

Prostate cancer screening

Mark Emberton interviewed by Damien Bolton

Mark Emberton, FRCS (Urol)
Reader & Honorary Consultant Surgeon
Division of Surgical & Interventional Sciences
University College London, England



Damien Bolton, FRACS
Associate Professor & Chairman of Urology
The Austin Hospital
Melbourne, Australia



1. Is there data in place to really provide justification for prostate cancer screening? After all it is advocated primarily by interest groups rather than cancer or national urologic groups who practice a more evidence based approach.

When we learn about screening in medical school we are told that a number of conditions have to be fulfilled prior to a screening programme being implemented. There is no need to go over them here as most of us have learnt in the past to be able to recite them for the purpose of passing an exam. In some areas of medicine, such as the population screening for hypertension with the aim of reducing cardiovascular morbidity and death through the use of hypotensive agents, it is generally felt that these conditions have been met.

The history of identifying sub-clinical cancers by screening populations reveals a rather different picture. Most screening programmes, irrespective of the disease area or the country in which they were implemented, were initiated on the back of either lobbying by interested groups or by policy initiatives that were politically motivated.

Cervical and breast cancer screening programmes are examples of these. This is not to say that these programmes do not confer net benefit on the community. They probably do, but at a cost. The argument about just how much benefit and at what cost continues to be played out in the leading journals.

It is worth noting that things are changing. In the UK, a two yearly repeated screen in 50-70 year olds for colorectal cancer via the use of fecal occult bloods has been proposed using evidence based and cost-benefit approach. This has been widely applauded by experts, patient groups and policy

makers. All that is currently missing is the allocation of adequate funding from central government.

2. We still face the issue that historically death rates from prostate cancer are relatively low: well below cardiovascular disease and less than colorectal carcinoma. Is there likely to be sufficient benefit to justify the cost?

Most evidence-based analyses, irrespective of the country of origin, have come out against prostate cancer screening for precisely this and other reasons that are explored below.

3. Should we be looking to screen an entire male population above a certain age, or would we be better off focussing on at-risk groups e.g. those with a family history of prostate cancer?

To quote Mike Barry, screening for prostate cancer irrespective of the method used increases the rate of prostate cancer rather than decreases it. Screening for colorectal cancer does the opposite given that it attempts to identify and treat premalignant lesions before they can be called a cancer.

I don't think prostate cancer screening will become recommended on an evidential basis until we have a relatively non-invasive way of identifying clinically significant disease from that which might be considered incidental.

4. If we go down the path of population based screening what PSA level is likely to be critical in determining the need for a biopsy: the standard upper limit of the assay?, an age related level?, above the 50th centile?

In a sense this relates to the previous question. The arguments recommending one policy over another fill our journals and populate our conferences, but they have not got us very far. It is likely that the lower our PSA thresholds and the greater the intensity of sampling will increase the proportion of men that are identified who would not have gone on to develop clinical disease in their lifetime. Just how many men we need to screen and then treat in order to prolong one life is a judgment that urologists, policy makers and taxpayers will eventually have to make. For low risk disease, Larry Klotz has recently estimated that 100 men with low risk prostate cancer would have to be treated in order to prolong one life.

5. What role do you see for free/total PSA ratios as a determinant for the need for prostate biopsy? Could you provide any justification as many do use this as a guide on when to biopsy?

I have always found PSA derivatives of this type difficult to use in clinical practice. The traditional advice has been that free/total PSA ratios are of greatest utility in helping to decide on whether or not to offer a man a re-biopsy. Yet, looking back, it is rare if ever that the judgement to re-sample a man has been based on this ratio alone.

There are many other strong drivers in the decision to re-biopsy or defer re-biopsy in a man who is considered to either have progressed (T0 to T1-2) or to have been the victim of a false negative test. The size of the gland, the extent of the initial sampling (number, length and position of cores), the presence or absence of inflammation, HGPIN or atypia, the age and comorbidity of the patient, the wishes of the patient in terms of the degree of certainty that he desires are all important factors.

I find, as I suspect so do many others, that the decision to re-biopsy is a complex one and relies therefore on old fashioned clinical judgement. That judgement can certainly be influenced by PSA ratios but it rare for it to be the key determinant. Once the decision is made that the patient may be at high risk of either progression or of an initial false negative – it is usual to want to bring in as much certainty as possible. This usually results in a second set of biopsies being requested.

6. How about those patients with an elevated PSA and a negative biopsy: do we really know what is best to advise them in terms of future prostate cancer screening?

Most urologists have come to realize that once a patient has a raised PSA they are in the system for life. Even if they test negative on biopsy, they will invariably be asked back in 6 months or a year for a further PSA estimation. The reassurance from testing negative never seems to be realized. Such is the concern of a false negative that many of these will be invited back for further sampling.

I think patients should be told the truth about this. A high PSA carries a prior probability of about 25% of detecting prostate cancer were they to proceed to biopsy. A negative biopsy results in a reduction of that probability to about 10%, were they to proceed to a second biopsy. A negative third set to less than 5%. Taken literally patients should really be asked, 'Just to what level would you like your risk reduced to?' The intensity of verification could then be tailored to their expectations and desires. Few of us do this. Instead we adopt the position of illegitimate certainty.

The reason is that we wish to reassure patients who are anxious about their prospect or otherwise of having prostate cancer. In our efforts to be humane doctors we tend to use phrases like 'You are all clear', 'It's all benign', '. The tests are fine, nothing to worry about'. When, what we mean is that no cancer was detected on the level of sampling that was undertaken.

7. What place is there for DRE as a screening tool in conjunction with serum PSA level? And also for TRUS alone?

Both sensitivity and specificity of both of these methods make them unlikely candidates to help us differentiate between clinically important and incidental disease.

I have great hopes for multi-sequence MRI as an, admittedly expensive, but essentially non-invasive method of screening. Perfusion and diffusion MRI using contrast media are increasing the specificity of peripheral zone tumors. 3T MRI is increasing the resolution and therefore the sensitivity of detection. MRI-spectroscopy and metabolic MRI may help in selecting out the higher grade lesions. For me, 2005 will be remembered as the year that MRI first outperformed prostate biopsy in the detection of prostate cancer both radio-recurrent and primary disease.

Non-invasive molecular or genetically based tests may also prove to be useful in selecting out men with high risk disease. It is obviously too early to have a view on this as the candidate tests are in the process of being introduced in phase I/II trials at present.

8. The target group chosen probably remains the key determinant of the success of any screening program, so whom should we be excluding from population based screening: men with previous cardiovascular disease? a past history of other malignancy? diabetics? no-one?

I find this increasingly difficult to have any control over. In the past the teaching was that if a man had a life expectancy of less than 10 years he was better left alone in that his overall probability of dying of other competing causes was considerably higher than the outside possibility of a prostate cancer specific death.

Men, often enter the screening cascade prior to being seen by a urologist and want to be as sure as they can be that their high PSA is not due to prostate cancer. Even if one were to give them the FTU lecture it is unlikely that many men will simply walk away. In my experience having explicit thresholds at which further evaluation is denied has led to nothing but misery and very disgruntled patients.

9. Do you see potential for better results from screening in the future with the advent of newer ultra sensitive PSA assays, or with the more recently identified PSA-like glycoprotein's?

The results from screening will only improve when we are able to improve on our number needed to treat ratio. The route to this is by better understanding of the determinants of disease aggressivity or by tests that select out those tumors that are more likely to reduce a person's life expectancy

10. In relation to using prostatic fluid in relation to detection : if an accurate non-invasive test were available coupled with a non-invasive effective treatment, how would this would change the issue?

This is a great question and probably gets to the heart of the screening issue. In their recent provocative article on the desirable attributes of screening

(BMJ 2006; 332: 11481150), Patrick Bossuyt and colleagues highlight the importance of consumer preferences when assessing the worth of population screening programmes. If the true harms (invasiveness, bleeding, pain, sepsis) of the screening test were reduced and its accuracy increased (fewer false negatives and reduced sensitivity for incidental clinically insignificant disease) there would be few if any reasons not to have the test. A molecular or genetically based test run on expressed prostatic secretions or better still ^ urine ^ might fulfil most if not all of these criteria. If a positive result were to be combined with a treatment that had virtually no side effects we are in danger of getting into what might be described as screening perfection. At present this might seem some years away. It is, however, likely to happen at some point in the future given the enormous investment in molecular diagnosis and the future possibility of image guided therapies that will treat the cancer and leave the surrounding (normal) urinary tract untouched.

11. What is it really going to take to make prostate cancer screening a valid proposition in the short -term?

Knowledge and agreement on what truly represents clinically important disease compared to that which is merely incidental.
