Prostate cancer

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Abstract

Prostate cancer is the most commonly diagnosed cancer in adult males. It has a multifactorial aetiology and its presentation varies from an indolent disease managed with surveillance to an aggressive malignancy requiring multidisciplinary treatment. Early diagnosis relies on prostate-specific antigen testing, imaging and prostate biopsy. Curative options for localized disease are guided by adequate image-guided disease stratification. New advances in treatment for advanced stages have prolonged patient survival and quality of life. This article summarises current knowledge of this complex and ever-changing disease.

Keywords Male health; prostate cancer; PSA; urology

Epidemiology

Worldwide, prostate cancer (PC) is the most commonly diagnosed cancer in adult males. In the (United Kingdom) UK, PC occupies the second place in the incidence of male cancer, with an estimated 56,000 new cases diagnosed in 2020, accounting for 20% of all new cancer cases. Overall, it is estimated that the lifetime risk of a male being diagnosed with PC is between 1 in 8 and 1 in 10.[1]

The incidence of PC varies widely between populations. This is due to different recommendations on prostate-specific antigen (PSA) screening testing, as an autopsy series review documented similar rates worldwide and little variation over time.[2]

Although most PC cases behave as an indolent, slow-developing disease, PC remains an important cause of mortality, with over 375,000 deaths recorded worldwide in 2020. In the UK, age-standardised mortality rates have decreased, from 17.2 per 100,000 males in 1992 to 12.2 in 2016.[1] Two reasons may account for this change; PSA screening decreases the incidence of metastatic disease at the point of diagnosis and improvements in treatments for advanced disease allows patients to live long enough to die from other causes.

Aetiology

Family history/hereditary factors

A family history of PC is a well-established risk factor, suggesting a strong genetic component. Relative risks for lethal PC are related to the number of affected first-degree relatives (FDRs) ranging from 2.49 for male patients with 1 affected FDR to 5.30 for $\geq$3 affected FDRs. Male patients with more than 1 relative are at higher risk especially if the diagnosis was made before age 50. However, true hereditary PC is rare. Studies on associated genomic loci have so far reported between 38 and 217 genes significantly associated with PC risk.[3]

Around 15% of all patients carry variants of genes associated with a higher incidence of PC. The most common pathogenic variants are BRCA2 (4.5%), CHEK2 (2.2%), ATM (1.8%) and BRCA (1.1%). BRCA1/2 mutations are associated with a more aggressive disease mainly grade group >4, T3/T4 stage, nodal involvement, and metastases at diagnosis compared to non-carriers.[4]

Risk factors

Hormonal factors have been implicated in the development of PC, peak incidence coincides with declining levels of serum testosterone, while serum oestrogen levels remain constant (serum testosterone/oestrogen ratio). While there are no significant differences in the levels of circulating testosterone and other androgens between different ethnicities, serum oestrogen levels are highest in patients with black ancestry, resulting in a more profound change in the androgen/oestrogen ratio.[5] As androgen levels fall, production of its receptor (androgen receptor e AR) increases in an attempt to maintain normal AR-dependent signalling. This increased production of AR, however, results in DNA damage and the production of abnormal genes, which subsequently drive the development of invasive cancer.

Multiple exogenous factors have been implied to be involved in the pathogenesis of PC such as obesity and diet. The decreased incidence of PC in Japanese males is thought to 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]

Vitamin D has a U-shaped association with low and high vitamin-D concentrations associated with an increased risk of PC. Other dietary and lifestyle factors have been studied and were previously thought to affect PC risk (such as vitamin E and selenium) but results from supplementation studies were negative.[6]

At the population level, metformin use appears to reduce the risk of PC diagnosis compared with never users (adjusted OR: 0.84, 95% CI: 0.74–0.96) but clinical trials have been inconclusive.[7] The ongoing Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) trial will assess metformin use in advanced PC (Arm K).[8]

5-alpha-reductase inhibitors have the potential of preventing or delaying the development of low-risk PC only. However, they are associated with treatment-related side effects and more importantly, no benefit in mortality is associated with their use. Therefore they are not approved for chemoprevention by current treatment guidelines.[9]

Diagnosis

Clinical diagnosis

PC diagnosis and screening is an area of continuous research, and PC diagnostics has become a subspecialty discipline in its

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Please cite this article as: Shaw G, Almeida-Magana R, Prostate cancer, Surgery, https://doi.org/10.1016/j.mpsur.2022.08.005

Take-home points

1. PC is an important health problem worldwide and its incidence will increase with the ageing of the population.
2. Genetic risk factors are multiple.
3. No dietary or preventive intervention has been shown to reduce the risk of PCa or improve prognosis.

own right. Clinical manifestations of PC are usually absent at the time of diagnosis. Nonetheless, in Europe and North America, most cases are diagnosed at a localized stage, with regional lymph node metastasis present in around 12% of cases, and only 6% presenting at the metastatic stage. Uncommonly, localized PC may present as non-specific lower urinary tract symptoms (LUTS), haematuria or haematospermia, but these symptoms are also common in benign conditions. Patients with advanced or metastatic disease may present with bone pain, weight loss, anaemia and spinal cord compression due to pathologic fractures or by direct tumour growth into the spinal cord.

Digital rectal examination (DRE) may detect nodules, induration or asymmetry in the gland, reflective of histological changes. However, DRE is not generally recommended as routine testing in the absence of symptoms. If done, only when an abnormality is encountered further evaluation is warranted.

Current diagnostic strategies revolve around the use of PSA serum tests. PSA is a glycoprotein serine protease enzyme almost exclusively produced by prostate epithelial cells making it a highly specific marker of prostatic disease. However, PSA is not specific to malignancy, and an elevated PSA can occur in several benign conditions; additionally, a PSA result in the normal range does not rule out the presence of PC. Therefore, an isolated raised PSA in itself should not automatically lead to a prostate biopsy but should prompt a discussion between patient and clinician about the potential risks and benefits of the procedure.[10]

Due to the low mortality associated with localized PC, and risks of over-diagnosis and over-treatment, PSA screening remains a controversial topic and is not currently undertaken in the UK. Several large PSA-screening trials have been published over the years with conflicting results; the European Randomized trial of Screening for Prostate Cancer (ERSPC) trial concluded that 27 patients needed to be screened to save one life.[11] In contrast, the CaP trial involving almost 420,000 male patients showed no improvement in PC-specific mortality using a single PSA screening test.[12] 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 male patients, and those thought to be at elevated risk of PC due to positive family history or other relevant risk factors.[10]

Multiple urine and blood-based molecular and genomic tests have been developed to help decide clinicians when a biopsy may be indicated. Prostate health index (PHI), the 4K score, SelectMDx, PCA3, and EPI are among these. None are yet recommended by guidelines due to weak evidence for their benefit for improving PC mortality.[13]

Multi Parametric Prostate Magnetic Resonance Imaging (mpMRI) is increasingly being used as an adjunctive tool in refining risk status for clinically meaningful prostatic disease and to inform decisions for performing biopsies. NICE guidelines currently recommend mpMRI as the first-line investigation for people with suspected clinically localized PC.[10]

In summary, after shared decision-making with the patient, a biopsy may be indicated if life expectancy is at least 10–15 years and the PSA is elevated above the range for the patient's age cohort, or PSA has increased more than 0.75 ng/mL over one year, or there is a palpable concerning abnormality on DRE. 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.

Take-home points

1. PC is asymptomatic in most cases, symptoms usually reflect advanced disease.
2. DRE should not be used as a screening tool.
3. Shared decision-making is imperative before undertaking PC diagnostic strategies.
4. Do not subject male patients to PSA screening without discussing the associated risks and benefits.
5. Offer individualized risk-adapted strategy to male patients with a life expectancy of 10–15 years.
6. Offer early PSA testing to male patients with high-risk factors (family history, black ancestry).

Prostate biopsy

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 guided by an ultrasound probe in the rectum. Common risks include 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.

The most important risk associated with TRUS biopsy is sepsis, occurring in 1–11% of patients, even with adequate antibiotic prophylaxis. This is a potentially life-threatening complication that warrants immediate evaluation and intervention. Prior fluoroquinolone use and extended post-biopsy antibiotic regimens appear to increase the risk of sepsis. The use of rectal cleansing with povidone-iodine before TRUS has shown to be beneficial.[14]

The European Association of Urology guidelines[13] recommends three different strategies for TRUS biopsy antibiotic prophylaxis:

1. Targeted prophylaxis - based on a rectal swab or stool culture.
2. Augmented prophylaxis - two or more different classes of antibiotics (of note: this option is against antibiotic stewardship programmes).

Please cite this article as: Shaw G, Almeida-Magana R, Prostate cancer, Surgery, https://doi.org/10.1016/j.mpsur.2022.08.005

3. Alternative antibiotics: • Fosfomycin trometamol (e.g., 3 g before and 3 g 24–48 hrs. after biopsy); • Cephalosporin (e.g., ceftriaxone 1 g i.m; cefixime 400 mg p.o for 3 days starting 24 hrs. before biopsy) Aminoglycoside (e.g., gentamicin 3 mg/kg i.v.; amikacin 15 mg/kg i.m)

The use of fluoroquinolones as monotherapy is now against the European Commission final decision on EMEA/H/A-31/1452.[13]

An alternative to TRUS biopsy is the transperineal prostate (TP) biopsy. In this technique, the prostate is biopsied by passing a needle through the skin of the perineum. 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. There is evidence to suggest a higher accuracy for the detection of clinically significant PC.[15]

NICE recommends that male patients with an initial negative TRUS biopsy undergo a TP biopsy due to the additional cancer yield over a repeat TRUS biopsy. Furthermore, there is a reduced risk of urinary tract infection and sepsis associated with the procedure, several large series, involving thousands of male patients, 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 TP biopsies are currently performed under general anaesthetic, however, some centres have now adopted local anaesthetic, clinic-based TP biopsies.

TRUS and TP biopsies carry an estimated false-negative rate of around 30%. Male patients with a negative biopsy result, with ongoing suspicion of PC (based on abnormal examination or elevated PSA level), are therefore candidates for repeat biopsies. In contemporary practice, however, the use of mpMRI scanning before a prostate biopsy has rapidly become commonplace, with two important research studies demonstrating its value. Firstly, the PROMIS study demonstrated that mpMRI-guided biopsy 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.[16] Secondly, the PRECISION study 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).[17] Furthermore, mpMRI biopsy-guided strategies can reduce over-diagnosis of low-risk disease (not clinically significant), as compared to systematic biopsy.

Take-home points

1. Post TRUS sepsis is a life-threatening complication and adequate prophylaxis should be instituted before the procedure.
2. TP biopsy is an alternative technique associated with a lower risk of sepsis and higher diagnostic yield.
3. Male patients with previous negative systematic biopsy should be offered a mpMRI and if positive a targeted biopsy.
4. mpMRI can increase the accuracy of initial biopsy and decrease detection of not clinically significant PC.

Classification

Pathology

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. The diagnosis of PC is based on the histology obtained during prostate biopsy. The vast majority of PC (over 95%) is adenocarcinoma, arising from epithelial glandular structures. Rare variant histologies include neoplasms with neuroendocrine differentiation, urothelial (transitional cell) carcinoma, carcinosarcoma, small cell carcinoma, lymphomas, and stromal sarcoma.[18]

Prostatic adenocarcinoma can be subclassified as acinar (97%) and ductal types. Diagnosis relies on the presence of small infiltrating glands with prominent nucleoli and absent basal cells. In less differentiated tumours the glandular pattern might be irregular, less organized, fused or even absent, with tumour cells growing in cords, nests or cribriform patterns. The cytoplasm of tumour cells is often darker on H&E staining and nuclear enlargement and irregularity are common.

When untreated, PC can develop into a locally advanced disease by invading surrounding structures, the periprostatic fat, 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. Metastases characteristically are attracted 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 acinar adenocarcinoma. A score of 1–5 is assigned to the tumour depending on the degree of glandular pattern de-differentiation which correlates with PC aggressiveness. Two scores are given representing the most prevalent patterns. 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 a smaller quantity of Gleason 3, then the prostate biopsy would be reported as Gleason 7 (4 + 3). 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).

In 2016, the World Health Organization (WHO) adopted a new 5-point grade group (GG) system (ISUP GG) based on the Gleason system, which provides more accurate risk stratification and simplifies patient understanding.[19]

- GG 1: Gleason score ≤ 6
- GG 2: Gleason score $3 + 4 = 7$ (hazard ratio [HR] for death 2.8 relative to GG 1)
- GG 3: Gleason score $4 + 3 = 7$ (HR 6.0 relative to GG 1)
- GG 4: Gleason score $= 8$ (including $4 + 4 = 8$, $3 + 5 = 8$, or $5 + 3 = 8$; HR 7.1 relative to GG 1)
- GG 5: Gleason scores 9 to 10 ($4 + 5$, $5 + 4$, or $5 + 5$; HR 12.7 relative to GG 1)

Take-home points

1. The most common histology of PC is acinar adenocarcinoma.
2. Gleason grading is based on the glandular pattern of growth and correlates with PC aggressiveness.
3. The new GG classification improves risk stratification for PC.

Please cite this article as: Shaw G, Almeida-Magana R, Prostate cancer, Surgery, https://doi.org/10.1016/j.mpsur.2022.08.005

Imaging

TRUS is not accurate in predicting the extent of disease and treatment decisions should not be guided by its findings. New technologies such as 3D or colour Doppler are under evaluation in ongoing studies.

In addition to its developing use as a diagnostic tool, mpMRI is used to determine local disease staging. These mpMRI scans incorporate T1, T2, dynamic contrast-enhanced and diffusion-weighted imaging modalities to identify and characterize lesions in the prostate. These images can then be used in surgical planning for radical prostatectomy (RP) to guide nerve-sparing (i.e. if the unilateral disease is seen close to or breaching the capsule a wider excision is made). mpMRI can also inform on the presence of enlarged pelvic lymph nodes.

Computed Tomography scans (CT) are indicated to evaluate patients with risk of metastatic pelvic or abdominal lymph nodes and can detect distant visceral metastasis. 99mTc whole-body bone scans evaluate active bone formation related to malignant and benign diseases. This can detect bone metastasis in the axial and appendicular skeleton. Any patient with a GG >3 or symptomatic (bone pain) should undergo a bone scan. These two standard staging techniques are the current standard of care although both have a relatively low sensitivity for oligometastatic disease.[13]

Prostate-specific membrane antigen (PSMA) based positron emission tomography (PET) has shown to be a more accurate tool than CT and bone scan for detecting lymph node and distal metastasis. However, there is still limited evidence on outcome data for subsequent treatment changes and therefore are not yet recommended as an initial stating tool. This may change in the near future as this is an area of active investigation. Figure 1 illustrates the correlation between mpMRI, PSMA-PET and definitive histology after radical prostatectomy.

Take-home points

1. mpMPI is the method of choice for local staging of PC.
2. CT and 99mTc-Bones are the standard of care for diagnosing metastatic spread.

Staging and risk stratification

After PC diagnosis, treatment recommendations should be discussed at a multidisciplinary team meeting (MDT) where a team of specialists including urologists, oncologists, radiologists and pathologists as well as cancer nurse specialists are present to review histology and imaging. Management options should be tailored to the individual patient and take account of their disease risk stratification, priorities, lifestyle factors and life expectancy.[10]

The TNM classification (Table 1) is the basis of disease stratification.[18] But treatment decisions are different for three main categories:

1. Localized disease (T1,2,3a N0 M0)
2. Locally advanced (T1/2 N1 M0 or T3b/4 N1/0 M0)
3. Metastatic disease (Any T/N M1).

Localized and locally advanced PC is further risk-stratified in 5 groups by the Cambridge Prognostic Group (CPG) criteria adopted by NICE (Table 2).[10]

Treatment of prostate cancer

Surveillance strategies

Watchful waiting: an essential initial consideration following the diagnosis of non-metastatic PC lies in trying to determine whether radical (intention-to-cure) treatment is expected to be beneficial to the patient. Long-term studies of large numbers of male patients have shown that 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.[20] It is therefore reasonable not to offer radical treatment to elderly patients, 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.

The watchful waiting strategy involves is a conscious decision to avoid any treatment until it is required for symptom relief. It is an option for all risk categories of PC and is generally used for elderly or comorbid patients with a life expectancy of fewer than 10 years. PSA monitoring should be infrequent and repeat biopsies are not recommended. Treatment with hormonal medications is commenced with the development of symptomatic disease or marked PSA progression. The aim of treatment for these patients is therefore palliative rather than curative (radical).

Active surveillance (AS): patients diagnosed with CPG 1 PC have a very low risk of dying from the disease even after 20 years of follow-up but are at risk of side effects from radical treatment that can decrease quality of life. Therefore, active surveillance was developed to offer an option for patients 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 patients eligible for radical treatment.

According to NICE guidelines it is the preferred treatment option for patients with CPG 1 and may be considered for selected, well-informed patients with CPG 2.[10] In contrast to watchful waiting, it is an active management process, which mandates regular PSA measurement and confirmatory biopsies at regular intervals 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. Outcomes from AS are excellent, with numerous studies demonstrating 100% cancer-specific survival after 10 years and better quality of life compared to patients undergoing radical treatment. However, patients with CPG2 must be informed of the small risk of progression and higher rates of requiring active treatment due to disease progression.[21]

Take-home points

1. Patients with a limited life expectancy of <10 years should undergo a watchful waiting strategy
2. AS is the preferred treatment option for patients diagnosed with CPG 1 and for selected GPC 2.

Please cite this article as: Shaw G, Almeida-Magana R, Prostate cancer, Surgery, https://doi.org/10.1016/j.mpsur.2022.08.005

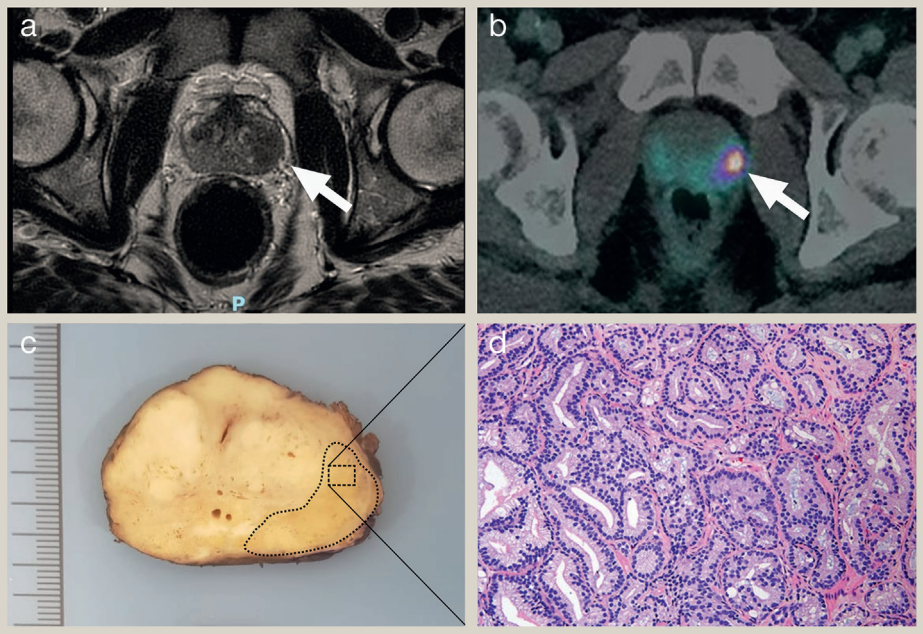

Figure 1 (**a**) mpMRI of the mid-gland prostate showing hypointense signal on T2 suspicious for PC (white arrow). (**b**) PSMA-PET showing increased uptake in left lobe (white arrow). (**c**) Macroscopic image of the prostate with corresponding tumour location (dashed line). (**d**) Photomicrography of an H&E stained slide confirms a Gleason 7 (3 + 4) ISUP 2 PC.

Intention to cure strategies

Radical prostatectomy: this operation involves the surgical removal of the entire prostate and seminal vesicles followed by restitution of the urinary tract by an anastomosis of the bladder neck to the urethra. A minimally invasive technique called robotic-assisted radical prostatectomy (RARP) is now the most common approach in the UK. 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 CPG1 (only if AS is declined), CPG 2, 3 and 4.[10] Patients undergoing RARP stay in the hospital for 1 or 2 nights and are discharged with a urethral catheter that will be removed in 7 −10 days.

Common side effects are urinary incontinence and erectile dysfunction (ED). Uncommon (<5%) side effects include thrombosis, urethral and bladder neck stricture, inguinal hernia or lymphocele formation (if lymph node dissection is performed). Rectal or ureteric injuries are rare complications. At present, open, laparoscopic and robotic-assisted techniques are regarded as equivalent concerning oncological outcomes. Laparoscopic and RARP 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 RARP.[22] However, it is the experience of the operating surgeon, rather than the technique used, which is the most likely determinant of outcome. Following RP, 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 external beam radiotherapy and/or hormonal therapy, cytotoxic chemotherapy or stereotactic radiotherapy depending on patient and disease characteristics.

Prostate cancer TNM classification.[18]

	TNM Staging Categories	Definition
T	Tx	Primary tumour cannot be assessed
	T0	No evidence of primarytumour
	T1	Clinically inapparenttumour not detectable on DRE/Imaging
	T1 a/b	Incidental finding in specimen resected for another pathology
	T2	Tumour detectable on DRE/Imaging confined to the prostate
	T3	Tumour is detected to be extend through prostatic capsule
	T3a	Extra prostatic extension including microscopic bladder neck involvement
	T3b	Extension to seminal vesicles(s)
	T4	Tumour is fixed or invades adjacent structures (external sphincter, rectum, levator muscles and/or pelvic wall)
N	Nx	Regional nodes cannot be assessed
	N0	No evidence of lymph node metastasis
	N1	Regional pelvic lymph node metastasis
M	Mx	Distant metastasis cannot be assessed
	M0	No evidence of distant metastasis
	M1	Distant metastasis
	M1a	Non-regional lymph node metastasis
	M1b	Bone metastasis
	M1c	Visceral metastasis (lung, liver, brain, etc.)

Table 1

Please cite this article as: Shaw G, Almeida-Magana R, Prostate cancer, Surgery, https://doi.org/10.1016/j.mpsur.2022.08.005

Radical radiotherapy: prostate-focused radiotherapy treatment (RT) is suitable for all CPG groups and is the preferred treatment for locally advanced diseases (CPG 4, 5 or N1).[10] It is delivered under the supervision of a clinical oncologist and the current recommended treatment protocol is called hypofractionated image-guided intensity-modulated radiation therapy (IMRT). In this treatment technique, a dose of 60 Gray is given in 20 fractions over four weeks. Compared to standard protocols, this new technique allows more accurate and precise delivery of the radiation, thus limiting the toxicity to adjacent organs (such as the rectum), and shorter treatments (4 weeks) without an increase in the toxicity profile.[23]

Common side effects include radiation cystitis and haematuria, less common side effects include urgency-related urinary incontinence, radiation proctitis and ED. In long-term survivors, there is a very low risk of developing secondary cancer after RT. Contraindications to RT are severe LUTS, previous pelvic RT and inflammatory bowel disease or severe proctitis.

RT is given in combination with adjuvant androgen deprivation therapy (ADT) for CPG >2 as it has been shown to increase overall and PC-specific survival compared to RT alone.[24]

Follow-up after RT relies on PSA monitoring. Disease recurrence (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.

Take-home points

1. Curative treatment options for PC are RP and RT, there is no definitive evidence of superiority for either treatment.
2. The benefits and harms of each treatment option should be discussed with the patient to guide treatment decisions.
3. RARP is now the most commonly used technique for the surgical treatment of PC.
4. IMRT is the current standard-of-care treatment protocol for radiotherapy treatment.

Adjuvant and palliative strategies

Hormonal therapy: ADT is commonly used to treat advanced and metastatic PC, and disease relapse after radical treatment. ADT aims 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:

- Luteinizing hormone-releasing hormone (LHRH) agonists: Goserelin, Leuprolide
- LHRH antagonists: Degarelix, relugolix
- Anti-androgens: Flutamide, Bicalutamide, Apalutamide, Darolutamide, Enzalutamide
- Surgical castration (i.e. bilateral orchidectomy).

Overstimulation of the anterior pituitary gland by LHRH agonists leads to a downregulation 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 an 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 patients 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.

Surgical castration in the form of bilateral subcapsular orchidectomy was the mainstay of treatment before the development of pharmacotherapy and achieves rapid castrate levels of testosterone. It is still a treatment option for patients 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 ED and loss of libido, weight gain, fatigue, gynecomastia, depression, cognitive changes and osteoporosis with an increased risk of bone fracture. Current NICE guidance states that individual patients' fracture risk should be assessed by calculating a FRAX score and evaluating the need for a DEXA scan to assess bone mineral density before commencing ADT, and if appropriate, should then receive treatment if osteoporosis is identified.[10]

Combination therapy: The STAMPEDE trial a multicentre UK-based study has reported clinically and statistically significant

Cambridge Prognostic Group classification.[10]

Cambridge Prognostic Group	Criteria
1	Gleason score 6 (GG 1) **and** PSA less than 10 microgram/litre **and** Stages T1-T2
2	Gleason score 3+4=7 (GG 2) or PSA 10 microgram/litre to 20 microgram/litre **and** Stages T1-T2
3	Gleason score 3+4=7 (GG 2)**and** PSA 10 microgram/litre to 20 microgram/litre **and** Stages T1-T2 **or** Gleason 4+3=7 (GG3)**and** stages T1-T2
4	Any of the following, Gleason score 8 (GG 4), PSA more than 20 microgram/litre, Stage T3
5	Two or more of: Gleason score 8 (GG 4), PSA more than 20 microgram/litre, stage T3 **or** Gleason score 9 to 10 (GG 5) **or** Stage T4

Table 2

Please cite this article as: Shaw G, Almeida-Magana R, Prostate cancer, Surgery, https://doi.org/10.1016/j.mpsur.2022.08.005

improvement in survival for patients with metastatic PC with a high volume of metastasis at diagnosis when hormone therapy was combined with docetaxel compared to hormone therapy alone.[8] The addition of docetaxel increased median survival by 10 months. Therefore, this is now regarded as the standard of care for newly diagnosed metastatic PC.

Castrate-resistant prostate cancer (CRPC): CRPC develops in virtually all patients treated with standard ADT as a result of 'selection pressure' arising from loss of normal androgen receptor activity. CRPC carries a poor prognosis, with a median survival of 18 months from diagnosis and is diagnosed when PSA levels rise despite castrate levels of serum testosterone <20 ng/dL (1 nmol/L).

Docetaxel chemotherapy is commonly used as a first-line treatment. In those who develop docetaxel resistance or those who have already had docetaxel, new androgen pathway targeting agents have been developed. Two of the most commonly used, abiraterone, a CYP17 inhibitor that works by suppressing the intracellular synthesis of testosterone and enzalutamide (2nd generation antiandrogen) have been shown to increase the survival of patients with metastatic CRPC.[25] As part of the STAMPEDE study, abiraterone has been shown to improve overall survival in hormone-sensitive diseases as compared with standard ADT alone.[8]

Take-home points

1. Hormonal treatment for PC is based on the reduction of available testosterone upon which PC cells are reliant.
2. Fracture risk assessment should be offered to all patients before ADT treatment.
3. CRPC is an advanced stage of PC in which docetaxel chemotherapy is the first-line treatment.

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; ureteric obstruction and malignant spinal cord compression. Other important complications include 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 bladder catheterization. Patients may present with acute kidney injury and symptoms of renal failure with or without hyperkalaemia. Definitive treatment requires 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 are essential to prevent a 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 male patients who present with sudden onset of this clinical picture. Definitive management requires high-dose steroids followed by either neurosurgical decompression or radiotherapy. If the patient is naïve to ADT an antiandrogen should be started promptly to prevent disease progression.

Summary

PC is a complex condition to diagnose and treat, with many treatment options available at each stage. All clinicians should be familiar with the basic knowledge of diagnosis and disease stratification. With an ageing population and increased awareness of the disease, 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 male patients. ◆

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Please cite this article as: Shaw G, Almeida-Magana R, Prostate cancer, Surgery, https://doi.org/10.1016/j.mpsur.2022.08.005

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Practice points

- Screening and diagnosis of PC must be based on shared decision making after informing patients of the associated risks and benefits.
- The use of mpMRI improves accuracy of biopsies and decreases risks of overdiagnosis of non-significant PC.
- TP biopsy of the prostate is associated with a lower risk of sepsis and higher diagnostic yield.
- TNM staging and CPG are the basis of disease risk stratification and guide treatment decisions.
- Active surveillance is the preferred option for patients with CPG 1 and selected patients with CPG 2.
- Curative treatment options for PC are RP and RT, there is no definitive evidence of superiority for either treatment.
- ADT and chemotherapy with docetaxel are indicated in advanced or metastatic non-curable PC.

Please cite this article as: Shaw G, Almeida-Magana R, Prostate cancer, Surgery, https://doi.org/10.1016/j.mpsur.2022.08.005