy, flexible cystoscopy, lower urinary tract surgery) Prolonged bicycle riding	Should settle 6 weeks after the event or 6 weeks after fully treated

Gleason grade and score

The Gleason grade is a histological assessment of the prostate's glandular pattern. It measures the aggressiveness of any cancer, predicts prognosis and guides treatment. The pattern is graded from 1 to 5, where 1 is normal, 2 shows minimal abnormality (not considered cancerous), 3 shows variable shapes and spacing of the glands, 4 shows glandular fusion and 5 shows solid sheets of cells.

As patterns tend to vary in different areas of prostate cancer, the two most common patterns are identified and added to give the Gleason score, which can therefore range from 6–10 (e.g. 3+4=7 or 4+4=8) for prostate cancer. Generally, a Gleason score of 6 implies mildly, 7 moderately and 8–10 severely aggressive prostate cancer.

Emergencies related to prostate cancer

This article will discuss five emergencies: acute retention of urine, haematuria, hypercalcaemia, bilateral ureteric obstruction and spinal cord compression.

Acute retention of urine

About 7% of men with lower urinary tract symptoms will develop acute retention of urine, almost always as a result of benign prostatic enlargement, which anatomically occurs in the transitional zone (*Figure 1*). Prostate cancer usually develops in the posteriorly located peripheral zone (80% of prostate cancers) and is therefore usually locally advanced before the cancer causes any impairment of urinary flow (Franks, 1954; Cheng et al, 2005). Such cancers should be easily detectable at digital rectal

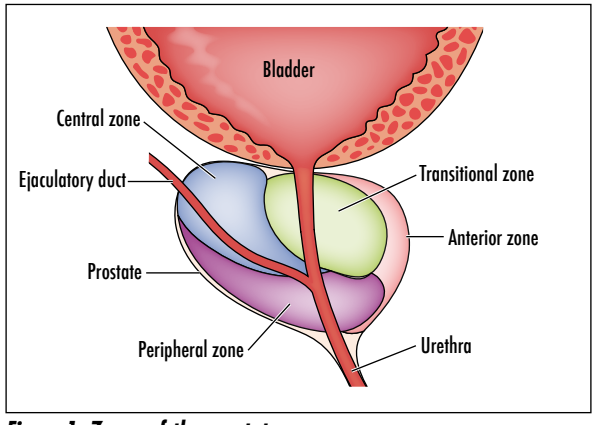


Figure 1. Zones of the prostate.

examination. Therefore, prostate-specific antigen testing is not indicated unless the digital rectal examination is clearly abnormal, in which case it should be arranged at a later date by a urologist.

Acute retention of urine can occur as a complication of ultrasound-guided needle biopsy of the prostate or as a complication of prostate radiotherapy treatment (with brachytherapy or external beam radiotherapy). Either situation should be easily identifiable during the history taking. The patient should be catheterized and send home with a catheter. The reason for retention will be localized oedema, which should be allowed to settle. Inform the treating urologist or oncologist of the event, so that appropriate follow up and trial without catheter can be arranged.

Haematuria

Haematuria may be caused by benign or malignant processes along the entire urogenital tract and should be fully investigated. Whenever possible this will be in a designated outpatient haematuria clinic. Benign prostatic bleeding is not uncommon, but bleeding as a result of prostate cancer is very rare. Similar to the situation with acute retention of urine, prostate cancer causing haematuria is usually locally advanced and should be easily palpable at digital rectal examination. A prostate-specific antigen test should only be undertaken after full counselling and may be delayed until after other investigations have been performed, which are more likely to identify the cause of bleeding (e.g. flexible cystoscopy, radiological imaging of upper urinary tract).

Haematuria can occur as a complication of ultrasound-guided needle biopsy of the prostate and as a complication of radiotherapy, which should be obvious from the history and is usually self-limiting. Inform the treating urologist or oncologist of the event, so that appropriate follow up can be arranged.

Hypercalcaemia

Hypercalcaemia can have many causes. In the context of prostate cancer, hypercalcaemia may be caused by bone metastases. It should be treated initially like any hypercalcaemia with rehydration and if necessary bisphosphonates. If not already started, androgen deprivation treatment (see below) may be commenced under the guidance of a urologist or oncologist.

Bilateral ureteric obstruction

Bilateral ureteric obstruction usually presents as acute renal failure with an ache in both loins. Benign causes include bilateral ureteric stones and retroperitoneal fibrosis.

More commonly, bilateral ureteric obstruction is caused by advanced pelvic malignancy, when either the primary mass itself or resulting lymph node masses compress both ureters. In men, this could be caused by locally advanced bladder, prostate or rectal cancer. The urgency of treatment is defined by the speed of deterioration in renal function and the overall health and wishes of the patient at that point. An inpatient urology review is needed to consider or arrange percutaneous nephrostomy or ureteric stenting or palliative care. If the primary cancer is in the prostate and depending on previous treatment, androgen-deprivation treatment and systemic treatment of castrate-resistant prostate cancer (see below) may also be options at this stage.

Spinal cord compression

Spinal cord compression can have many causes, but if prostate cancer is suspected, a digital rectal examination and prostate-specific antigen measurement should be done. The advice of a urologist should be sought if either is abnormal.

Spinal cord compression is a rare complication of vertebral metastases in prostate cancer patients, but it is a urological emergency. Provided the patient is not already receiving androgen deprivation treatment, the immediate treatment options are prompt castration (surgical or medical) and emergency radiotherapy to the responsible metastases. Often both treatments are combined and it is best to involve both the urologist and oncologist urgently. Neurosurgical decompression may also be necessary.

Treatment options for localized or locally advanced prostate cancer

Localized and locally advanced cancers include everything from incidental cancers to most screen-detected cancers to cancers with local symptoms. The natural history and clinical importance of early screen-detected prostate cancer remains unclear as discussed above.

Active surveillance

In light of the difficulties around screening, many men with apparently low risk prostate cancer (prostate-specific antigen <10 ng/ml, Gleason 3+3=6, normal digital rectal examination, small volume on biopsy) and some men with intermediate risk prostate cancer (prostate-specific antigen 10–20 ng/ml, Gleason 3+4=7, normal digital rectal examination, small volume) are offered a

programme of active surveillance. This includes regular prostate-specific antigen tests (every 3–12 months) and repeat biopsies (at predefined time points or if the prostate-specific antigen level is persistently increasing). The rational for active surveillance is that radical treatment will be undertaken if the cancer appears to be progressing. Therefore, the man's life expectancy has to be >10 years irrespective of the prostate cancer. Many patients can avoid treatment using this approach and 10-year survival is excellent (Albertson, 2011). For patients with <10 years life expectancy, a less pro-active 'watchful waiting' approach should considered (see below).

Radical prostatectomy

Radical prostatectomy is the surgical removal of the entire prostate, with or without the neurovascular bundles running alongside the prostate. The intention of treatment is curative, and hence the patient must have >10-year life expectancy. A pelvic lymph node dissection may be included depending on the Gleason score and expected stage. Morbidity following radical prostatectomy is significant, including major bleeding, rectal injury, incontinence, impotence and penile shortening (Heidenreich et al, 2011).

Radical radiotherapy

Radical external beam radiotherapy is directed at the prostate and can include areas of invasion beyond the prostate itself as well as regional lymph nodes. The intention of treatment is curative, and hence the patient must again have >10-year life expectancy. Patients may be treated at a more advanced stage than with radical prostatectomy and may be treated in case of progression after radical prostatectomy. The treatment is usually combined with neoadjuvant (3 months) and adjuvant androgen deprivation treatment (usually 3 years) as this is proven to improve survival (Milecki et al, 2007). The radiotherapy itself lasts 7 weeks. Side effects include cystitis, haematuria, urethral stricture, urinary incontinence, proctitis, erectile dysfunction and secondary malignancy (Heidenreich et al, 2011).

Table 3. Androgen deprivation therapy

Anti-androgens	Bicalutamide
	Cyproterone acetate
	Flutamide
Luteinizing hormone-releasing hormone analogues	Goserelin
	Leuprorelin
	Triptorelin
Luteinizing hormone-releasing hormone antagonists	Degarelix
Surgical castration	Bilateral subcapsular orchidectomy

Treatment options:
1. Anti-androgen alone – luteinizing hormone-releasing hormone agonist or antagonist can be introduced later
2. Anti-androgen for 4 weeks, after 2 weeks start luteinizing hormone-releasing hormone agonist and continue luteinizing hormone-releasing hormone agonist alone – anti-androgen can be added later, and then again withdrawn
3. Luteinizing hormone-releasing hormone antagonist alone
4. Surgical castration alone

Brachytherapy

Brachytherapy is the implantation of radioactive seeds into the prostate to irradiate the tumour. The intention of treatment is curative, and hence the patient must once more have >10-year life expectancy. The treatment cannot be as extensive as in external beam radiotherapy and therefore can only be offered for relatively limited disease. However, it is increasingly combined with external beam radiotherapy to improve survival in high-risk localized or locally advanced tumours. Side effects include worsening of pre-existing lower urinary tract symptoms, acute retention of urine, haematuria, urethral stricture, erectile dysfunction and proctitis (Heidenreich et al, 2011).

Focal therapies (e.g. high intensity focused ultrasound, cryotherapy)

Any focal therapy for prostate cancer aims to only treat the cancer and not the normal portions of the gland, in an attempt to limit side effects. All these treatments are relatively new and no long-term data are available, therefore they remain investigational at this stage (Nguyen and Jones, 2011).

Watchful waiting

Watchful waiting is a sensible option for patients with a <10-year life expectancy with non-metastatic prostate cancer and no significant local symptoms. Regular reviews are undertaken, but are less stringent than in the active surveillance group. There are no repeat biopsies. The intention is to commence androgen deprivation treatment as and when symptoms occur.

Androgen deprivation treatment

The rationale for androgen deprivation treatment is that most prostate cancers are androgen dependent. Androgen deprivation treatment (*Table 3, Figure 2*) frequently shrinks the cancer, leading to resolution or at least improvement of symptoms, but androgen deprivation treatment cannot cure prostate cancer. Response to androgen deprivation treatment lasts a median of 1–2 years, and around 25% remain progression-free after 5 years (Payne et al, 2011). When androgen deprivation treatment fails the cancer is termed 'castrate resistant'. Side effects of androgen deprivation treatment are hot flushes, gynaecomastia, lethargy, reduced quality of life, loss of libido or impotence, osteoporosis or increased fracture risk, increased cardiovascular risk, increased risk of developing diabetes and dyslipidaemias (Heidenreich et al, 2011). These side effects are the reason for delaying treatment in

asymptomatic patients with <10-year life expectancy and for not offering it to fitter patients with early disease.

Castrate-resistant prostate cancer

Castrate-resistant prostate cancer may be locally advanced or metastatic. Treatment is discussed below.

Treatment options for metastatic disease

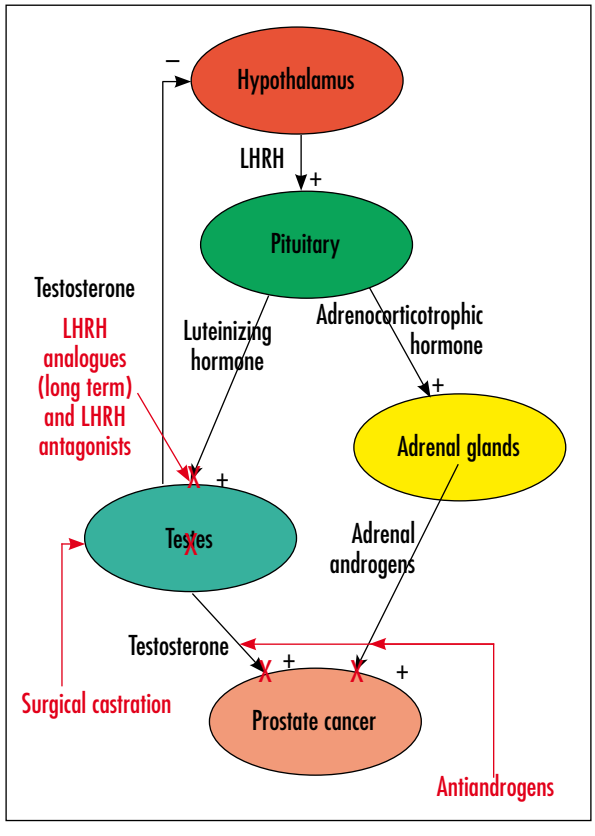
Prostate cancer most commonly metastasizes to bone, but visceral metastases are increasing. The standard treatment for metastatic prostate cancer is androgen deprivation treatment, progressing to treatment of castrate-resistant prostate cancer. Treatment at this stage continues to be life-prolonging with a median survival of 1–2 years (Bahl and Persad, 2011). Chemotherapy in metastatic castrate-resistant prostate cancer also clearly improves quality of life (Payne et al, 2011).

Treatment of castrate-resistant prostate cancer is usually coordinated by the oncologist and includes:

1. Further hormone therapy with oestrogens, steroids or abiraterone
2. Chemotherapy with docetaxel or carbazitaxel
3. Many other new agents in the context of clinical trials, including several bone-targeting agents (Bahl and Persad, 2011).

Additional treatments for metastatic disease are palliative radiotherapy to relieve pain from bone metastases and, ultimately, palliative care.

Figure 2. Mechanism of androgen deprivation therapy. LHRH = luteinizing hormone-releasing hormone.



Conclusions

Prostate cancer is common, but may take an indolent course. There is no screening programme and requests for 'screening' prostate-specific antigen should be discussed by the patient's urologist or GP. Most prostate cancer should be viewed as a chronic disease and should rarely influence management of other diseases. Emergency presentations caused by prostate cancer are rare, except in advanced stages. Survival even with metastatic disease is usually measured in years. BJHM

Conflict of interest: none.

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KEY POINTS

- Prostate cancer is common and has become a chronic disease in many cases.
- Most cases are diagnosed at a treatable stage, but overdiagnosis and overtreatment as a result of screening are common.
- Emergency presentations caused by prostate cancer are rare, except in advanced stages.
- There are many and increasing treatment options even in metastatic disease.
- Do not request measurement of prostate-specific antigen for emergency patients unless advised to do so by a urologist.
- Always counsel the patient before requesting prostate-specific antigen measurement – ideally done by the patient's GP or a urologist.