Alan MF Stapleton
BHB, MBChB, PhD, FRACS, is Director, Urology Research, Repatriation General Hospital, Adelaide, South Australia.

Richard L Johns
MBBS, is Continuing Professional Development GP Advisor, Southern Division of General Practice, Adelaide, South Australia.

Tina Kopsaftis
BSc, is Clinical Data Coordinator, Urology Unit, Repatriation General Hospital, Adelaide, South Australia.

David J Tamblyn
BHSc, is Data Manager, Urology Unit, Repatriation General Hospital, Adelaide, South Australia.

Abnormal PSA tests

Delays in referral

Background
The main benefit of prostate specific antigen (PSA) testing is to help detect prostate cancer at an early, curable stage. Delays between the first abnormal PSA test and biopsy can undermine that benefit, but have not yet been studied. We investigated delays before biopsy together with associated PSA increases as an indicator of disease progression.

Methods
We identified 241 patients with a primary care referral because of an elevated PSA result (>4 ng/mL) and no previous prostate biopsy. Prostate specific antigen results and intervals between PSA testing, specialist clinic referral, appointment and biopsy were stratified by age.

Results
Median times between first abnormal PSA, referral, consultation and biopsy were modest but associated with increases in PSA. Extended delays (>20 months) between first abnormal PSA and referral occurred in 25% of younger men. A PSA result less than 10 ng/mL was the best predictor of a delay to refer.

Discussion
Rising PSA and possible cancer progression during investigation for prostate cancer suggest that prompt care is advisable.

Prostate cancer is now the most common notifiable male cancer and second most common cause of cancer death after lung cancer.[1] It occurs later in life in most men and tends to be slow growing.[2] Late occurring, slow growing disease is frequently not a threat, particularly in older men.[3] However, a man diagnosed with prostate cancer at an early age (ie. at 50 years of age) has a high likelihood of dying from prostate cancer prematurely (ie. before 80 years of age). This risk was 60% according to one study,[4] while the same risk for a man diagnosed at 70 years of age was only 38%.

Prostate specific antigen (PSA) testing can help detect prostate cancer while it is still localised to the prostate and when a range of potentially curative surgical and radiotherapy treatments are still available.[3] Treatment for localised prostate cancer has been shown to improve survival.[5] Concerns about PSA testing centre on the low positive predictive value of an abnormal result (30% in some studies),[3] significant number of false negatives,[3] and the high chance of detecting some prostate cancers that will never be a threat (over detection).[6]

Most authorities – including the United States Preventive Services Taskforce,[3] the Urological Society of Australia and New Zealand[7] and The Royal Australian College of General Practitioners[8] – do not recommend population based PSA screening. They do suggest however, that all men should be able to undertake a program of early detection for prostate cancer if they wish to do so after being informed of the benefits and risks. Men at high risk – such as those with a father or brother diagnosed at an early age – may consider testing from an earlier age (40–45 years), while men aged 75 years and over, or with less than 10 years life expectancy, are unlikely to benefit.

Rates of opportunistic screening for prostate cancer in Australian general practice are high,[9,10] with one estimate of 204 000 screening PSA tests performed annually in Australian general practice.[11] If only 12% of such tests return abnormal,[3] 24 500 decisions concerning referral or follow up would need to be made.

Carole B Pinnock
PhD, MSc, is Principal Research Scientist Urology Unit, Repatriation General Hospital, Southern Division of General Practice, Adelaide, South Australia. carole.pinnock@rgh.sa.gov.au

While referral for further investigation is clearly needed if an abnormality is detected on rectal examination, there are no clear cutoffs based on PSA testing. Historically a threshold PSA level of 4 ng/mL has been defined as the upper limit of 'normal', however we now know that significant numbers of cancers occur in men with PSA levels below these thresholds.[12] On the other hand, as many as two-thirds of men with levels at 4–10 ng/mL are not diagnosed with cancer on the first biopsy,[3] and so PSA levels alone are falling from favour as triggers to further investigation. Age based reference ranges and free-to-total ratio of PSA have been proposed to improve specificity of cancer detection between PSA levels 4–10 ng/mL, but again, thresholds for biopsy are debated.[13] Prostate specific antigen rate of change (velocity or doubling time) is the most recently proposed detection measure, but on its own is not a good predictor of cancer diagnosis.[14,15] Another approach combines the major indicators (PSA, digital rectal examination [DRE] findings, family history, race, age) to calculate the risk of cancer presence.[16,17]

Prostate specific antigen level immediately before diagnosis not only helps predict cancer presence, but is also a useful measure of the risk that cancer has spread beyond the prostate.[18] The risk is continuous across the spectrum of PSA levels. The Partin tables[19] show that the risk of extraprostatic extension (EPE) increases from 33% (PSA 2.6–4.0 ng/mL) to 40% (PSA 4.1–6.0 ng/mL) to 48% (PSA >10 ng/mL) for an impalpable tumour with only a moderate Gleason score (4+3=7). Delays in care may allow time for unforeseen but significant increases in risk of EPE, undermining the purpose of the test.

A number of studies have examined delays between the diagnosis of clinically localised prostate cancer and treatment. In most cases they have found that a moderate delay (eg. 3 months or less) does not affect treatment outcome.[20–24] Delays before diagnosis, however, have not been studied. These include delays between a first abnormal PSA test and referral from primary health care, and delays between referral and first clinic appointment and subsequent prostate biopsy. These delays are potentially longer, of greater clinical significance, and may have a range of causes including: variation in referral practices, biopsy practices, patient initiated delays and clinic waiting list delays.

We undertook a retrospective analysis of intervals between points of care and associated PSA changes before diagnosis among patients attending a South Australian public hospital.

Methods

All hospital records were searched to identify patients with a diagnosis of prostate cancer and a primary care referral, for whom at least one serum PSA was recorded before referral. Patients were ineligible if they had a previous prostate biopsy, were referred indirectly through private specialists, were diagnosed through transurethral resection or if either referral or biopsy data were unavailable.

Medical and laboratory records were searched for additional PSA results before referral, outpatient consultation history, biopsy data and treatment. Not all patients had PSA results available at each point of care. Intervals between abnormal PSA (defined as >4 ng/mL), referral, specialist clinic appointment, prostate biopsy and first treatment dates were recorded. Because benefits from curative treatment are most likely in patients with a life expectancy of 10 or more years,[25] patients were stratified by age at diagnosis into group A if aged <75 years, and group B if aged 75 years or over. Patients were referred between October 1998 and November 2005.

The Repatriation General Hospital Research and Ethics Committee provided ethical approval.

Results

Data were available for 241 patients who had had a direct primary care referral, of whom 121 were aged <75 years (group A) and 120 were aged 75 years or over (group B).

The median first PSA was above the 'normal' threshold of 4 ng/mL, which with high clinical stage and grade (*Table 1*) suggested a high likelihood of clinically significant disease. Men in the older group were diagnosed at a later stage, with median PSA almost twice as high at diagnosis as in the younger group. Among the younger group, 75.1% chose treatment with intent to cure.

Most men received timely care (*Table 2*). Median time from first abnormal PSA to referral was only 1.15 months in the younger group and 1.87 months in the older group. Similarly short intervals were found between clinic appointment, biopsy and treatment. However 25% of younger and older men waited more than 20 and 28 months respectively between first abnormal PSA and referral for further investigations.

Although median time intervals were short, PSA levels did advance at each successive point of care (*Figure 1, 2*). In the younger group, between first abnormal PSA and treatment, PSA advanced from <10 ng/mL to >10 ng/mL at point of treatment in 18% of cases. This increase in PSA was positively correlated with delay in months (Spearman's correlation coefficient 0.549, $p<0.0001$) between first abnormal PSA and treatment. In the older group, median PSA levels advanced even higher, with 63% of men advancing to >10 ng/ml at point of treatment. This PSA rise was similarly correlated with delay in months (Spearman's correlation coefficient 0.561, $p<0.0001$) between first abnormal PSA and treatment.

Prostate cancer is frequently slow growing, and it would be reasonable to expect that patients who experienced a long delay before referral (ie. >6 months) would be at lower risk than patients referred sooner. We compared first abnormal PSA, PSA velocity and (for those patients proceeding to radical prostatectomy) 5 year recurrence free probability based on Kattan's preoperative nomogram[26] in a group of patients who experienced a delay up to or equal to 6 months between first abnormal PSA and referral, and a

Table 1. Clinical characteristics by age grouping

	Group A (age <75 years)		Group B (age >=75 years)	
	N	Median (interquartile range)*	N	Median (interquartile range)*
Age at biopsy	121	67 (59–72)	120	81 (77–83)
First PSA	121	6.8 (4.5–12.0)	120	9.8 (5.9–24.6)
First abnormal PSA	114	7.6 (5.5–13.9)	118	11.2 (7.2–25.6)
Last PSA before biopsy	120	9.2 (6.6–15.3)	120	17.4 (9.8–31.8)
Last PSA before treatment	98	9.8 (7.1–15.6)	85	23.6 (13.3–44.8)
PSA velocity (ng/mL/yr)	50	1.05 (0.6–1.8)	61	2.07 (0.77–3.94)
Primary treatment choice**				
Watchful waiting		3 (2.5)		17 (14.2)
Radiotherapy		50 (41.3)		20 (16.7)
Surgery		41 (33.9)		0 (0.0)
Hormone therapy		18 (14.9)		71 (59.2)
Undecided/unknown		9 (7.4)		12 (10.0)
Gleason total**				
2–6		50 (41.3)		41 (34.7)
7		48 (39.7)		38 (32.2)
8–10		23 (19.0)		39 (33.1)
Clinical stage**				
T1		22 (20.2)		7 (6.8)
T2		69 (63.3)		54 (52.4)
T3		13 (12.0)		39 (37.8)
T4		5 (4.6)		3 (2.9)

* 25th quartile – 75th quartile

** N (%)

group who experienced a delay of 6 months or more. There was no difference between these groups in PSA velocity or the probability of biochemical recurrence, however there was a significant difference in first abnormal PSA. Median first abnormal PSA was 10.3 and 5.7 ng/mL in 'not delayed' versus 'delayed' groups respectively (p<0.0001). All but one patient with referrals delayed for more than 6 months had a PSA <10 ng/mL. Prostate specific antigen level therefore seemed to be the main basis on which referral was delayed.

Discussion

This study of patients referred to a public hospital suggests that most patients receive timely care. Unknown biases in patient selection mean that we cannot be sure that this report reflects the experience of all public patients diagnosed with prostate cancer. Based on their clinical characteristics, these patients appeared to have significant disease and, unlike patients in a current USA case series,[27] were not being routinely screened for prostate cancer.

Despite timely care, median PSA increased at each subsequent point of care. The progression in PSA levels from first test through referral to diagnosis and treatment is a concern given that increasing PSA levels are related to reduced chance of organ confined disease.[28]

One quarter of men waited more than 20 months for referral after the first abnormal PSA. For these men, first abnormal PSA <10 ng/mL seemed to be a precondition for the longer wait. However, PSA at this level is associated with significant levels of extraprostatic spread.[18] For men with more than 10 years life expectancy, such a delay could reduce the chance of diagnosis with organ confined disease and thereby limit treatment options and opportunity for cure.

While referral for further investigation is clearly needed if an abnormality is detected on rectal examination, there is uncertainty regarding a cutoff for PSA and its derived forms. Based on data reported here, a tacit cutoff of 10 ng/mL applied for those men with extended referral delay. This approach is not supported by our current understanding that risk of extra prostatic spread increases continuously as PSA rises above 4 ng/mL. Waiting for PSA to rise is not the same as 'watchful waiting' or 'active surveillance', a treatment strategy for low risk cancers established after histological diagnosis. Before biopsy, it is not possible to know whether the risk of cancer is low, moderate or high.[18]

The patient's expectations are important in deciding the timing of further investigation. If the patient was PSA tested after

Table 2. Median duration (months) between points of care

Points of care	Number of months between points of care	
	Group A median (interquartile range)	Group B median (interquartile range)
First PSA to referral	5.1 (0.5–34.0)	11.3 (0.6–41.9)
First abnormal PSA to referral	1.15 (0.29–20.3)	1.87 (0.4–28.3)
First abnormal PSA to biopsy	3.75 (1.9–20.4)	9.5 (2.7–35.3)
First abnormal PSA to treatment	5.79 (3.53–24.6)	18.93 (4.4–40.4)
Referral to outpatients department	1.18 (0.6–2.0)	1.57 (0.6–2.7)
Referral to biopsy	1.81 (0.9–3.5)	2.42 (1.0–4.3)
Biopsy to treatment	1.96 (1.1–3.4)	1.55 (0.3–4.7)

being informed of the benefits and uncertainties of testing (as recommended by current guidelines),[8] he expects to benefit from the early detection of cancer. It follows that if the patient himself wishes to defer further investigation, then his decision should be a fully informed one.

For this reason, and given the uncertainty regarding when to perform a prostate biopsy, shared decision making may be the best approach (*Table 3*). The patient should be aware that PSA reflects a continuum of risk, and that if cancer is present, he will maximise the chance of detection at a localised stage by avoiding delay in diagnosis. On the other hand, there is a chance that further investigation may not detect cancer, and that further investigation carries its own risks. We do not yet have evidence that early investigation after an abnormal PSA result will improve survival in a screened population. There is evidence, however, that early detection improves the patient's chance of being diagnosed with localised disease,[29] increasing his access to treatment options with outcomes that are potentially more favourable. Informed consent therefore applies not only to testing but to the follow up of an abnormal result. If there is uncertainty about the timing of referral, the patient should be informed of the potential risks of delaying further investigations.

Conclusion

Most men in this case series received timely care, however PSA levels increased at subsequent points of care consistent with increased

Figure 1. Median PSA at different points of care

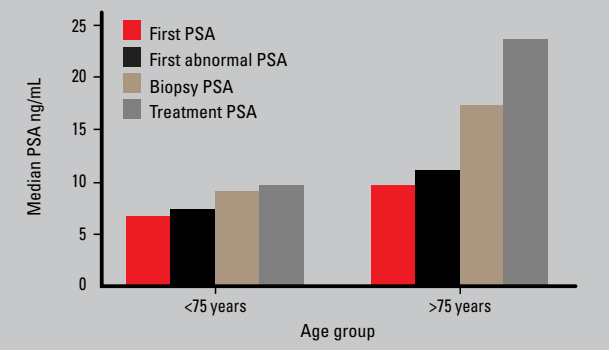

Figure 2. Percentage of patients with PSA >10 ng/mL

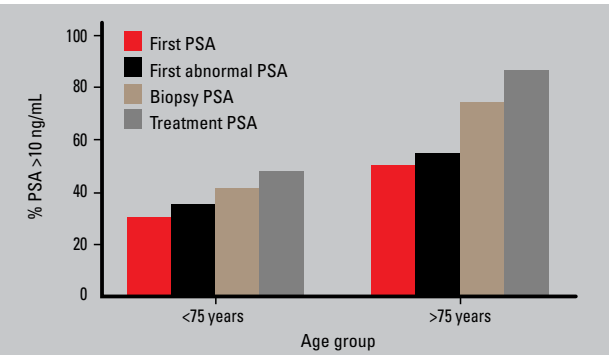

Table 3. Should I refer on a raised PSA?

Consider noncancer causes:

- benign prostatic hypertrophy
- urinary tract infection
- prostatitis
- recent catheterisation or instrumentation of urethra
- infarction of prostatic adenoma (seen in large glands and sometimes associated with acute urinary retention requiring catheterisation)

Consider referral if:

- digital rectal exam shows nodularity or hard prostate
- PSA exceeds upper limit of normal for age or 4 ng/mL
- PSA velocity is high (>0.75 ng/mL/year)*

Consider closer follow up if:

- PSA is in upper range of normal for age
- patient has a family history of prostate cancer
- patient requests testing for purpose of early detection

* A lower threshold of 0.4 ng/mL per year has been suggested for men younger than 60 years[30]

Source: The Cancer Council Queensland/Australian Prostate Cancer Collaboration. Early detection of prostate cancer in general practice, October 2007

risk of extraprostatic disease. One quarter of men waited extended times between first abnormal PSA and referral. This is of concern, particularly for younger men. While there are no agreed indications for referral and prostate biopsy, once the decision to test has been made, the patient should be involved in the effort to detect any tumour in a timely manner.

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AFP CORRESPONDENCE afp@racgp.org.au