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The role of PSA in detection and management of prostate cancer

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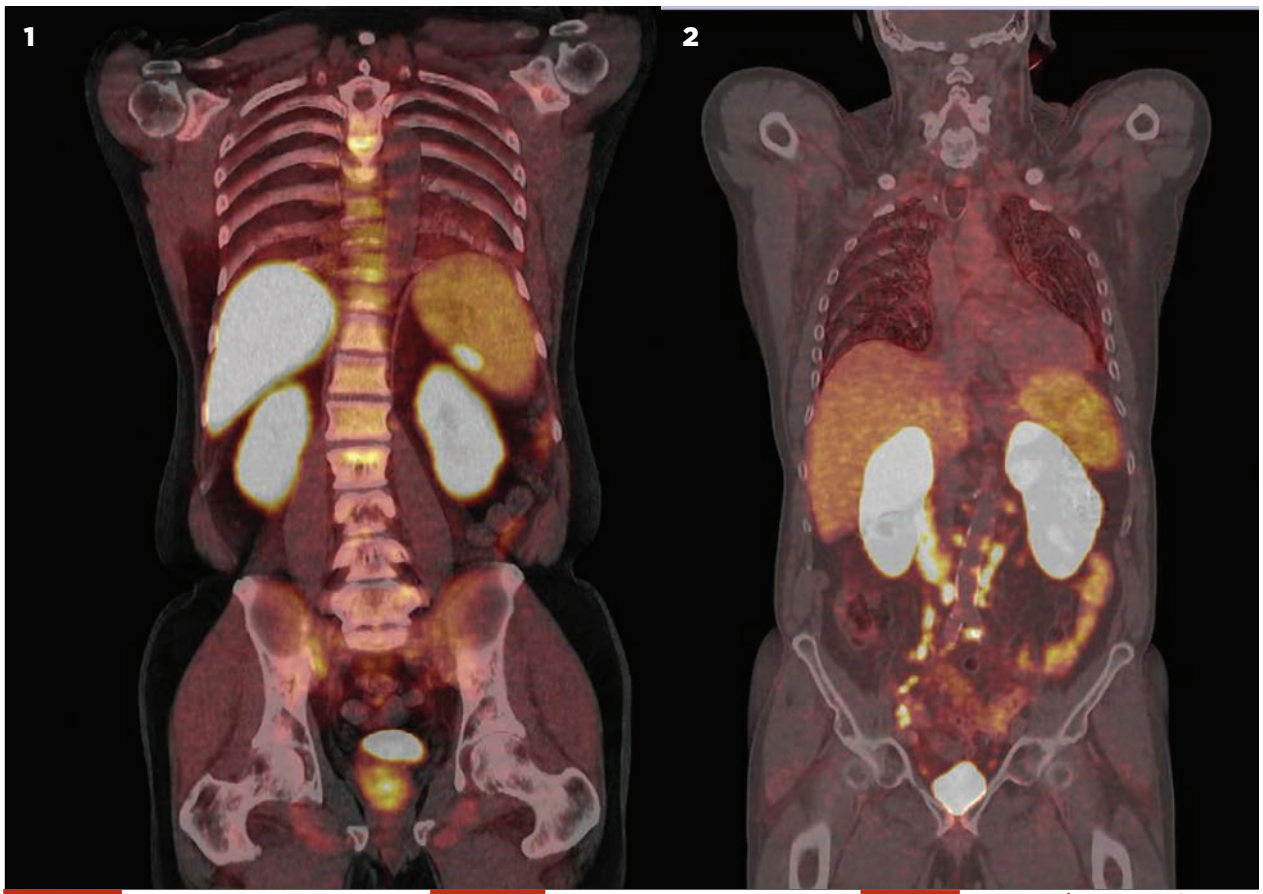


FIGURE 1 (left) Choline PET CT scan demonstrating bone metastases from prostate cancer

FIGURE 2 (right) PMSA PET CT scan demonstrating lymph node metastases from prostate cancer

What are the pros and cons of PSA testing?

RECENTLY THE PROSTATE CANCER RISK MANAGEMENT PROGRAMME (PCRMP) PUBLISHED UPDATED guidance on prostate specific antigen (PSA) testing for primary care[1] and the NHS screening committee has reviewed the evidence surrounding the utility of PSA screening.[2] NICE published updated guidelines on the diagnosis and management of prostate cancer in 2014.[3]

PSA is a glycoprotein responsible for liquefying semen. It is expressed in both benign and malignant disorders that impact upon the integrity of the epithelial cells of the prostate. As the result of alterations in the architecture of PSA secreting prostatic glands in conditions such as prostatitis and benign prostatic enlargement (BPE), as well as prostate cancer, PSA is able to leak out, leading to increased levels in the bloodstream.

The PSA test clearly provides the opportunity for clinically relevant prostate cancer to be detected at a stage when treatment options are greater and outcomes may be improved. However, in some patients the PSA test may lead to investigations which can identify clinically insignificant cancers which would not have become evident in a man's lifetime. Nowadays however, these cases are managed by active surveillance. In addition, a raised PSA may often indicate BPE, and this may provide an opportunity for treatment of this condition before complications develop.

There are both advantages and disadvantages for men of having a PSA test (see box 1, p18), and these should be clearly explained to patients before the test is requested.

What other biomarkers are available?

How can detection of early prostate cancer be improved?

OTHER BIOMARKERS

Recent research has been focused on identifying biomarkers to improve stratification of men with low-risk versus high-risk aggressive disease, so that men can be managed appropriately, minimising the potential harm of overdiagnosis and overtreatment.[4,5] »

There are two promising urinary RNA biomarkers, prostate cancer antigen 3 (PCA3) and fusion gene TMPRSS2:ERG, both of which aim to distinguish between men with low-risk (indolent) and those with aggressive (clinically significant) cancers.[6]

PCA3 is highly overexpressed in more than 95% of prostate cancers, or up to 100 times greater in men with cancer than in those with a normal prostate.[7,8] A systematic review found that the sensitivity of the PCA3 test (54-82%) was found to be less than PSA testing (81-98%) but the specificity for PCA3 was much better than for PSA (66-89% vs 5-28%).[9] Potentially, the higher specificity would reduce overdiagnosis and overtreatment of lower risk cases. A weakness of these studies was that none of them used PCA3 scores as a screening test to indicate the need for prostate biopsy, making it difficult to interpret its clinical value. However, PCA3 has also been considered as a reflex test for diagnosing prostate cancer in men who have already had a prostate biopsy, and found to be useful in reducing the rebiopsy rate.[10]

Prostate gene fusion between TMPRSS2 and ERG, an ETS (e-twenty-six) transcription factor is also overexpressed in about 50% of prostate cancers from PSA-screened cohorts.[11,12] However, population-based cohorts have shown a much lower prevalence of 15%.[12] The reasons for these differences in prevalence are not well understood, but the prevalence of TMPRSS2:ERG was found to be lowest in men with early stage tumours (T1), suggesting this marker may be useful in identifying men who harbour more aggressive disease.

Further research is still needed to understand fully its clinical utility in screening and its potential use in prostate cancer management as well as its prognostic utility.

Box 1

Pros and cons of PSA testing

Potential benefits of having a PSA test

- It may lead to the detection of cancer before symptoms and spread develop
- It may lead to the detection of cancer at an early stage when the cancer could be cured or treatment could extend life
- Repeat PSA tests may provide valuable information, aiding a prostate cancer diagnosis
- A raised PSA value may identify benign prostatic hyperplasia – a common cause of lower urinary tract symptoms

Potential limitations or risks of having a PSA test

- The PSA test is not diagnostic: those with an elevated PSA level may require further investigation, possibly a TRUS-guided prostate biopsy and histology to confirm the presence of prostate cancer
- PSA is not tumour specific within the prostate.

PSA levels can increase due to a number of other factors:
— Benign prostatic enlargement
— Older age, PSA levels normally increase with age
— Prostatitis (infection or inflammation of the prostate gland)
— Ejaculation may increase PSA levels for a short time

PSA levels can be influenced by drugs such as 5-alpha-reductase inhibitors (e.g. finasteride or dutasteride)

Obese men tend to have lower levels of PSA

- The PSA test may give false-positive results. A man may have an elevated PSA level but have no cancer. About 75 out of every 100 men who have an elevated PSA level have a false-positive result
- The PSA test result may not be elevated and therefore provide false reassurance. A one-off test is therefore not reliable enough to provide complete reassurance
- The PSA test may lead to the identification of prostate cancers which might not have become clinically significant in the man's lifetime
- A single PSA test will not distinguish between aggressive tumours which are at an early stage but will develop quickly and those which are not, but further tests are likely to provide this information

IMPROVING DETECTION OF EARLY DISEASE

False-negative rates with standard TRUS-guided biopsy can be as high as 45%.[13] Up to half of men who are initially diagnosed with low-risk disease are under-staged and actually have a higher burden of high-risk disease. However, the utilisation of multiparametric MRI (mp-MRI) before prostate biopsy has the potential to improve the accuracy of the diagnosis and staging of prostate cancer. Lesions seen on a pre-biopsy mp-MRI can be used to select appropriate targets for TRUS or template biopsy, and may add additional information that can help decide what treatment should be used to manage patients with low- and intermediate-risk disease.[14,15]

'The PSA test provides the opportunity for clinically relevant prostate cancer to be detected at a stage when treatment options are greater and outcomes may be improved'

Triage of men with clinical suspicion of prostate cancer (elevated PSA and abnormal DRE) to mp-MRI prior to prostate biopsy could increase the detection of men with clinically significant cancer that is likely to require treatment. This strategy could reduce the number of men with clinically

insignificant disease who undergo unnecessary biopsy and treatment. This would also reduce the rate of biopsy-related complications, including infections, which occasionally can be severe.[16,17]

The use of the transperineal as opposed to the transrectal route for biopsy can also reduce the risk of infection.

NICE guidelines[3] currently recommend that men whose biopsies are negative on TRUS 10 to 12 cores biopsy should be further evaluated with mp-MRI. If the man is negative on mp-MRI, then another biopsy should not be recommended unless there are other significant risk factors. Current evidence suggests this strategy will reduce the number and frequency of repeat biopsies required compared with routine systematic TRUS re-biopsy, and more information on this, and on the utility of mp-MRI, should soon to be available from the PROMIS trial which is due to report later this year.[18]

'The use of mp-MRI before prostate biopsy has the potential to improve accuracy of the diagnosis and staging of prostate cancer'

TREATMENT OPTIONS FOR LOCALISED DISEASE

NICE has published guidance on the various treatment options for localised prostate cancer.[3] Evidence suggests that any benefit to a man from undergoing radical treatment for prostate cancer is likely to be maximal for those whose comorbidities and age suggest a life expectancy of more than ten years. Men with advanced prostate cancers are less likely to benefit from radical treatment alone.

Active surveillance and active monitoring

During active surveillance or monitoring the patient is followed up regularly by an oncologist or urologist. This option is offered to men who are generally younger and fitter and who wish to avoid the possibility of unnecessary treatment of indolent cancers.

The downside is that potentially disease may spread locally and advanced disease may develop which may be more difficult to treat.

The aim is to monitor those with stable disease and identify where radical treatment may be appropriate for those whose cancer progresses. Men on active monitoring will be monitored by serial PSA tests. Men on active surveillance will be monitored by serial PSA tests, mp-MRI and repeat prostate biopsies. Radical treatment with curative intent is offered if there are signs of disease progression.[19]

Radical prostatectomy (open, laparoscopic and robotic)

The aim of radical prostatectomy is to remove the entire prostate gland and thereby cure the disease. Complete tumour excision is not always achieved and approximately 20% of men go on to develop biochemical or clinical recurrence of the disease. Recurrence does not necessarily equate with death from prostate cancer, as second-line treatment with radiotherapy is an option. Complications of surgery include sexual dysfunction and stress urinary incontinence.

A study in the *BMJ* in 2014 reported improved survival in patients treated with surgery compared with those treated by radiotherapy.[20]

Radiotherapy (external beam and brachytherapy)

Radiotherapy such as external beam radiotherapy (EBRT) and brachytherapy also aims to cure the disease. EBRT involves an external source of radiation targeted at the tumour.

Short-term side-effects relate mainly to bowel and bladder problems from the radiation. Longer-term complications include sexual dysfunction and urinary problems as well as a significantly increased risk of secondary cancers in the pelvis. This treatment is not usually recommended for men with less than ten years' life expectancy.

Brachytherapy may be given by two very different techniques. Low dose rate (LDR) brachytherapy involves the permanent implantation of tiny radioactive seeds into the prostate to deliver a high radiation dose into the gland.

High dose rate (HDR) brachytherapy requires fine catheters to be inserted into the prostate, through which a radioactive source is temporarily passed. Although the isotope used has a higher dose rate, the overall dose is lower than that given by LDR brachytherapy, so it is usually given in conjunction with EBRT. This latter technique is much more recent, with limited clinical data, and is usually reserved for patients with high-risk disease. Possible side-effects include urinary symptoms and sexual dysfunction.

Brachytherapy is best avoided in men with pre-existing lower urinary tract symptoms and bladder outflow obstruction as it may precipitate acute urinary retention.

High-intensity focused ultrasound and cryotherapy

High-intensity focused ultrasound (HIFU) and cryotherapy are newer radical therapies for the treatment of localised prostate cancer and are not currently recommended other than in the context of controlled clinical trials. HIFU aims to cure the disease by heating the prostate gland using ultrasound waves to cause tissue damage by mechanical and thermal effects as well as by cavitation. Cryotherapy aims to cure the disease by freezing the prostate gland.

QUALITY OF LIFE

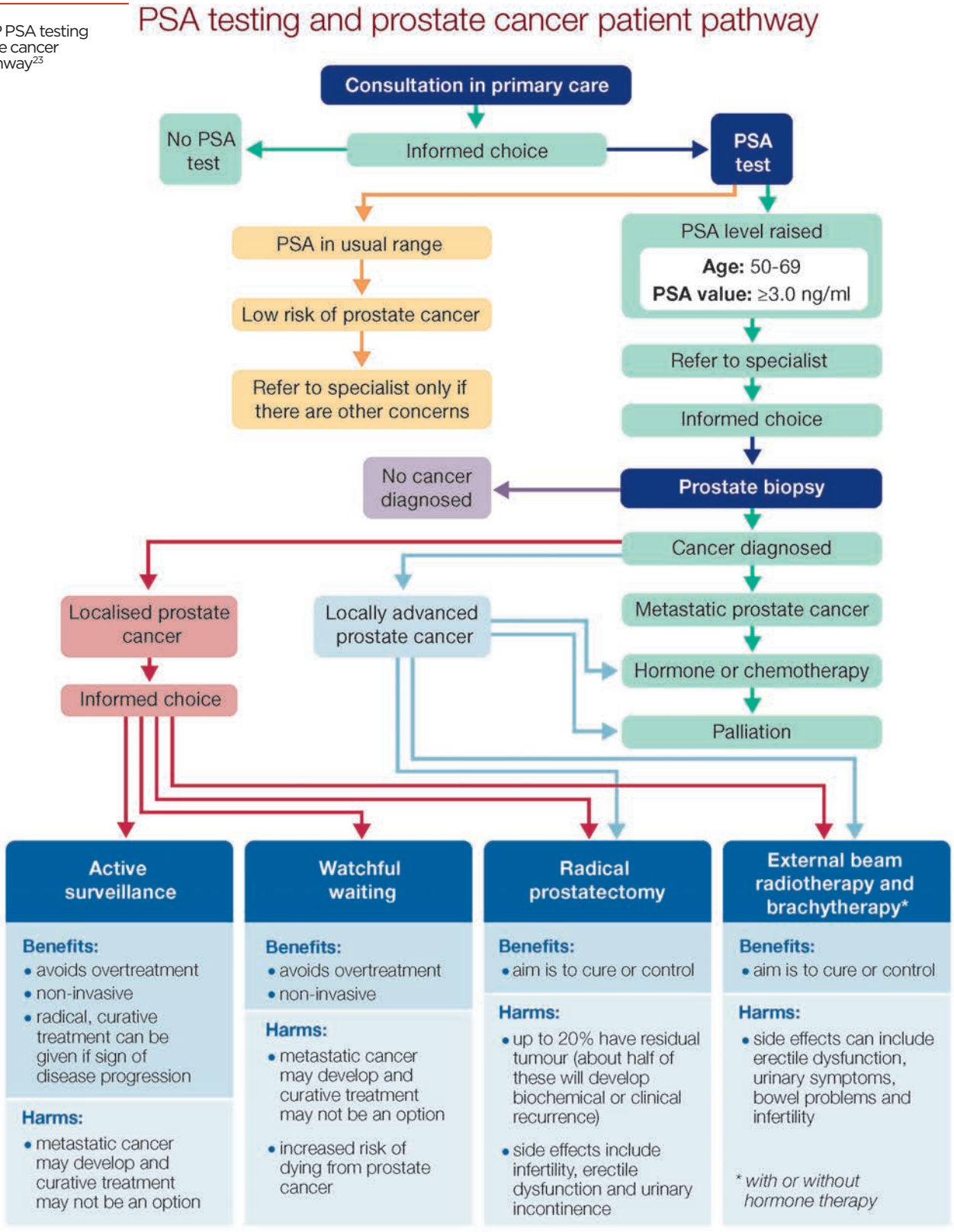
Before choosing a treatment regimen, it is important that men should be appropriately counselled about the important quality of life differences between the options.

'The downside of active surveillance or monitoring is that disease may spread locally and advanced disease may develop which may be more difficult to treat'

Both surgery and radiotherapy aim to extend life by curing the cancer. However, there is a trade off as surgical removal of the prostate can result in loss of erectile function, ejaculation, fertility, and urinary continence. Radiotherapy is associated with persisting lower bowel disturbance and an increased incidence of secondary malignancies.

Active surveillance may result in increased anxiety and the psychological stress of a cancer diagnosis. »

FIGURE 3
The PCRMP PSA testing and prostate cancer patient pathway[23]



www.gov.uk/government/uploads/system/uploads/attachment_data/file/509193/Prostate_Summary_Sheet.pdf

The PCRMP resources also include a patient information sheet and full evidence review: see **www.gov.uk/guidance/prostate-cancer-risk-management-programme-overview**

key points

SELECTED BY

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The prostate specific antigen (PSA) test clearly provides the opportunity for clinically relevant prostate cancer to be detected at a stage when treatment options are greater and outcomes may be improved. However, in some patients the PSA test may lead to investigations which can identify clinically insignificant cancers which would not have become evident in a man's lifetime. In addition, a raised PSA may often indicate benign prostatic enlargement, and this may provide an opportunity for treatment of this condition before complications develop.

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NICE guidelines currently recommend that men whose biopsies are negative on TRUS 10 to 12 cores biopsy should be further evaluated with mp-MRI. If the man is negative on mp-MRI, then another biopsy should not be recommended unless there are other significant risk factors.

Evidence suggests that any benefit to a man from undergoing radical treatment for prostate cancer is likely to be maximal for those whose comorbidities and age suggest a life expectancy of more than ten years. Men with advanced prostate cancers are less likely to benefit from radical treatment alone.

The lack of sensitivity and specificity that characterises PSA testing in the initial diagnosis of prostate cancer largely disappears after treatment of localised prostate cancer, especially after surgery. Three monthly PSA measurement is usually recommended for the first year after primary treatment. Subsequently less frequent testing is required. A PSA rise after primary treatment usually indicates biochemical recurrence and often the need for further therapy.

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MONITORING AND FOLLOW-UP

The lack of sensitivity and specificity that characterises PSA testing in the initial diagnosis of prostate cancer largely disappears after treatment of localised prostate cancer, especially after surgery. Three monthly PSA measurement is usually recommended for the first year after primary treatment. Subsequently less frequent testing is required.

A PSA rise after primary treatment usually indicates biochemical recurrence and often the need for further therapy. In this context it has often been difficult to determine the exact location of the recurrence, but recently the availability of PMSA PET CT scanning has helped differentiate between disease recurrence in the prostate bed, lymph nodes or bones, see figures 1 and 2, p17. This information can facilitate the selection of second-line treatment, including hormone therapy or radiotherapy.

CONCLUSIONS

The debate about the benefits and potential risks of PSA testing seems certain to continue. The two major studies of PSA as a screening test for prostate cancer did not utilise mp-MRI in advance of the biopsy to target the lesion and select out those men with higher risk disease who are more likely to benefit from treatment.[21,22] Had they done so it seems likely that a greater benefit would have been seen, and the risk of overtreatment of men with clinically insignificant disease would have been greatly reduced.

In any case, nowadays, men with low volume, low-risk, Gleason pattern 3+3=6 cancers are nearly all managed initially by active surveillance, at least in the first instance, so the consequences of overdiagnosis are very much less significant.[3]

Current guidance from the PCRMP recommends that GPs refer informed men between the ages of 50 and 69 with a PSA value $\geq$ 3.0 ng/ml for further assessment including possible mp-MRI and biopsy, see figure 3, opposite.[23]

After initial treatment, PSA testing at regular intervals during follow-up is of considerable value, as a rising PSA usually indicates a recurrence and second-line therapy can then be deployed.

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Useful information

Prostate Cancer UK
www.prostatecanceruk.org

The Urology Foundation
www.theurologyfoundation.org