UROLOGICAL SOCIETY OF
AUSTRALIA AND NEW ZEALAND
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Urological Society of Australia and New Zealand PSA Testing Policy 2009

Executive summary

1. Prostate cancer is a major health problem and is the second leading cause of male cancer deaths in Australia and New Zealand. The Urological Society of Australia and New Zealand (USANZ) currently does not recommend the use of mass population-based Prostate Specific Antigen (PSA) screening as public health policy, as published studies to date have not taken into account the cost effectiveness of screening, nor the full extent of over-detection and over-treatment.
2. However, based on recent data from one of two large randomised screening studies, there was a reduced risk of prostate cancer death with PSA testing and treatment in those patients in the 55-69 year age group after 7-8 years. Therefore PSA based testing, together with digital rectal examination (DRE), should be offered to men in this age group, after providing information about the risks and benefits of such testing.
3. Men under 55 years of age are less likely to be diagnosed with prostate cancer but, if they are diagnosed, they are more likely to die from prostate cancer than men greater than 55 years of age due to a reduced likelihood of dying from co-morbid illnesses.
4. Men interested in their prostate health in these younger age groups could have a single PSA test and DRE performed at or beyond age 40 to provide an estimate of their prostate cancer risk over the next 10-20 years based on age-specific median PSA values, with the intensity of subsequent monitoring being individualised accordingly.
5. Prostate cancer can be detected at all levels of PSA. However, those men with PSA levels above age-specific median levels should be carefully monitored and considered for biopsy. Other factors including family history, ethnicity, digital rectal examination findings, PSA velocity and PSA derivatives such as the free/total ratio should also be considered. Men with levels below age-specific median can be reassured that they are at lower risk and monitored less frequently.
6. In early prostate cancer, PSA levels cannot predict the cancer volume or level of aggression. This information can only be provided by prostate biopsy. USANZ strongly supports research into novel diagnostic markers to enhance the selection of prostate cancers that will require therapy.
7. Many cancers currently found by PSA based testing will be low grade, small volume disease that have excellent cause specific survival rates at 10 years without immediate therapy. Active surveillance, with delayed treatment upon progression, should be discussed with selected patients with newly diagnosed prostate cancer to minimise morbidity of treatments and to reduce the incidence of the over-treatment effect noted in the larger screening studies. USANZ strongly supports the development of protocols to enhance active surveillance safety, to reduce the likelihood of more aggressive cancer being found outside of the biopsy field, and to reduce any psychosocial distress associated with this conservative therapy.

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Discussion

Does PSA based testing reduce prostate cancer mortality?

PSA based testing remains a highly controversial and contentious subject. Recently 2 major screening trials have published preliminary results about the efficacy of PSA based testing. These studies have enhanced our knowledge and have led to the Urological Society of Australia and New Zealand (USANZ), along with several other peak international bodies, revising its position statement on PSA testing.

The European Randomised Study of Screening for Prostate Cancer (ERSPC) results are based on 72952 men aged 55-69 years who were randomised to screening, and compared 89435 men in the same age group randomised to control with a median 9 year follow up. With the exception of one centre the screening interval was 4 years and the PSA trigger for biopsy was 3 ng/ml. Non compliance rate was 17% (those in the screening arm who were never tested), and after correction for this non compliance (therefore only looking at those men who were actually tested), there was a reduction in the incidence of advanced disease and a 27% reduction in the risk of death from prostate cancer. Survival curves began to separate at 7 years and, as such, men with a life expectancy less than 7 years are unlikely to derive any benefit from the early detection and treatment of prostate cancer. The trial demonstrated that 1410 men were required to be screened, and 48 men required management (either treatment or surveillance) for each life saved suggesting a significant over-treatment effect (1).

The Prostate Lung Colorectal and Ovarian Cancer Screening Trial (PLCO) conducted in the USA looked at 38343 men aged 55-74 years randomised to screening and 38350 men randomised to control (usual care) with a follow up of 7 years. The screening procedure was an annual PSA for 6 years and annual digital rectal examination (DRE) for 4 years with the trigger point for biopsy set at 4 ng/ml. 15% of patients in the screening arm were non compliers, and 44% of men within the control group had previously been tested for prostate cancer prior to the commencement of the study and, as such, the number of prostate cancer events during the short follow up of this study was much smaller than in the European study. 52% of men within the control arm were tested for prostate cancer with PSA during the course of the study demonstrating a high level of contamination within this control arm. As such the US study effectively compared an 85% tested group to a 52% tested group. Due to the short follow up, high pre-testing rates, low number of prostate cancer events and high contamination of the control group no mortality benefit was noted in this study (2).

In a non randomised study, the Tyrol Prostate Cancer Demonstration Project, 86.6% of eligible men aged 45-75 years were tested at least once with PSA after 1993 in Tyrol, Austria. Results were compared to standard care across the other states of Austria. By 2005 prostate cancer deaths had reduced by 54% in Tyrol, compared to a 29% reduction across the remainder of Austria (p=.001) representing an improvement of 25%, similar to that demonstrated in the ERSPC (3).

Overall there is growing evidence that PSA based testing can reduce prostate cancer mortality and should be offered to appropriately selected patients.

Which men should be tested?

The ERSPC findings, in which there was a prostate cancer survival benefit applied to men aged 55-69 years of age, is considered relevant to clinical practice in Australia and New Zealand. Given that a prostate cancer survival benefit continued to increase from 7-8 years for the screened arm and that both these trials are preliminary reports, this difference is likely to increase beyond the 9 years ERSPC median follow-up period making these findings even more compelling for us. Subgroup analyses from the ERSPC trial indicate that PSA screening may have little effect in men > 70 years of age (1), which is in line with a report from the Scandinavian Prostate Cancer Group Study 4 (SPCG4) (4). This latter group did find a 35% reduction in both incidence of metastases and prostate cancer deaths in favour of men undergoing radical prostatectomy

compared with watchful waiting at a median follow up of 10.8 years. This benefit was more apparent in men < 65 years of age, further supporting testing in this age group. More information about the effect of different treatments on outcomes will be provided by the Prostate Cancer Intervention Versus Observation study (PIVOT) being conducted in the USA and the Prostate Testing for Cancer and Treatment study (ProtecT) being conducted in the UK. Results from these studies are not expected for some years.

Whilst the survival benefit from PSA testing and treatment for younger patients is currently unknown, it is likely that these benefits would be greater than those seen in men > 55 years of age (ERSPC study) due to a reduced risk of dying from causes other than prostate cancer in the younger patients. Therefore it would seem prudent to offer testing to these patients if fully informed, understanding that the incidence of cancer in the < 50 years age group remains low.

What is the best way to test for prostate cancer?

Although PSA testing is the best single test for the detection of prostate cancer, especially at low PSA levels (where the positive predictive value (PPV) of DRE in men with PSA < 3 ng/ml is only 4-11%), the combination of PSA and DRE remains the most sensitive investigation for prostate cancer detection, especially for the detection of higher grade cancers. Based on ERSPC sub-group data, the PPV of an abnormal DRE in the PSA 4-10 ng/ml range is 48%, approximately twice as high as the PPV for PSA alone (5). The risk of missing a significant high grade cancer by omitting the DRE was estimated at 17% in this study. Therefore it appears appropriate that both serum PSA and DRE are used in the assessment of patients for prostate cancer, especially cancers of higher grade.

Can PSA predict future cancer risk in interested younger patients?

Prostate cancer can be detected at all levels of PSA based on results from the Prostate Cancer Prevention Trial (6). As such, the decision to biopsy should depend on many factors including age, family history and DRE findings; PSA velocity and PSA derivatives such as the free/total ratio may also be helpful. Longitudinal studies provide guidance as to the risk of cancer development over the next 10-20 years of life, so that testing could be applied more rationally and in a more cost effective manner (7).

The Baltimore Longitudinal Study of Aging has demonstrated that if a man has a PSA level above the age-specific median (0.6 ng/ml for man 40-49 years and 0.7 ng/ml for a man aged 50-59 years) they exhibit a 3.5 fold increased risk of cancer over 25 years compared to men with levels below median. These men also demonstrated a worse prostate cancer survival with the survival curves separating at 15 years (8).

The Malmo Preventative Medicine Study demonstrated that men aged 40-55 years whose PSA was 0.5-1 ng/ml had a 2.5 times risk of cancer diagnosis by age 75 years, compared with men with PSA < 0.5 ng/ml. This risk increased with further PSA elevations, with the relative risk being 7 if PSA was 1-2 ng/ml, 17 if PSA was 2-3 ng/ml and 39 if PSA > 3 ng/ml (9). The ERSPC has shown a 7.5 fold increased risk of cancer development if PSA > 1.5 ng/ml.

It would seem appropriate that those men with PSA levels below the median be offered less intensive testing due to the low risk of developing prostate cancer in the short to medium term. Those with levels above the median wishing to have prostate cancer detected should be monitored closely and in particular younger men with serum PSA > 1.5 ng/ml who are at high risk should undergo more intensive monitoring (10).

Do all prostate cancers require treatment?

We have to acknowledge the results of the ERSPC, which found that a large over-treatment effect is present. As responsible clinicians, we need to develop methods of reducing these rates. Results from ERSPC indicate that with repeat screening 42.6% of patients diagnosed with cancer fulfilled the criteria of minimal cancer

(impalpable stage T1c, PSA < 10 ng/ml, Gleason ≤ 6, less than 3 cores involved with cancer) (11). A concern with surveillance is disease progression and the inability to cure the disease once progression occurs. This is compounded by the discrepancy between biopsy findings and subsequent findings at radical prostatectomy which occurs in 27% of cases, with misclassification of patients as having clinically insignificant cancer when they were, in fact, harbouring more clinically significant disease (12). This information requires careful discussion with patients, as well as discussion of the psychosocial aspects of surveillance in this population.

Most studies of active surveillance have short follow up. However a cohort study from the ERSPC, examining 988 men diagnosed with cancer and treated with surveillance, has shown a 10 year cause specific survival of 100%. 23% died of other causes but 57% of patients would have required treatment by that time (13). Of those who required treatment, only 9% demonstrated PSA failure postoperatively. A large study from Canada of 453 patients with median follow up of 7.2 years has shown a cause specific survival of 99%, with 17% dying of other causes. One third of patients have required treatment, however of those treated radically the PSA failure rate was 52%, demonstrating that this approach does have to be used cautiously, especially in younger patients, and with early intervention if progression is identified biochemically or through pathological upgrading (14).

Nonetheless, the avoidance of morbidity of therapy and the excellent long term cause specific outcomes with a significant risk of death from other causes, suggests that this active surveillance is an approach that should be discussed in detail with all patients diagnosed with prostate cancer, especially those diagnosed with low volume and low grade disease, and with a life expectancy in the 10-15 year range. It is essential to explain to patients that salvage therapies upon progression cannot be expected to cure every patient, and that by avoiding over-treatment, it is inevitable that some cases of under-treatment will occur.

Conclusion

Whilst our knowledge of prostate cancer has advanced rapidly over recent years, together with our understanding of the value of PSA testing, early detection and treatment, we must continue to support research into the development of biomarkers superior to PSA which might allow the detection of clinically significant cancers requiring therapy, at the same time avoiding detection of cancers that do not require treatment. In the meantime PSA based testing, and subsequent treatment where appropriate, has been shown to reduce prostate cancer mortality in large randomised studies and therefore should be offered to men after informing them of the risks and benefits of such testing. Valuable predictive information can be obtained through even a single PSA test and prognostic information can be obtained by biopsy where indicated. Where possible, over-treatment should be avoided and surveillance with early intervention discussed with carefully selected patients.

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