



NZ must not return to the pre-PSA era

In their recent paper 'Screening for prostate cancer: a survey of New Zealand general practitioners' (<http://www.nzma.org.nz/journal/116-1176/476/>) the authors, Durham, Low and McLeod, make several conclusions.¹

The study was widely reported in the public media as indicating that men were being put at risk by their doctors testing them for prostate cancer, and these attempts at early diagnosis should be discouraged.² Rather, men should not seek or permit early diagnosis by prostate specific antigen (PSA) and digital rectal examination (DRE) testing.

Whilst acknowledging that the authors are widely read with regard to the epidemiology of prostate cancer I suggest that the conclusions reached, and the advice given to New Zealand men and their doctors, including use of the public media, concerning the early diagnosis and management of this condition are out of step with prudent management at this time for the following reasons.

The response rate in the study was low (66.3%) and an assumption is made that there would be no difference between responders and non-responders because age and year-of-registration demographics are similar. It is possible that selection bias occurred, with those not interested in PSA testing tending not to respond. One does not have the impression that 'nearly all' offer these tests as stated. It follows that the conclusions reached with regard to proportions of GPs offering testing are suspect.

The term 'screening' is not appropriate in this context; rather what has been described in the questionnaire case vignettes is early diagnosis after informed consent in a consultation setting, an activity sanctioned by virtually all relevant peer groups, and a far cry from random population 'screening' as implied by the authors. Indeed, in two (and possibly all) of the questionnaire vignettes concern about prostate cancer was the primary reason for consultation.

The statements concerning the 19 'published reviews' and that 'New Zealand GPs support a programme of no proven benefit and the potential to cause considerable harm' are not conclusions drawn from the survey that is the subject of the paper but represent an opinion of the authors. If the 19 reviews mentioned are studied it is found that only six were published in recent years, since 1999.³ The other 13 were published early in the 'PSA era', 1997 or earlier, long before any mortality benefit could be expected, nor would their authors have considered them definitive statements in this regard. It is surprising they have been used in the context of the current paper given the lead author's statement, commenting on the Austrian study (which found a benefit for PSA testing), that 'at least 5 years, probably more than 10 years from initiation of prostate cancer screening need to pass before mortality benefit occurs.'^{3,4} Concerning the more recent six reviews it is simplistic to merely state that screening is not supported; they present more complex analysis of the issues surrounding early diagnosis. For example, the high-quality review article by Bunting presents a careful analysis of the risks and benefits of early diagnosis.⁵ While caution is advised, a return to the days of no early diagnosis is not.

The narrowness of the authors' view is perhaps best revealed by their comments on the study by Holmberg et al concerning the trial of 645 Swedish men with early, localised prostate cancer randomised to watchful waiting or radical prostatectomy reported in 2002.⁶ They do mention that no difference in overall mortality was found, but fail to offer perspective by outlining other aspects of this study: 8.9% died of prostate cancer in the watchful waiting group, versus 4.6% in the radical prostatectomy group; 27.3% developed metastases in the watchful waiting group compared with 13.4% in the prostatectomy group; 61.1% of the watchful waiting group experienced local progression of the primary, versus 19.3% of the surgical group; 24.7% of those watchful waiting required androgen deprivation therapy versus 17% of the surgical group. These differences all reached significance except for the last.

In interpreting the significance of this study it is important to realise that poorly differentiated tumours were excluded from entry; had they been included the results in the watchful waiting group would have been unacceptably worse. No responsible clinician manages these tumours by watchful waiting where the man is a candidate for potentially curative treatment.

The authors infer that localised prostate cancer has a 90% disease-specific survival at 10 years in the absence of active treatment. In a *Lancet* review of 18 238 men managed conservatively, those with Gleason 8 or more lesions had a 10-year cancer-specific survival of 45%; for Gleason 5,6 and 7 this was 77%; only for well differentiated Gleason 2–4 lesions was this figure close to the authors' at 93%.⁷ Albertson, in a study of 771 men with localised disease managed conservatively followed for 15 years, found that those with Gleason 7–10 lesions faced a high risk of death from prostate cancer; for 8–10 lesions this was from 60% to 87%.⁸

This leads to consideration of arguably the most dangerous aspect of advocating that New Zealand GPs abandon and discourage attempts at early diagnosis: it means that there is a group of men who would miss the opportunity for potentially curative treatment of an aggressive lesion. Their doctors then face the prospect of facing those men and their families later in the course of the disease. Given the commonality of prostate cancer this could be a frequent event in general practice. If an earlier request to test was refused or brushed aside there is a substantial risk of a complaint to disciplinary (and perhaps legal) authorities being successful, indeed this has already occurred in New Zealand.

Nor would it be of much use to quote the authors that 'it is unknown whether treatment for screen-detected cancer is effective.' There are many series reporting good results for surgery and radiotherapy; for example, Ohori with 90% biochemically free of disease (bned) at 10 years,⁹ Catalona with 71% bned at 10 years in another large surgical series,¹⁰ and Walsh with 70% bned at 10 years.¹¹ Many New Zealand urologists relate similar, albeit earlier, experiences; for example, my own of 123 prostatectomies, follow up one to 9 years (mean 3.8), bned 74%, cancer-specific survival 99.1%.

The authors have focussed on overall survival as their most important parameter in assessing management. This is, I suggest, the most difficult and nebulous parameter because of the comorbidity of many of these patients. Others, such as cancer-specific survival, metastases development, local progression, and bned offer more scientific

appraisal. These are ignored in the authors' approach. Patients seeking advice are primarily concerned with avoiding dying of prostate cancer, which they know to be prolonged and unpleasant. They do not expect deaths of other causes to be prevented. There is clear evidence, as outlined above, that early curative treatment prevents prostate cancer deaths.

A further problem with using overall survival as the most important parameter is that androgen deprivation therapy has a profound effect on the survival of those with metastases. If this was not the case the consequences of missing the opportunity for cure would be greater. This benefit comes with a price, high for some, in terms of mentation, body habitus and function and is usually temporary. Cure, if possible, is better. That death from prostate cancer usually occurs with elephantine slowness further reduces the usefulness of overall survival as a parameter.

The definitive investigation for a raised PSA is transrectal ultrasound scanning with biopsy (TRUS). This, while not to be embarked upon lightly, is now an acceptable, safe, office investigation thanks to the widespread use of prophylactic antibiotics, intravenous sedation and local anaesthetic, and modern equipment. Many in New Zealand have a similar experience to myself with 796 procedures performed with no major complications. It does provide information of sufficient quality to cautiously advise patients.¹² To describe it as 'potentially harmful and costly' as the authors have done, could be seen as being somewhat dismissive given the importance of the condition it is attempting to assess.

Nor is it inevitable that all prostate cancer found will be actively treated. There is a profound awareness amongst clinicians regarding the high incidence in autopsy series of prostate cancer, especially small foci of well differentiated lesions, and the risk of over treatment. This is of major concern in view of the significant morbidity of all treatments. By carefully interpreting data from TRUS, including Gleason score, core length involvement and number of involved cores, this risk can be minimised. That this approach is successful is suggested by data from radical prostatectomy series showing that the great majority of removed prostates contain significant lesions, positive margin rates of 25–35% being common.^{9,10} My own experience is 35% positive margins, 19% poorly differentiated. It has been shown to be difficult to detect the common small foci, 97% of which have Gleason scores less than 7, by PSA and TRUS.^{5,13} More than 90% of detected lesions have been shown to be clinically significant.¹⁴ There is also strong clinical awareness that for many older men with comorbidities their prostate cancer will be of little consequence to them. It is common for these groups to be managed by surveillance or watchful waiting only. In my own practice, of 562 with prostate cancer 24% have been managed this way.

It seems the authors would have New Zealand men return to the pre-PSA era, when the mortality ratio was almost 50%, and 70% of men diagnosed, who had largely waited for symptoms as suggested by the Cancer Society and mentioned by the authors, already had metastases. Meanwhile, elsewhere in the advanced world early diagnosis is now so common that it is difficult to recruit and follow groups for no-treatment arms of trials. Half of my career has been spent working in the pre-PSA era and I have no desire to return to it. It would seem that many GPs and their patients agree.

Perhaps, when trying to help men with this disease we should learn to use the tools we have as best we can, rather than dismiss them as imperfect, leaving men to their fate.

Robin Smart
Urologist
Auckland

References:

1. Durham J, Low M, McLeod D. Screening for prostate cancer: a survey of New Zealand general practitioners. *NZ Med J* 2003;116(1176). URL: <http://www.nzma.org.nz/journal/116-1176/476/>
2. New Zealand Herald, 27 June 2003.
3. Durham J. Population screening for prostate cancer: a systematic review. Wellington: New Zealand Guidelines Group; 2002. Available online. URL: http://www.nzgg.org.nz/library/gl_complete/prostate_cancer/Prostate_Cancer_review.pdf Accessed September 2003
4. Auvinen A, Alexander FE, de Koning HJ, Miller AB. Should we start population screening for prostate cancer? Randomised trials are still needed. *Int J Cancer* 2002;97:337–8.
5. Bunting PS. Screening for prostate cancer with prostate-specific antigen: beware the biases. *Clin Chim Acta* 2002;315:71–97.
6. Holmberg L, Bill-Axelsson A, Helgesen F, et al. A randomized trial comparing radical prostatectomy with watchful waiting in early prostate cancer. *N Engl J Med* 2002;347:781–9.
7. Lu-Yao GL, Yao SL. Population-based study of long-term survival in patients with clinically localised prostate cancer. *Lancet* 1997;349:906–10.
8. Albertsen PC, Hanley JA, Gleason DF, Barry MJ. Competing risk analysis of men aged 55 to 74 years at diagnosis managed conservatively for clinically localised prostate cancer. *JAMA* 1998;280:975–80.
9. Ohori M, Goad JR, Wheeler TM, et al. Can radical prostatectomy alter the progression of poorly differentiated prostate cancer? *J Urol* 1994;152:1843–8.
10. Catalona WJ, Smith DS. 5-year tumor recurrence rates after anatomical radical retropubic prostatectomy for prostate cancer. *J Urol* 1994;152:1837–42.
11. Walsh PC, Partin AW and Epstein JI. Cancer control and quality of life following anatomical radical retropubic prostatectomy: results at 10 years. *J Urol* 1994;152:1831–6.
12. Smart R. Outcomes of transrectal ultrasound scan of the prostate with sector biopsies for 323 New Zealand men with suspicion of prostate cancer. *NZ Med J* 1999;112:465–9.
13. Catalona WJ, Smith DS, Ratliff TL, Basler JW. Detection of organ-confined prostate cancer is increased through prostate-specific antigen-based screening. *JAMA* 1993;270:948–54.
14. Oesterling JE. Prostate specific antigen: its role in the diagnosis and staging of prostate cancer. *Cancer* 1995;75:1795–1804.