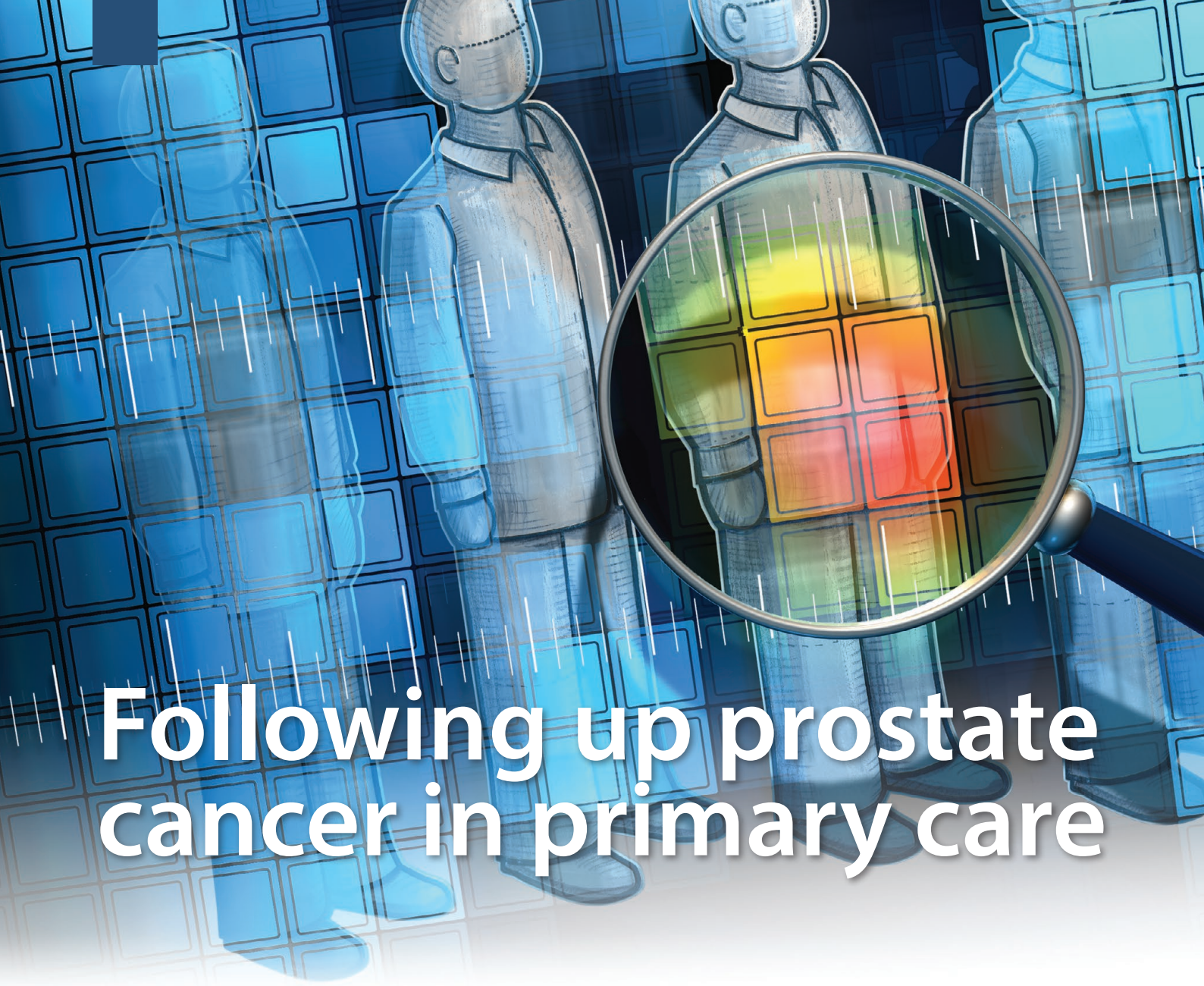

# Following up prostate cancer in primary care

Cancer services in New Zealand are undergoing major changes over the next few years. Primary care clinicians are likely to have a much greater involvement in providing management for their patients with cancer, especially in regards to follow-up after cancer treatment has been completed. Many General Practitioners already manage patients after prostate cancer. We give guidance on interpreting PSA levels for surveillance, and other associated follow-up tests.

## Prostate cancer is one of the most common cancers in New Zealand

In 2009, prostate cancer had the greatest incidence of all cancers in New Zealand, accounting for 16.1% of cancer registrations (30.2% of all male registrations).[1] Although prostate cancer is the third most common cause of cancer death in males, it has a favourable survival ratio: between 2004 and 2009, 91.3% of men with prostate cancer survived past five years, compared with 61.8% of people with colorectal cancer.[2]

There are a number of different options for treatment of localised prostate cancer, that vary depending on the health and age of the patient, the stage of the disease (largely determined by biopsy results and prostate-specific antigen [PSA] level), and personal preference. These options include surgery and/or radiotherapy with intent to cure, hormone treatment or monitoring for progression of disease.

The majority of men with a diagnosis of localised prostate cancer undergo definitive treatment, e.g. radical prostatectomy, external beam radiotherapy or brachytherapy (internal radiotherapy using radioactive "seeds") with intent to cure.

Follow-up treatment after definitive treatment for localised prostate cancer includes:

- Patient and family/whānau education and psychosocial support
- Clinical assessment for local or distant recurrence, primarily with PSA testing
- Ongoing assessment and treatment of adverse effects secondary to the definitive treatment, such as urinary incontinence, erectile dysfunction
- Monitoring of long-term adverse effects from the definitive treatment

Because prostate cancer is generally slow growing, some patients with low-risk localised cancer may be offered "active surveillance" through regular PSA testing and have definitive treatment only if there is evidence of progression of the cancer. Men are considered to be at low risk if they have a:[3]

- PSA level of < 10 ug/L, and
- Gleason score (histological grade) of ≤ 6, and
- Clinical stage of T1-T2a (confirmed tumour involving no more than one half of the prostate gland)

A "watchful waiting" approach may be taken in men with prostate cancer who are unsuitable for radical treatment, e.g. those with disseminated disease, co-morbidities precluding radical treatment, or older men with limited life expectancy where the cancer is unlikely to progress significantly over this time.[3] If PSA levels begin to rise rapidly, or if symptoms develop, hormonal treatment (e.g. androgen blockade) is the preferred treatment option.[3]

Androgenic hormones can stimulate prostate cancer growth, therefore androgen deprivation treatment (or androgen blockade) may also be used in various other circumstances, such as an addition to radical radiotherapy, pre- or post- surgery or as a means of treating metastatic prostate cancer.[3]

Table 1 summarises the follow-up procedures for the different treatment options for men diagnosed with localised prostate cancer.

## Surveillance Tests

A rise in serum PSA is usually the only indication of a recurrence in men who have been treated for localised prostate cancer with radical prostatectomy or radiotherapy. Although the role of PSA for prostate cancer screening is not clear and often controversial, PSA is a reliable and sensitive tumour marker that increases in the majority of men with recurrent cancer. However, there is little evidence that determines the frequency that PSA should be requested after definitive treatment, and the significance and extent of the increase in the PSA level depends on the type of definitive treatment. Most clinicians are guided by the PSA velocity (the rate of the change) and the grade of the tumour rather than by absolute levels.

### PSA testing intervals

Men who have undergone radical prostatectomy or radiotherapy should have their PSA level checked:[3]

- Six weeks after treatment (unless adjuvant hormonal treatment is being given)
- At least every six months for the first two years
- Then annually

Men in an active surveillance protocol should have their PSA level checked regularly, e.g. every six months, however, the PSA velocity should be used to guide the frequency of testing.

Men who adopt a watchful waiting approach (no intention to cure) should have their PSA measured at least annually, as guided by the velocity of change.[3]

### The significance of an increase in PSA

An increasing PSA level after treatment is regarded as a biochemical recurrence of cancer. Regardless of the initial treatment, it is estimated that one-third to one-half of patients will have a biochemical recurrence.[5] The significance of this recurrence, however, is not always clear, e.g. it does not necessarily indicate metastatic disease, which is estimated to occur in less than one-third of patients that have rising PSA levels after radical prostatectomy.[5]

Velocity and the PSA doubling time are used to guide further investigation and treatment during monitoring. Velocity refers to the rate of change over time between

PSA measurements. The PSA doubling time is the length of time for PSA to double based on an exponential growth pattern. PSA doubling time has been shown to be a strong predictor of clinical progression and cancer mortality.[5] A man with a PSA level that has doubled slowly, e.g. over 12 months, is more likely to have local recurrence and a less aggressive tumour than a man with a PSA doubling time of less than six months.[5, 6]

The measurement and use of PSA velocity and doubling time to guide management has been described as "an art, not a science" because the ideal number of times that PSA should be tested and the time period between these tests has not been determined.[6] NICE guidelines (United Kingdom) recommend that a minimum of three PSA measurements be carried out over a least a six-month period to estimate the PSA doubling time.[3]

Rises in PSA level must also be interpreted in the context of the specific treatment received. During a radical prostatectomy, almost all the prostate tissue is removed and PSA should become undetectable within three to six weeks. PSA levels > 0.2 ug/L (or > 0.05 ug/L if an ultrasensitive PSA assay is used) after this time, would indicate that there may be residual or recurrent cancer, and this should be discussed with an urologist.[5, 7]

**Table1:** Summary guideline for primary care follow-up in men following diagnosis of localised prostate cancer[3]

| Treatment | Follow-up testing frequency | Comments |
|---|---|---|
| **Watchful waiting** | ■ PSA testing at least annually<br>■ Clinical assessment | DRE is not recommended if the PSA level remains at baseline levels |
| **Active surveillance** | ■ PSA testing | Frequency of PSA testing is not clear. Three to six monthly testing may be appropriate but testing should be guided by the rate of change (velocity).<br>DRE is not recommended if the PSA level remains at baseline levels although some guidelines recommend 6 –12 monthly DRE[4] |
| **Radical prostatectomy or radiotherapy** | ■ PSA testing starting from six weeks at the earliest, and at least every six months for the first two years, and then annually<br>■ Clinical assessment | DRE is not usually indicated if the PSA remains undetectable as it is unlikely to change the clinical outcome, however, DRE can be of value in detecting local relapse particularly in people with high grade tumours where PSA may be misleading<br>NICE guidelines recommend sigmoidscopy to check for colorectal cancer every five years for men who have received radical radiotherapy, however, this should be determined on an individual patient basis |
| **Hormonal treatment** | ■ Baseline DEXA scan and then follow-up DEXA scan at 12 months or earlier (six months) if appropriate<br>■ Reassess cardiovascular risk, e.g. lipids and $HbA_{1c}$ | DEXA scans are indicated for men treated with androgen blockade |

DRE = Digital rectal examination PSA = Prostate specific antigen

The fall in PSA levels after radical radiotherapy is much slower, and may take 18 months to four years to reach the lowest point. An increase in PSA level to > 2 ug/L (or any persistently increasing levels) after radical radiotherapy warrants discussion with a radiation oncologist, but this can generally only be assessed two to three years after treatment.[5, 7] A further complicating factor is the PSA bounce phenomenon, which is a benign rise in PSA levels in some patients after radiotherapy (most commonly brachytherapy) due to apoptosis (cell death). This tends to resolve spontaneously within 12 months.[8]

N.B. 5α-reductase inhibitors such as finasteride and dutasteride lower PSA levels by approximately 50%. PSA results should be doubled to get an indication of the patient's true PSA level, if they have been using these medicines.[5, 7]

The Memorial Sloan-Kettering Cancer Centre has an online nomogram to calculate PSA doubling times, see: **http://nomograms.mskcc.org/Prostate/PsaDoublingTime.aspx**

## Clinical assessment

A clinical assessment should include history and examination to check:

- Adverse effects of treatments such as urinary and sexual dysfunction after radical prostatectomy and bowel problems after radiotherapy
- Symptoms that might suggest local recurrence, although usually men are initially asymptomatic and any recurrence is likely to be first detected by an increase in PSA
- Symptoms that may suggest metastatic spread such as bone pain or weight loss
- Psychosocial aspects

Guidelines vary in their recommendations as to whether a digital rectal examination (DRE) should be part of routine follow-up.[9] After radical prostatectomy, DRE is not particularly useful as early local recurrence is not usually able to be felt. A DRE should detect an empty prostatic fossa. After radical radiotherapy, the scar tissue that remains may not be able to be distinguished on DRE from areas that may have residual or recurrent cancer. DRE is therefore of limited clinical value and clinicians usually rely on the PSA level for monitoring recurrence. The exception is in patients with high grade prostate cancers (e.g. Gleason 9 or 10) as the PSA level in these patients may not be representative of the clinical situation.[9]

## Associated Tests

Patients should be referred for an isotope bone scan if symptoms and rising PSA trends are suggestive of metastatic disease.[3]

Men who report lower gastrointestinal tract symptoms after radiotherapy should be investigated due to the risk of radiation-induced enteropathy or secondary malignancies. The NICE guidelines recommend flexible sigmoidoscopy every five years for men who have previously received radical radiotherapy.[3]

There are no consistent guidelines in relation to bone mineral density scanning for men using androgen deprivation therapy. A baseline DEXA scan should be performed. In general, the follow-up DEXA scan should occur at 12 months, or earlier (six months) if the baseline DEXA scan suggests pre-existing osteopenia or a borderline result.[10]

### STOP PRESS: Prostate Cancer Taskforce release working document

The Prostate Cancer Taskforce, commissioned by the Ministry of Health, has developed recommendations for the diagnosis and management of prostate cancer in men in New Zealand. This document has now been released to the health sector for further consultation. The Taskforce recommends that General Practice has a central role in providing information about PSA testing, and supporting men after an initial diagnosis of prostate cancer, and through subsequent treatment. There is a strong focus throughout the recommendations on achieving equity for Māori in the rate of prostate cancer testing and treatment.

The consultation document is currently available on the RNZCGP website (members only section): w**ww.rnzcgp.org.nz/consultation-requests-2**

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