

# ACTIVE SURVEILLANCE APPROACH TO PROSTATE CANCER

The aggressiveness of prostate cancer varies considerably. Active surveillance aims to minimise unnecessary treatment and help define the factors that contribute to disease outcome.



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## Prostate cancer: Occurrence and risk

- Prostate cancer is the most common cancer in UK men, with 30,000 new cases diagnosed each year.
- As many as 80% of men develop prostate cancer during their lifetime, but in most cases it does not cause any ill health. Around 6% of men experience symptoms of the disease, while 3% of men die of prostate cancer.
- Screening for prostate cancer using the Prostate Specific Antigen (PSA) blood test remains very controversial but, for better or worse, PSA testing of healthy men is increasing.
- The first randomised trial comparing surgery versus watchful waiting in men with prostate cancer, reported in 2005, showed a 5% survival advantage for surgery but with a 28% risk of urinary incontinence and a 35% risk of impotence.

## Active surveillance of early prostate cancer

Most prostate cancers will never cause any problems and do not need any treatment. On the other hand, some prostate cancers will grow and spread, and become life threatening. Unfortunately, it can be difficult to distinguish between these two types of the disease. One solution is to treat all cases, 'to be on the safe

side'. However, while curative treatment for prostate cancer may or may not improve a man's longevity, it can certainly have a big impact on his lifestyle with side-effects including impotence and incontinence. Ideally, treatment should be restricted to those who need it. Active surveillance aims to individualise the management of early prostate cancer by selecting only those men with significant cancers for curative treatment.

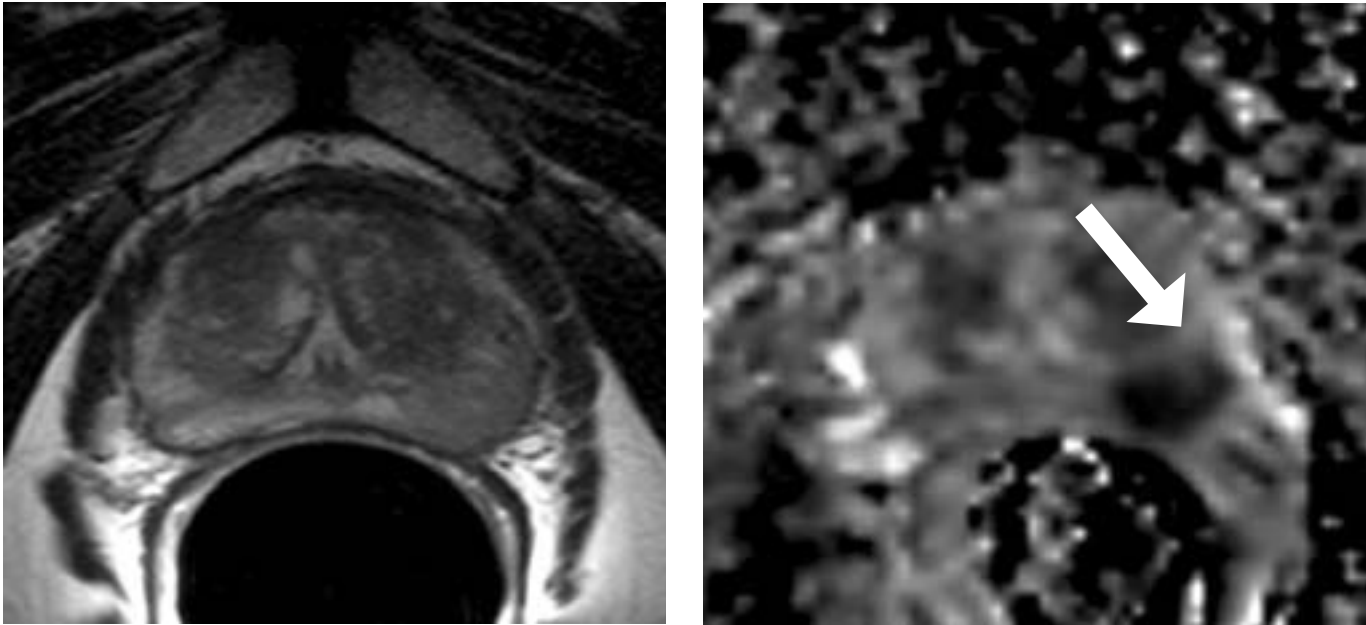
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**Patients on active surveillance are closely monitored using PSA blood tests and repeat prostate biopsies. The choice between continued observation and curative treatment is based on evidence of disease progression during this monitoring.**

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## Studies at the Royal Marsden

In 2002, we began a prospective study of active surveillance of prostate cancer at the Royal Marsden. This initiative, funded by the National Cancer Research Institute Southern Prostate Cancer Collaborative, has grown to become the largest study of its kind and has already recruited over 300 men with prostate cancer. Currently,



**Figure 1.** Diffusion-weighted magnetic resonance imaging (DW-MRI) provides image contrast through measurement of the diffusion properties of water within tissues. The white arrow indicates an area of abnormal water diffusion within the prostate gland. It is possible that DW-MRI may provide a better indication of prostate cancer behaviour than conventional MRI techniques.

around 20% of these men have received curative treatment, while the rest have continued on observation. None of these patients have developed any symptoms from prostate cancer, or any spread of the disease, and none have died of prostate cancer. These preliminary results are most encouraging and have established the feasibility of active surveillance for men with localised prostate cancer.

The initial findings from the Marsden active surveillance study suggest that the size of a man's prostate gland may be more important than had previously been appreciated. As men get older, their prostate gland enlarges but the degree of enlargement can vary as much as 10-fold between individuals. We found that the ratio of the PSA level in the blood to the size of the prostate gland, which is known as the 'PSA density', is an important predictor of disease progression in men with prostate cancer undergoing active surveillance. If this finding were to be confirmed, it would provide one very simple way of helping to individualise treatment for men with localised prostate cancer.

Those with a small prostate might be better suited to immediate curative treatment, while observation may be more appropriate for those with a larger prostate. However, there will always be exceptions to this general rule, and it remains vital to identify better predictors of individual prostate cancer behaviour.

At present, repeat prostate biopsy is the gold standard method to identify tumour progression, and hence the need for treatment, in men on active surveillance. Prostate biopsy can be uncomfortable for patients, and also carries risks of bleeding and infection. In collaboration with Dr Nandita deSouza (Cancer Research UK Clinical Magnetic Resonance Research Group at The Institute), we are evaluating novel magnetic resonance techniques in men on active surveillance to see whether they can provide a non-invasive indicator of tumour progression (see article by Professor Martin Leach and Dr Nandita deSouza, p.34).

Another trial (designated Prostate START) is due to open at the Royal Marsden during 2006. Prostate START is an international, multicentre study that will compare active surveillance

against standard curative treatment for prostate cancer in 2,000 men. The main endpoint of the trial, to be coordinated at The Institute's Clinical Trials Unit (UK Principal Investigator: Cr Chris Parker), is long-term survival.

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**It is hoped that active surveillance will avoid 'unnecessary' treatment, and its associated side-effects, without detriment to long-term survival.**

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### **Psychological impacts of active surveillance**

One concern about active surveillance is that men may find it difficult to deal with the knowledge that they have a cancer that is not being treated. Dr Maggie Watson and Miss Katrina Burnet, from the Psychology Research Group at The Institute, are evaluating the prevalence of anxiety and depression in men on active surveillance, in order to better understand the underlying

psychological factors. Their initial findings are reassuring. It appears that men on active surveillance for prostate cancer are no more anxious than those receiving active treatment, or indeed than UK cancer doctors!

**Active surveillance provides an excellent opportunity for research to identify markers of prostate cancer behaviour.**

**Markers of prostate cancer behaviour**

Men taking part in the Royal Marsden study have given samples of blood, urine and prostate tissue for research. These samples are uniquely valuable because, unlike samples in any other prostate tissue bank, they are linked to information on the natural history of each individual cancer. They are now being used in a range of studies, both within The Institute of Cancer Research and elsewhere, to evaluate prostate cancer biomarkers. For example, Dr Sameer Jhavar, working in Professor Colin Cooper's laboratory at The Institute, has devised a new technique that allows prostate biopsy tissue to be used to make microarrays. This technique

enables many candidate biomarkers to be evaluated rapidly and makes highly efficient use of the small amounts of prostate tissue available. Dr Jhavar is now studying biopsies from the active surveillance patients in this way in order to identify which pattern of markers best predicts prostate cancer behaviour.

**Accurate prediction of individual prostate cancer behaviour will be invaluable in helping to decide which men need treatment and which do not.**

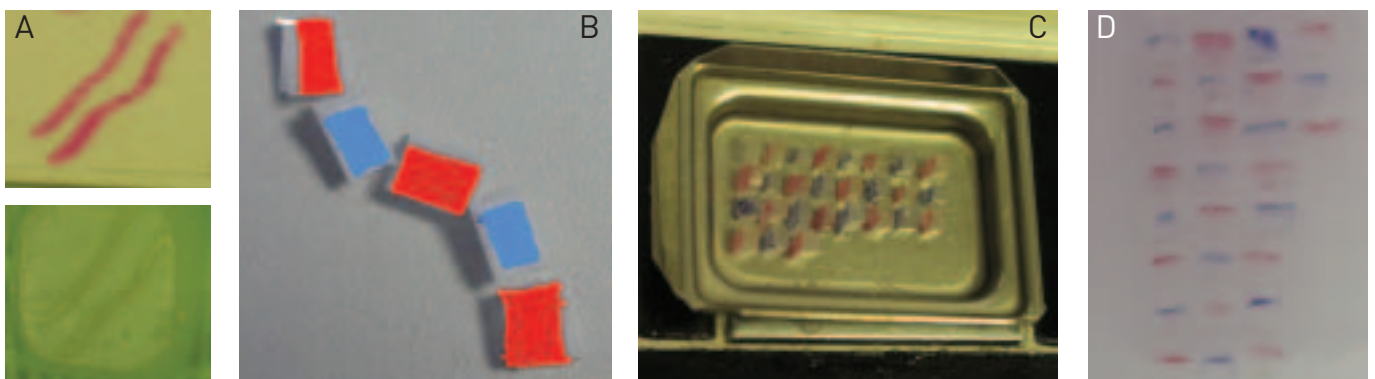
**The future of active surveillance**

In the future, active surveillance could be the setting for trials to test low-toxicity interventions designed not to eradicate the disease but rather to alter its natural history. At present, using regular PSA testing in healthy men, it is possible to diagnose prostate cancer 10-15 years before it would cause any symptoms. A well-tolerated intervention that slowed the rate of progression still further could turn prostate cancer into a chronic condition to be controlled, rather than a disease to be

surgically excised. Several nutritional factors have been implicated in the development and progression of prostate cancer. For example, initial studies have suggested that supplements containing selenium, vitamin E or vitamin D may reduce the risk of the disease.

**We plan to study the effect of nutritional supplements on the rate of disease progression in men with localised prostate cancer on active surveillance.**

In summary, active surveillance is an attractive and increasingly popular approach to the management of early prostate cancer. It is also an ideal setting for research to identify new markers of prostate cancer behaviour. Such markers could transform our ability to target treatment to those who need it. A long-term hope is that nutritional intervention studies in men on active surveillance could lead to a whole new way of managing prostate cancer, aimed at disease control rather than cure. This would be a major step forward because it would avoid the burden of adverse effects such as impotence that are associated with conventional surgical treatment.



**Figure 2.** Prostate needle biopsies (A) are usually sectioned longitudinally.

In order to create biopsy tissue microarrays, the biopsies are cut into multiple chequers (B) and embedded in a new paraffin block (C).

They can then be sectioned transversely (D), enabling multiple tissue markers to be assessed in each case.