Integrating disparate snippets of information in an approach to PSA testing in Australia & New Zealand

RA Gardiner, J Yaxley, PD Baade

Abstract: An invited response to ‘Stricker P, Frydenberg M, Kneebone A, Chopra S. Informed Prostate Cancer Risk-adjusted Testing - a New Paradigm’

In a climate of confusion about testing for prostate cancer, Stricker and colleagues advance support for a proposed risk-adjusted testing programme [1]. Their intention is to increase the prevalence of testing of men who stand to benefit most from prostate cancer detection but reduce the prevalence of those who stand to benefit little. However, there are several points that warrant consideration with respect to the evidence cited and in relation to their suggested testing paradigm.

In much of the scientific literature on this topic, the terms screening and testing have been used interchangeably, and often erroneously. The word screening is best limited to the concept of testing every man. The World Health Organization defines screening as the presumptive identification of unrecognised disease or defects by means of tests, examinations or other procedures that can be applied rapidly. Screening is intended for all people, in an identified target population, who do not have symptoms of the disease or condition being screened and that the process can identify a pre-disease abnormality, early disease or disease risk markers [2]. In Australia, PSA testing is estimated to involve approximately 20% of men between 45 and 74 years of age [3] which is far from population screening using the above definition. We suggest that very few people would endorse screening the whole male population for early detection of prostate cancer so the term screening is best avoided in patient selections strategies advocated by clinicians. Stricker et al. use the word ‘testing’ in their title but resort to using the word ‘screening’ repeatedly in their proposal [1]. Semantics are important particularly in this contentious topic and wording, unless accurate, is likely to compound the high level of confusion currently abounding.

Along these lines, mortality benefit rates in *population screening* studies cannot be considered to equate with mortality benefits to be expected with *selective testing*, which Stricker et al. advocate. For this reason, references to the increasing prostate cancer mortality benefit in terms of numbers to treat with longer follow-up times in the randomised PSA screening trials need to be interpreted with some caution which, hopefully, understate the survival benefits expected to result from these authors’ suggested testing approach.

There are well-known limitations with the recently published trials of PSA screening, some of which are mentioned in Stricker et al.’s manuscript. None of these trials had adequate statistical power to detect an overall survival benefit with PSA screening. In addition, deaths from conditions other than prostate cancer dominated the causes of death thus the ability of these studies to show an advantage for screening in relation to prostate cancer mortality was limited as deaths from cardiovascular disease undermined this goal. Nevertheless, valuable information can be gleaned from these trials: however, in doing so, their limitations need to be considered when used to inform future strategies for PSA testing.

Although it is tempting to include recently published findings from the randomised study of radical prostatectomy and watchful waiting by Bill-Axelsson et al. (2011) [4] when considering PSA testing, that trial has limited relevance to contemporary practice in Australia

and New Zealand even with its latest median follow-up of 12.8 years. Men detected with prostate cancer were at a later stage than is usually diagnosed currently - only 12% had impalpable disease on DRE - and by using methods not used routinely in contemporary urological practice. This trial, limited to men with well or moderately differentiated prostate cancer, was a selected population further along the prostate cancer natural history time course than most patients detected and treated at present. Despite demonstrating an approximate 6% absolute reduction in prostate cancer and all-cause mortality with benefit seemingly limited to men younger than 65 years, caution is warranted in extrapolating these findings directly to PSA testing.

Results from the very recently published PIVOT study [5] also fail to resolve the question of whether or not radical prostatectomy provides a survival benefit for patients with clinically localised disease. As a result these do not aid in establishing PSA testing strategies. Recruitment difficulties and patient compliance issues affected numbers, meaning the trial is considered to be underpowered [6]. An overall survival benefit for men randomised to radical prostatectomy, the primary end-point, compared with those randomised to observation was not demonstrated at a median follow-up of 10 years. It was only when secondary end-point subgroup analyses were performed that a benefit for prostatectomy was shown with reduced all-cause mortality among men with a PSA value >10 ng/ml and possibly among those with intermediate-risk or high-risk tumours. Differences between histological reporting at participating sites and by a central pathologist affected risk stratification and, consequently, secondary endpoint results. Using a less predictive pre-2005 ISUP Consensus Gleason classification, about 25% of patients had Gleason scores of 7 or higher reported at the peripheral sites compared with 48% with Gleason scores 7 or higher by a central pathologist. In addition, competing mortalities exacted a significant toll with 47% of men randomised to prostatectomy and 49.9% assigned to observation having died with only 5.8% of the former's deaths and 8.4% of the latter' attributed to prostate cancer. Notably, only 10% of participants were younger than 60 years of age, compared with 20% of men diagnosed with prostate cancer in Australia in 2008 [7].

In recommending selective testing, Stricker et al. acknowledge the advantage of excluding patients with comorbidities, noting the evidence from the SPGC4 Scandinavian trial that patients with more than two significant co-morbidities did not benefit from PSA testing [8] and that a recent follow up analysis of the PLCO study by Crawford et al. showed a striking mortality benefit in men with minimal or no co-morbidities viz. a 44% drop in prostate cancer specific mortality and a number needed to treat of only 5. It is pertinent to note however that, for those men with at least one significant co-morbidity, there was no significant difference in prostate cancer mortality compared with those in the usual care arm [9].

Any recommendation needs to clearly define what constitutes a significant co-morbidity. The ambiguity in this term presents a perplexing issue facing clinicians on a daily basis. According to the National Health Data Dictionary, a co-morbid condition is "a condition or complaint either coexisting with the principal diagnosis or arising during the episode of care or attendance at a health care facility" [10]. Crawford et al. [9] chose an expanded definition of comorbidity that included both 'standard' Charlson comorbidity index conditions and hypertension (even if it was well controlled), diverticulosis, gallbladder disease and obesity. When the analysis was repeated using only validated measures of comorbidity (that is Charlson comorbidity index conditions only), an interaction was no longer seen [11]. In practice, clinicians tend to give patients the benefit of the doubt in relation to relation to

cardiovascular prognosis and have a tendency to be unduly optimistic in relation to selecting men for prostate cancer treatment [12-14].

Many instruments are available for investigating general comorbidity-related deaths [15], the best known of which is the Charlson Index, reported to have a good correlation with non-cancer death risk in prostate cancer populations in its native form [12, 16-18] and in a simplified version [19]. A simple patient-reported index, a modified form of the Total Illness Burden Index modified for prostate cancer has also demonstrated good utility for predicting death in a large prostate cancer cohort [20, 21] and may have future relevance clinically. Recent evidence suggests that erectile dysfunction alone may prove to be a simple surrogate measure, with a large, recently published study from Western Australia reporting that the median time interval between the onset of erectile dysfunction and cardiovascular death was 10 years [22].

That the PSA screening/testing debate focusses exclusively on mortality is distracting since there are other reasons that prompt testing and prostate cancer treatment [11]. Although it is less open to dispute to refer to mortality data, notwithstanding some concerns regarding the accuracy of cause of death coding, it is appropriate that urologists emphasise the fact that mortality is only one factor to consider in determining whether or not to test for and treat prostate cancer whenever discussing the topic.

Stricker et al have correctly acknowledged the high over-diagnosis rate with early detection and recognise an increasing role for active surveillance without a detrimental effect on patient outcome in terms of disease progression. However, it is also important to also appreciate the psychological turmoil experienced by men with a positive PSA test, including the quandary posed as a result of the imprecision of the PSA/biopsy detection process, the often ambiguous decisions about treatment, and misinformation propagated about the significance of a prostate cancer diagnosis of any sort [23]. Higher anxiety related to uncertainty surrounding cancer has been shown to increase the likelihood of choosing active treatment. Decisional conflict impacts upon the probability of patients continuing with active surveillance [24].

One of the aspects commonly overlooked in considering the pros and cons of early detection and PSA testing in particular is the ability of a very low PSA reading to provide reassurance to men by indicating that they are highly unlikely to have prostate cancer. Men with a PSA level <1 at the age of 65 [25] or <3 at the age of 75 [26] have a very low chance of contracting fatal cancer. Providing reassurance is a most valuable part of clinical practice often overlooked by epidemiologists so this benefit from PSA testing also warrants promotion by clinicians in early detection discussions.

The concept of informed consent is an important component of Stricker et al.'s suggested testing paradigm. Implicit in obtaining informed consent is the process of shared decision-making resulting from an integration of evidence and patient preferences [27] but it remains unclear exactly what shared decision-making means [28]. Given that lengthy discussion(s), frequently involving a man's wife or partner, are usually required in providing informed consent for PSA testing, it may be that there is a role for special councillors as advocated by Denman et al (2010) [29]. However such a model would require rigorous evaluation to determine the most effective form of shared decision making and outcomes for our patients [30].

Finally, although reasoned and evidence-based, the protocol proposed by Stricker et al. needs to be tested through a prospective trial, with provision to integrate better markers for both

detection and prognosis when these become available. Otherwise this promising paradigm will, unfortunately, remain just another proffered opinion among a multitude.

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