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Improving the early detection and management of prostate cancer

Aning J. Improving the early detection and management of prostate cancer.
Practitioner April 2022;266(1857):11-15

Abstract

Prostate cancer is the most common cancer in men in the UK; each year around 52,254 men are diagnosed with the condition. The following symptoms that lead men to present to their GP should stimulate a discussion about prostate cancer risk: problems with urination; blood in the urine or semen; erectile dysfunction; pain in the hips, back, or bones; weakness or numbness in the lower limbs or loss of bladder control. The risk of prostate cancer increases with age, most patients are aged over 50 at diagnosis. Black men have a lifetime risk of 1 in 4 compared with the estimated 1 in 8 risk faced by the general population. Prostate cancer risk is 2.1-2.4 times higher in men whose father has/had the disease and 2.9-3.3 times higher in men whose brother has/had the disease. Overweight men are at increased risk of being diagnosed with advanced prostate cancer. An assessment of LUTS, relevant risk factors and past medical history are essential. NICE recommends performing a DRE; this will give an impression of prostate size. If the prostate feels malignant on DRE this should trigger a fast-track referral to secondary care, via a suspected cancer pathway referral even if the PSA is normal. A PSA test should also be offered to men with LUTS or an abnormal DRE. Men who would be eligible for curative treatment will be offered an MP-MRI scan. This can identify abnormal areas in the prostate, consistent with significant prostate cancer which merit further investigation, better than untargeted prostate biopsies alone. If MP-MRI is performed first and abnormal lesions are identified, targeted biopsies of these lesions improve the detection of clinically significant prostate cancer. A tissue diagnosis is usually mandated for curative treatment options to be considered.

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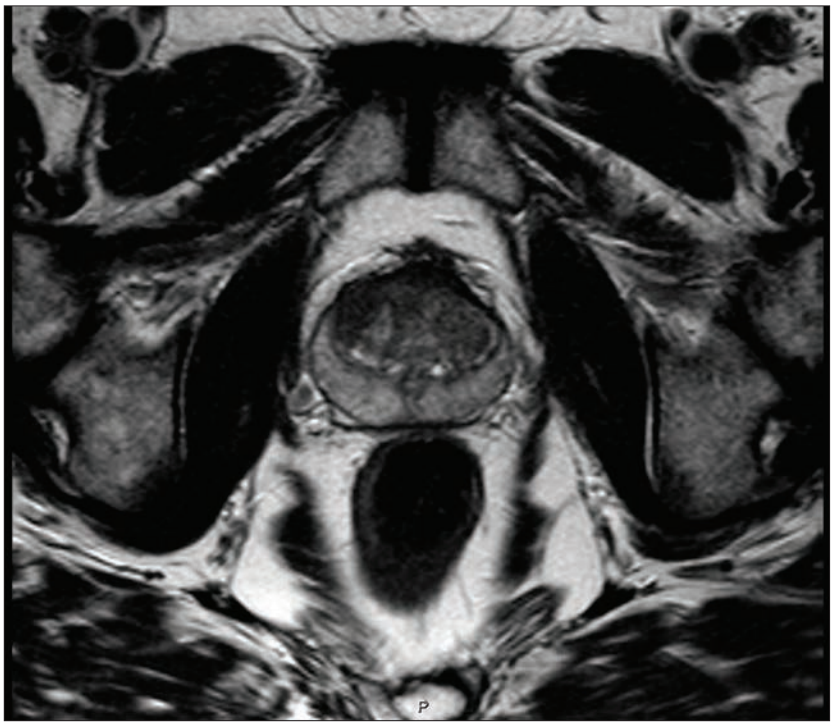

Axial MRI prostate showing right peripheral zone prostate cancer

What are the risk factors for prostate cancer?

How should men be examined and investigated?

What are the management options?

PROSTATE CANCER IS THE MOST COMMON CANCER OCCURRING IN MEN IN THE UK; EACH YEAR AROUND 52,254 men are diagnosed with the condition.[1]

GPs play a major role in identifying and referring men with suspected prostate cancer for further investigation and are increasingly responsible for managing men who have been treated for prostate cancer in the community. An estimated 400,000 men were living with, or had had treatment for, prostate cancer in the UK in 2017.[2]

Evidence-based updates in practice were incorporated into the NICE guideline *NG131. Prostate cancer: diagnosis and management* in December 2021.[3]

PRESENTATION

The majority of men with early prostate cancer presenting in primary care will have no signs or symptoms of the condition. Asymptomatic men may present because of awareness campaigns, the experience of relatives or friends or after prompting by their partner.

The COVID-19 pandemic has had a profound impact on the care provided to patients with prostate cancer. There was a 54% reduction in the number of patients newly diagnosed during April-June 2020 compared with the same period in 2019. Of the men diagnosed with prostate cancer since April 2020, a higher proportion were diagnosed at stage IV compared with 2019.[4]

The NHS in partnership with Prostate Cancer UK launched a campaign in February 2022 to try to encourage the estimated 14,000 men who were not diagnosed during the pandemic to come forward. Consequently many men may be prompted to seek medical advice if they have concerns or just want to get 'checked out'.

The following common symptoms that lead men to present to their GP should stimulate a discussion about prostate cancer risk: problems with urination; blood in the urine or semen; erectile dysfunction (ED); pain in the hips, back, or bones; weakness or numbness in the lower limbs or loss of bladder control.

It is crucial to explore the patient's reasons for attending as well as his fears and understanding of prostate cancer risk even if you suspect that any lower urinary tract symptoms (LUTS) reported are due to another cause. Many men do not know where the prostate is located, or what its function is, and appreciate a brief explanation.

RISK FACTORS

The aetiology of prostate cancer remains poorly understood but genetic and environmental factors are likely to contribute. Factors known to be associated with an increased risk of prostate cancer are: age, ethnicity, family history, gene mutations and obesity. The risk of prostate cancer increases with age, most patients are aged over 50 years at diagnosis.[5]

Prostate cancer is more common in men of Black African heritage. Black men have a lifetime risk of 1 in 4 compared with the estimated 1 in 8 risk faced by the general population.[6] The risk of prostate cancer is increased if a first-degree relative has been affected. Prostate cancer risk is 2.1-2.4 times higher in men whose father has/had the disease and 2.9-3.3 times higher in men whose brother has/had the disease.[7]

Around 5-10% of all prostate cancers are likely to be associated with hereditary gene mutations.[8] Men with BRCA2 mutations are more likely to develop »

clinically significant prostate cancer and have poor survival outcomes.[9] The IMPACT study found that after 3 years of screening with prostate-specific antigen (PSA) testing, compared with noncarriers, BRCA2 mutation carriers were more likely to have a higher incidence of prostate cancer, younger age of diagnosis, and clinically significant tumours.[10]

Men who are overweight are at increased risk of being diagnosed with advanced prostate cancer.[11] The risk of advanced prostate cancer increases by 9% for every 5-unit increment in BMI.[12]

EXAMINATION AND INVESTIGATION

An assessment of LUTS, relevant risk factors and past medical history are essential.

NICE recommends performing a digital rectal examination (DRE).[3] A DRE will give an impression of prostate size. If the prostate feels malignant on DRE this should trigger a fast-track referral to secondary care, via a suspected cancer pathway referral[13] even if the PSA is normal. A normal DRE does not exclude cancer. Performing a PSA test immediately after DRE does not compromise the value of the PSA result.[14]

An abdominal examination is useful to exclude a palpable bladder, a sign of urinary retention, or other abdominal pathology and should be routinely performed.

If the man reports bothersome LUTS a midstream urine sample should be collected and dipstick analysis carried out to exclude urinary tract infection (UTI). If a UTI is suspected a specimen should be sent for microscopy and culture.

Men over 50 years old who request a PSA should be fully informed about the test beforehand. It is important to explain that the PSA test is not specific for prostate cancer, and that raised levels may be due to other factors such as inflammation or benign enlargement. A PSA test should also be offered to men with LUTS or an abnormal DRE.[3]

Asymptomatic men under 50 years presenting to their GP requesting a PSA test should be managed on an individual case by case basis. They should all be counselled to use a prostate cancer risk calculator tool as part of the shared decision-making process (see Useful information box, p15).

A raised PSA may be associated with significant prostate cancer, and the test is used to stratify referral for further investigations. Men with PSA values above the age-specific reference range should be referred to urology urgently, via a suspected cancer pathway referral.[13] The recommended age-specific reference ranges to guide referral in men with possible symptoms have recently been updated and are shown in table 1, above left.

Although it has limitations the PSA remains the best and most established method for identifying men who are at risk of having a significant prostate cancer at an early stage when treatment options and survival outcomes may be better. It is important to reassure men that not all those with an abnormal PSA will undergo invasive prostate biopsies. Where low risk or suspected clinically insignificant prostate cancer is identified active surveillance (disease monitoring) is the nationally accepted primary management option. Box 1, below, lists frequently asked questions about PSA testing.

Table 1

Age-specific PSA thresholds for men with possible symptoms of prostate cancer[13]

Age (years)	PSA threshold (µg/L)
Below 40	Use clinical judgement
40-49	> 2.5
50-59	> 3.5
60-69	> 4.5
70-79	> 6.5
Above 79	Use clinical judgement

Box 1

Frequently asked questions about PSA testing

What is the current position on prostate cancer screening in the UK?
There is no formal PSA screening programme in the UK. Evidence from the largest screening study to date which included more than 182,000 European men, aged 55-69 years, with 16 years of follow-up showed that regular PSA screening reduced the risk of prostate cancer metastases and mortality. The numbers needed to be invited to screening and diagnosed to prevent 1 death were 570 and 18 respectively.[15]

Do younger men benefit from PSA testing?
Data suggest that younger men potentially have the most to gain from early detection of prostate cancer. If a high-risk cancer is detected intervention will improve overall survival.[16]

If the PSA blood test is abnormal is there any value in repeating the PSA test?
Repeating the PSA test prior to referral to secondary care is valid if history and examination findings are consistent with infection or if the patient describes a factor that may have caused this such as a history of ejaculation within 48 hours of performing the test. A repeat PSA in a not insignificant proportion of men may return to within normal limits, and sometimes this will be unexplained.[17]

What is the value of a single PSA screening test?
Current evidence shows that a single PSA screening intervention (once in a lifetime) in a UK population when compared with standard practice without screening does not lead to a significant difference in prostate cancer mortality at a median follow-up of 10 years.[18] Based on this a pragmatic approach should be that if a PSA is performed in primary care and found to be normal the PSA should be repeated at regular intervals e.g. annually.

CONFIRMING DIAGNOSIS

Patients referred to urology with suspected prostate cancer will be reviewed either face to face or remotely by a member of the multidisciplinary team (MDT).

Men who would be eligible for curative treatment will routinely be offered a multiparametric magnetic resonance imaging (MP-MRI) scan of their prostate.[3] MP-MRI can identify abnormal areas in the prostate, consistent with significant prostate cancer which merit further investigation, better than untargeted prostate biopsies alone.[19]

If MP-MRI is performed first and abnormal lesions are identified, targeted biopsies of these lesions improve the detection of clinically significant prostate cancer.[20] This approach, recommended by NICE, enables approximately 28% of men to avoid a biopsy when compared with the previous strategy of performing untargeted systematic biopsies alone.[20]

Men investigated using this pathway who are at low risk of having a significant prostate cancer will receive counselling and be discharged back to

primary care for follow-up with triggers for re-referral. In general, men will be advised to get their PSA checked at 6 months and then annually with a trigger based on either PSA density (a PSA value which leads to the PSA density rising above 0.15 ng/ml/ml) or velocity (a PSA rise which is greater than 0.75 ng/year).[3] The PSA density is calculated by dividing the serum PSA level (ng/ml) by the volume of the prostate (ml). The prostate volume is normally measured from the MRI scan or transrectal ultrasound scan image. Both these parameters are indicative of significant prostate cancer.

PSA and MRI abnormalities alone are not enough to confirm a diagnosis of prostate cancer. A tissue diagnosis is usually mandated for curative treatment options to be considered. Prostate biopsy is generally carried out under local anaesthetic using ultrasound guidance via the transrectal or transperineal route.

After a prostate cancer diagnosis is made, the International Society of Urological Pathology (ISUP) prostate cancer grading system[21] is used to risk stratify the disease (see box 2, below).

Imaging is carried out to determine the extent of local and distant spread.

If no evidence of spread outside the prostate gland is shown the cancer is defined as localised disease. All new prostate cancer cases are discussed at an MDT meeting with at least core members (radiologists, oncologists, surgeons and cancer nurse specialists) present. Investigation results are reviewed and checked and decisions made regarding recommended treatment options.

In December 2021, NICE updated the risk stratification criteria for localised or locally advanced prostate cancer. Instead of low-, intermediate- and high-risk stratification terms being used alone, it is now recommended that risk categorisation using the Cambridge Prognostic Group criteria is used to guide the treatment recommendations made by urological cancer MDTs, see table 2, left.

Before making a decision about treatment, men will have the opportunity to discuss all their treatment options with the specialist MDT including the potential side effects as well as benefits.

Predict Prostate is an online individualised prognostic modelling tool, endorsed by NICE for men with newly diagnosed non-metastatic prostate cancer to help them decide between »

Table 2

Risk stratification and treatment recommendations for localised or locally advanced prostate cancer[3]

Cambridge Prognostic Group (CPG)	Criteria	Treatment recommendation
1	Gleason 6 (grade group 1) **and** prostate specific antigen (PSA) < 10 µg/L **and** stages T1-T2	● Offer active surveillance ● Consider radical prostatectomy or radical radiotherapy if active surveillance is not suitable or acceptable to the person
2	Gleason score 3 + 4 = 7 (grade group 2) **or** PSA 10-20 µg/L **and** stages T1-T2	● Offer a choice between active surveillance, radical prostatectomy or radiotherapy if radical treatment is suitable
3	Gleason score 3 + 4 = 7 (grade group 2) **and** PSA 10-20 µg/L **and** stages T1-T2 **Or** Gleason 4 + 3 = 7 (grade group 3) and stages T1-T2	● Offer radical prostatectomy or radical radiotherapy ● Consider active surveillance for people who choose not to have immediate radical treatment
4	One of: Gleason score 8 (grade group 4), PSA > 20 µg/L, stage T3	● Offer radical prostatectomy or radical radiotherapy when it is likely that the prostate cancer can be controlled in the long term ● Do not offer active surveillance
5	Two or more of: Gleason score 8 (grade group 4), PSA > 20 µg/L, stage T3 **Or** Gleason score 9 to 10 (grade group 5) **Or** stage T4	● Offer radical prostatectomy or radical radiotherapy when it is likely that the prostate cancer can be controlled in the long term ● Do not offer active surveillance

Box 2

The ISUP prostate cancer grading system[21]

Grade group	Gleason score	Morphological appearance
1	≤ 6	● Only individual discrete well formed glands
2	3 + 4 = 7	● Predominantly well formed glands with a lesser component of poorly formed/fused/cribriform glands
3	4 + 3 = 7	● Predominantly poorly formed/fused/cribriform glands with a lesser component of well formed glands
4	8	● Only poorly formed/fused/cribriform glands or ● Predominantly well formed glands with a lesser component lacking glands or ● Predominantly lacking glands with a lesser component of well formed glands
5	9-10	● Lacks gland formation (or with necrosis) with or without poorly formed/fused/cribriform glands

key points

SELECTED BY

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Prostate cancer is the most common cancer in men in the UK; each year around 52,254 men are diagnosed with the condition. The following symptoms that lead men to present to their GP should stimulate a discussion about prostate cancer risk: problems with urination; blood in the urine or semen; erectile dysfunction; pain in the hips, back, or bones; weakness or numbness in the lower limbs or loss of bladder control. It is crucial to explore the patient's reasons for attending as well as his fears and understanding of prostate cancer risk even if you suspect that any LUTS reported are due to another cause.

The risk of prostate cancer increases with age, most patients are aged over 50 at diagnosis. Black men have a lifetime risk of 1 in 4 compared with the estimated 1 in 8 risk faced by the general population. Prostate cancer risk is 2.1-2.4 times higher in men whose father has/had the disease and 2.9-3.3 times higher in men whose brother has/had the disease. Overweight men are at increased risk of being diagnosed with advanced prostate cancer.

An assessment of LUTS, relevant risk factors and past medical history are essential. NICE recommends performing a DRE; this will give an impression of prostate size. If the prostate feels malignant on DRE this should trigger a fast-track referral to secondary care, via a suspected cancer pathway referral even if the PSA is normal. A PSA test should also be offered to men with LUTS or an abnormal DRE.

Men who would be eligible for curative treatment will be offered an MP-MRI scan. This can identify abnormal areas in the prostate, consistent with significant prostate cancer which merit further investigation, better than untargeted prostate biopsies alone. If MP-MRI is performed first and abnormal lesions are identified, targeted biopsies of these lesions improve the detection of clinically significant prostate cancer. Men investigated using this pathway who are at low risk of having a significant prostate cancer will receive counselling and be discharged back to primary care for follow-up with triggers for re-referral. In general, men will be advised to get their PSA checked at 6 months and then annually with a trigger based on either PSA density or velocity. A tissue diagnosis is usually mandated for curative treatment options to be considered.

Radical prostatectomy aims to cure prostate cancer by removing the prostate gland in its entirety. Following radical prostatectomy, successful treatment should result in a PSA which is either undetectable or < 0.1 ng/ml. A PSA rise to > 0.2 ng/ml is considered indicative of recurrent disease and should trigger an urgent referral for specialist review. Following radiotherapy, successful treatment should result in the PSA being very low. Biochemical evidence of disease recurrence after treatment is defined as a rise of 2 ng/ml or more above the lowest PSA value after treatment. A rise above this level should trigger an urgent referral for specialist review so that salvage treatments may be considered if appropriate.

conservative and radical treatment strategies,[22] (www.prostate.predict.nhs.uk).

Cancer nurse specialists act as a point of contact for patients and support their holistic needs.

LOCALISED PROSTATE CANCER TREATMENTS

Active surveillance

Active surveillance is recommended for men with CPG 1 risk disease, should be offered as a management option to men with CPG 2 and considered in men with CPG 3 disease who choose to defer radical treatment because of the potential side effects. In clinical practice, patients' comorbidities are taken into account in addition to their preferences.

Patients on active surveillance have regular tests, scans and consultations to detect if their prostate cancer has spread. If there is evidence of disease progression either radiation or surgery can be offered. Active surveillance aims to enable men to avoid, or delay, the potential side effects from prostate cancer treatments such as incontinence, ED and bowel problems.

UK data from a randomised controlled trial showed that 50% of men on active surveillance (before the addition of MRI to the diagnostic pathway) did not require treatment within ten years of diagnosis.[23]

Other long-term prospective series have demonstrated the safety of this approach within a 15-year timeframe.[24] Recommended protocols are described in the NICE guideline.[3]

Radiotherapy

External beam radiation is more effective when given in combination with androgen deprivation therapy (ADT). Patients will be started on ADT before radiation treatment and continue this for a period after treatment. External beam radiation usually involves 4-6 weeks of daily outpatient treatment during the week.[25]

In brachytherapy very small radioactive seeds are inserted into the prostate gland under anaesthetic. The seeds release radiation into the prostate slowly over a 6-12 month period. ADT is not routinely given in combination with brachytherapy, the nuances of this and whether additional external beam radiation is required should be discussed by the specialist.

In high dose rate brachytherapy, temporary hollow needles are inserted into the prostate through which radiation is passed. The source of radiation is then removed. The side effects of radiation include urinary symptoms, bowel symptoms, ED, fatigue and those associated with ADT. Loss of libido, ED, hot flushes, changes in body composition including weight gain and gynaecomastia are commonly recognised side effects of ADT.

Surgery

Radical prostatectomy aims to cure prostate cancer by removing the prostate gland in its entirety. This is usually carried out using a robot-assisted approach in the UK;[4] although conventional laparoscopic and open surgery are still sometimes performed.

The surgeon will discuss the surgical approach and their outcomes with the patient. It has been shown that the experience of the surgeon, rather than the surgical modality, is the most important factor in oncological outcomes. Men undergoing minimally invasive surgery are more likely to have a shorter hospital stay and be less likely to require a blood transfusion after surgery. Centre reported outcomes after radical prostatectomy are published online and patients can access this information.[26] The side effects of surgery include incontinence and ED.

Watchful waiting

In watchful waiting treatment is not started unless symptoms caused by prostate cancer develop. Close monitoring is not carried out.

Some patients with localised prostate cancer may have significant comorbidity, which is more likely to affect their life expectancy. Others may not wish to undergo treatment.

Other treatment approaches

High intensity focused ultrasound and cryotherapy aim to eradicate prostate cancer by heating or freezing the prostate respectively. Currently there are no long-term follow-up data for these treatments and consequently they are not recommended by NICE outside clinical trials or centres which contribute their outcome data to registries.[3]

FOLLOW-UP

The aims of follow-up after treatment of localised prostate cancer are to detect and treat side effects of therapy and to monitor individuals' response to treatment. Follow-up should also address men's holistic needs whether physical, emotional or psychological. The care of patients beyond the diagnosis and treatment phases of cancer is termed survivorship and is increasingly important as the number of men living with, and beyond, a prostate

cancer diagnosis continues to rise exponentially.[27] The role GPs can play in prostate cancer survivorship programmes has been described in a previous article in this journal.[28] PSA is used to monitor patients after active treatment. The aim of follow-up is to identify recurrent disease at a stage where further treatment might be effective.

Although conventional follow-up was predominantly hospital based NICE now recommends that after 6 months' follow-up, a remote follow-up strategy for men with a stable PSA should be considered.[3] Patients should be empowered to self-manage their own follow-up where appropriate. When stable, prostate cancer patients who have undergone active treatment are discharged to primary care for follow-up and a clear management plan should be detailed by the discharging team.

Following radical prostatectomy, successful treatment should result in a PSA which is either undetectable or < 0.1 ng/ml. A PSA rise to > 0.2 ng/ml is considered indicative of recurrent disease and should trigger an urgent referral for specialist review.[29]

The rationale behind assessment and investigation in secondary care at this point is to establish whether or not any prostate cancer recurrence is confined to the pelvis. If there is no evidence of disease outside the pelvis then men may be offered salvage treatment with the intention of curing their disease. After surgery (a radical prostatectomy) the most common salvage treatment is radiotherapy.

Patients who have biochemical recurrence with no evidence of visible disease detected on imaging are counselled very carefully before making their treatment decision. All additional treatment carries a risk of side effects and the chance it may ultimately not cure their disease. Some men will have a greater probability of dying from other comorbidities or old age than their prostate cancer even if it has recurred. For these reasons many men may opt initially for close observation with PSA monitoring alone in secondary care.

Following radiotherapy, successful treatment should result in the PSA being very low. Biochemical evidence of disease recurrence after treatment is defined as a rise of 2 ng/ml or more above the lowest PSA value after treatment. A rise above this level should trigger an urgent referral for specialist review so that salvage treatments may be considered if appropriate. Salvage radical prostatectomy is the most common treatment offered after failed radiotherapy.[30] However, the risk of side effects impacting on quality of life after salvage surgery is significantly higher than after surgery as a first-line treatment.

CONCLUSION

GPs play a pivotal role throughout patient pathways from facilitating early diagnosis of clinically significant prostate cancer to long-term follow-up. GPs have expertise in managing patients with coexisting chronic medical conditions and supporting patients to lead as healthy and active a life for as long as possible. Men who are prostate cancer survivors value a holistic approach and it is important for GPs to be aware of individuals' oncological, functional and psychological needs and where to signpost patients for additional support locally if required.

The American Cancer Society has issued guidelines for GPs responsible for managing men with prostate cancer in the community. They provide a comprehensive summary of the evidence base for managing the wide variety of long-term effects survivors may present with.[31]

Competing interests: None

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Useful information

Prostate cancer risk calculator tools
SWOP
The Prostate Cancer Research Foundation
www.prostatecancer-riskcalculator.com

The Prostate Cancer Prevention Trial Risk Calculator
https://riskcalc.org/PCPTRC