Current Controversies in Prostate Cancer and Androgen Replacement – Murray PHN 2016

Mr Stephen Lindsay
Urological Surgeon
Bendigo

www.bendigourology.com
Prostate Cancer Risk Assessment
Prostate Cancer (CaP)

- most common cancer diagnosed in Australian men (since 1989) with approx 20,000 new cases/year

- second most common cause of cancer death in men (> 3000 deaths/year or 4.1% of all male deaths)
Between 1987 to 1997

- the number of CaP diagnoses doubled
- the total number of CaP specific deaths also doubled

BUT age-adjusted deaths only increased 7% - improved life expectancy meant that more older men were alive in the at risk age groups
Prostate cancer specific survival in Victoria has improved dramatically over the last 20 years.
Prostate Cancer in Victoria

Figure 8
Age-specific prostate cancer mortality by median year of birth, Australia 1950–98
Why?

- Male life expectancy increased – more men alive in the at risk age group (over 50)
- Improved risk assessment tools – PSA, TRUS
- Community awareness
- Improved access to GP’s and Urologists
- Better treatment, less morbidity
Incidence of Metastatic Disease

Incidence of Prostate Cancer that was Metastatic at First Presentation
USA 1975–2012

Welch/Albertsen, N Engl J Med 2015
Prostate Cancer

International Incidence

Figure 2
International incidence of prostate cancer

The countries chosen for international comparisons are from registries included in Cancer incidence in five Continents Vol VII. They include Australia (Victoria), New Zealand (non-Maori), USA (SEER whites & SEER blacks), Italy (Parma), Israel (All Jews), England (UK), England & Wales), Japan (Miyagi), China (Shanghai) and Poland (Cracow City).


Annual age-standardised rate per 100,000 men
Prostate Cancer

International Incidence and Mortality

Figure 3
Prostate cancer incidence (1988–1992) and mortality (1990) in the UK (England & Wales), Denmark, Victoria, Canada and USA (SEER, whites)

Incidence data from Cancer Incidence in Five Continents Vol VII.1
Mortality data from the WHO Cancer Mortality data bank.
9.8 Prostate cancer

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<td>Screening for prostate cancer is not recommended unless:</td>
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<td>2. he is fully counselled on the pros and cons</td>
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Routine screening for prostate cancer with DRE, PSA or transabdominal ultrasound is not recommended. DRE has poor ability to detect prostate disease. Yet some cancers missed by PSA testing alone are detected by DRE, which is why those recommending screening advocate DRE as well as PSA.

The recommendation is contentious. Two large RCTs found none or marginal benefit. However, analysis of the data from one centre contributing to one of these showed an increased survival from prostate cancer (but not mortality from any cause) beyond 10 years. Two recent systematic reviews concluded that screening is not effective.

Even if we were to conclude there was a survival benefit (from current or future trial data), this survival would need to be balanced against the harms of cancer overdetection and treatment.

GPs need not raise this issue, but if men ask about prostate screening they need to be fully informed of the potential benefits, risks and uncertainties of prostate cancer testing. When a patient chooses screening, both PSA and DRE should be performed.
### Table 9.8.1 Prostate cancer: identifying risk

<table>
<thead>
<tr>
<th>Who is at risk?</th>
<th>What should be done?</th>
<th>How often?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Average risk</strong></td>
<td>Respond to requests for screening by informing patients of risks and benefits of screening (I,A)</td>
<td>On demand <a href="#">557-559</a> (Practice Point)</td>
</tr>
<tr>
<td>- The risk of developing prostate cancer increases with age and positive family history. However, because prostate cancer is normally slow growing, men older than age 75 years or with a life expectancy of less than 10 years are at reduced threat of dying from a diagnosis of prostate cancer.</td>
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<td>- Men with uncomplicated lower urinary tract symptoms (LUTS) do not appear to have an increased risk of prostate cancer. The most common cause of LUTS is benign prostate enlargement. Early prostate cancer often does not have symptoms.</td>
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<tr>
<td><strong>High risk</strong></td>
<td>Respond to requests for screening by informing patients of risks and benefits of screening (Practice Point)</td>
<td>On demand <a href="#">558-559</a> (Practice Point)</td>
</tr>
<tr>
<td>- Men with one or more first-degree relatives diagnosed under age 65 years</td>
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<td>- Men with a first-degree relative with familial breast cancer (BRCA1 or BRCA2)</td>
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</table>

* indicates additional consideration.
Table 9.8.2 Screening for prostate cancer

<table>
<thead>
<tr>
<th>Not recommended</th>
<th>Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA screening</td>
<td>The most common adverse effect of radical prostatectomy is erectile dysfunction, which affects most men (it is less common in younger men, those with a lower PSA, and when nerve-sparing surgical techniques are used). Other complications are common as well, including urinary incontinence (which is very common in the months after treatment, but returns to normal in 75–90% men after 2 years, depending on treatment type), and to a lesser extent, urinary irritation and bowel symptoms. General feelings of ‘vitality’ are lost in about 10% of men. Both suicide and CVD increase enormously (8 and 11 times more, respectively) in the week after men are given their diagnosis of prostate cancer. Even diagnostic procedures following positive screening are harmful, with Australian data showing that the risk of life-threatening sepsis needing intensive care admission is not uncommon after biopsy. Despite large trials, their meta-analysis suggests that prostate cancer screening does not save lives.</td>
</tr>
</tbody>
</table>
Implementation

Strategy

Patients who request testing should be informed about the risks and benefits of tests for prostate cancer, and assisted to make their own decision. Written material, particularly decision aids, may be useful for this purpose: see the RACGP green book and a free book providing a balanced presentation of facts at http://ses.library.usyd.edu.au/bitstream/2123/6835/3/Let-sleeping-dogs-lie.pdf

Responding to the patient’s concerns and fulfilling medico-legal responsibilities are considerations in discussion with patients.
What does the RACGP mean by Screening?

Population-based Screening

- Large scale testing of an entire geographical population of apparently healthy volunteers for the presence or absence of disease
  
  eg Breastscreen (infrastructure - screening centres, mailed invitations)

Selective Screening of at-risk populations

- limited testing targeted at high risk populations
  
  eg family history, African-American

Opportunistic testing (or Case Finding)

- investigation of men, with or without symptoms, as part of a routine medical consultation
What is Screening?

WHO Screening Criteria – (Revised 2008)

1. The screening programme should respond to a recognized need.
2. The objectives of screening should be defined at the outset.
3. There should be a defined target population.
4. There should be scientific evidence of screening programme effectiveness.
5. The programme should integrate education, testing, clinical services and programme management.
6. There should be quality assurance, with mechanisms to minimize potential risks of screening.
7. The programme should ensure informed choice, confidentiality and respect for autonomy.
8. The programme should promote equity and access to screening for the entire target population.
9. Programme evaluation should be planned from the outset.
10. The overall benefits of screening should outweigh the harm.

WHO 2008
The Melbourne Consensus Statement on the early detection of prostate cancer

Declan G. Murphy\textsuperscript{1,2,3}, Thomas Ahlering\textsuperscript{4}, William J. Catalona\textsuperscript{5}, Helen Crowe\textsuperscript{2,3}, Jane Crowe\textsuperscript{3}, Noel Clarke\textsuperscript{10}, Matthew Cooperberg\textsuperscript{6}, David Gillatt\textsuperscript{11}, Martin Gleave\textsuperscript{12}, Stacy Loeb\textsuperscript{7}, Monique Roobol\textsuperscript{14}, Oliver Sartor\textsuperscript{8}, Tom Pickles\textsuperscript{13}, Addie Wooten\textsuperscript{3}, Patrick C. Walsh\textsuperscript{9} and Anthony J. Costello\textsuperscript{2,3}

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- Various conflicting guidelines and recommendations about prostate cancer screening and early detection have left both clinicians and their patients quite confused. At the Prostate Cancer World Congress held in Melbourne in August 2013, a multidisciplinary group of the world’s leading experts in this area gathered together and generated this set of consensus statements to bring some clarity to this confusion.

- The five consensus statements provide clear guidance for clinicians counselling their patients about the early detection of prostate cancer.

Keywords

guideline, prostate cancer, PSA testing, risk stratification, screening

BJU Int 2014; 113: 186-188

wileyonlinelibrary.com

- **Consensus Statement 1:** For men aged 50-69 years, Level 1 evidence shows that PSA testing reduces the incidence of metastatic prostate cancer and prostate cancer-specific mortality rates.

- **Consensus Statement 2:** Prostate cancer diagnosis must be uncoupled from prostate cancer intervention.

- **Consensus Statement 3:** PSA testing should not be considered on its own, but rather as part of a multivariable approach to early prostate cancer detection.

- **Consensus Statement 4:** Baseline PSA testing for men in their 40s is useful for predicting the future risk of prostate cancer and its aggressive forms.

- **Consensus Statement 5:** Older men in good health with a > 10-year life expectancy should not be denied PSA testing based on their age.

Consensus Statement 1:

For men aged 50-69, Level 1 evidence demonstrates that PSA testing reduces prostate cancer specific mortality and incidence of metastatic prostate cancer.

ERSPC Trial
- 1991-2003 182,160 men from 7 centres, age 50-74 years
- screening reduced prostate cancer specific mortality by 21% and progression to metastatic disease by 30% (at 11 years follow-up)
- To prevent one death (at 11 years follow-up) – 936 men would need to be invited to screen and 33 cancers would need to be diagnosed.

Göteborg Subgroup of ERSPC
- randomised population-based trial (20,000 men screened from age 50 years) showed reduction in prostate cancer specific mortality by 44% at 14 years follow-up
- To prevent one death (at 14 years follow-up) – 293 men would need to be invited to screen and 12 cancers would need to be treated

Consensus Statement 2:

Prostate cancer diagnosis must be uncoupled from prostate cancer intervention.

– Active surveillance protocols have been developed and shown to be a safe option for many men with low volume, low risk prostate cancer. This does not address the issue of over-diagnosis, but does reduce excessive intervention.
The Natural History of Prostate cancer can vary enormously:

- slow indolent cancers with a long latent period of 10-15 years before they develop clinical disease (obstructive symptoms, metastases) and need treatment
- very aggressive cancers with progression to metastatic disease within a few years despite maximal treatment

Active surveillance programs use this long interval of “latent disease” in patients who have less aggressive cancers with a low risk of progression.

In Australia now, around 30% of newly diagnosed men with Prostate cancer are on active surveillance programs, with treatment with curative intent offered to those who show signs of cancer progression.
Consensus statement 3:

*PSA testing should not be considered on its own, but rather as a part of a multivariable approach to early prostate cancer detection.*

- Age specific PSA (reduces false negatives in young men, false positives in older men)
- PSA Velocity (or doubling time)
- Prostate Health Index (phi) – mathematical formula combines total PSA, free PSA and (-2) pro-PSA (a PSA isoform) (approx $95)
- Urinary PCA3, other new biomarkers

Online tools
- ERSPC risk calculator
- Prostate Cancer Prevention Trial risk calculator
Consensus statement 4:

**Baseline PSA testing for men in their 40s is useful for predicting the future risk of prostate cancer.**

An assessment at 40 years allows risk stratification before BPH-related PSA elevation occurs.

- Men with PSA levels below the median are less likely to develop Prostate cancer and need not be tested as often.
- Men with PSA levels above the median are at increased risk and should be tested more often.
Baseline Prostate-Specific Antigen Testing at a Young Age

Stacy Loeb, H. Ballentine Carter, William J. Catalona, Judd W. Moul, Fritz H. Schroder

Context: Prostate cancer screening is highly controversial, including the age to begin prostate-specific antigen (PSA) testing. Several studies have evaluated the usefulness of baseline PSA measurements at a young age.

Objective: Review the literature on baseline PSA testing at a young age (<60 yr) for the prediction of prostate cancer risk and prognosis.

Evidence acquisition: PubMed was searched for English-language publications on baseline PSA and prostate cancer for the period ending April 2011.

Evidence synthesis: In most published series, median PSA levels in the general male population range from approximately 0.4 to 0.7 ng/ml in men in their 40s and from approximately 0.7 to 1.0 ng/ml in men in their 50s. Evidence from both nonscreening and screening populations has demonstrated the predictive value of a single baseline PSA measurement for prostate cancer risk assessment. Specifically, men with baseline PSA levels above the age-group-specific median have a greater risk of prostate cancer diagnosis during the next 20–25 yr. Additional studies confirmed that higher baseline PSA levels in a young age are also associated with a greater risk of aggressive disease, metastasis, and disease-specific mortality many years later.

Conclusions: Baseline PSA measurements at a young age are significant predictors of later prostate cancer diagnosis and disease-specific outcomes. Thus baseline PSA testing may be used for risk stratification and to guide screening protocols.

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Prostate Cancer Risk Assessment

PSA Reference Ranges

<table>
<thead>
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<th>Age (years)</th>
<th>MEDIAN (µg/L)</th>
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<tr>
<td>20–29</td>
<td>0.7</td>
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<tr>
<td>30–39</td>
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<td>40–44</td>
<td>0.8</td>
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<td>45–49</td>
<td>0.86</td>
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<td>75–79</td>
<td>1.5</td>
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<td>80+</td>
<td>1.6</td>
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- Below the Lower Reference Limit (URL)
- PSA reference interval (95% of the population)
- The median is the PSA value at junction of green and lime bands
- Above the Upper Reference Limit (URL)
- Below average risk
- Above average risk
- Increased risk
Consensus Statement 5:

*Older men in good health with over 10 year life expectancy should not be denied PSA testing on the basis of their age.*

- As life expectancy improves, a small proportion of older men may benefit from an early diagnosis of more aggressive forms of prostate cancer, just as it is clear that men with .. competing co-morbidities are unlikely to benefit irrespective of age.

- Men should be assessed on an individual basis, particularly as life expectancy increases.
# NCCN Clinical Practice Guidelines in Oncology™

## Prostate Cancer

**V.1.2010**

<table>
<thead>
<tr>
<th>INITIAL PROSTATE CANCER DIAGNOSIS</th>
<th>INITIAL CLINICAL ASSESSMENT</th>
<th>STAGING WORKUP (TNM staging refers to 2002 Classification)</th>
<th>RECURRENT RISK</th>
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<tbody>
<tr>
<td><strong>Life expectancy ≤ 5 y and asymptomatic</strong></td>
<td><strong>No further workup or treatment until symptoms except for high risk patient</strong></td>
<td><strong>Bone scan if T1-T2 and PSA &gt; 20 ng/mL or Gleason score ≥ 8 or T3, T4 or symptomatic</strong></td>
<td>Clinically Localized:</td>
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<tr>
<td>DRE</td>
<td>PSA</td>
<td>Gleason primary and secondary grade</td>
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<td><strong>Life expectancy &gt; 5 y and symptomatic</strong></td>
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<td>Pelvic CT or MRI if T3, T4 or T1-T2 and nomogram indicated probability of lymph node involvement &gt; 20%</td>
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<td>Preferred treatment for any therapy is approved clinical trial.</td>
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**Note:** All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

*See Principles of Life Expectancy (PROSA).

*In selected patients where complications such as hydronephrosis or metastasis can be expected within 5 y, androgen deprivation therapy (ADT) or radiation therapy (RT) may be considered. High risk factors include bulky T3-T4 disease or Gleason score 8-10.

*Patients with multiple adverse factors may be shifted into the next higher risk group.
Prostate cancer: diagnosis and treatment

Issued: January 2014

NICE clinical guideline 175
guidance.nice.org.uk/cg175
Active surveillance

- Offer active surveillance (in line with the following recommendation) as an option to men with low-risk localised prostate cancer for whom radical prostatectomy or radical radiotherapy is suitable. [new 2014]

- Consider using the protocol in table 2 for men who have chosen active surveillance. [new 2014]

Table 2 Protocol for active surveillance

<table>
<thead>
<tr>
<th>Timing</th>
<th>Tests</th>
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<tbody>
<tr>
<td>At enrolment in active surveillance</td>
<td>Multiparametric MRI if not previously performed</td>
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</tbody>
</table>
| Year 1 of active surveillance         | Every 3–4 months: measure PSA²  
                                         | Throughout active surveillance: monitor PSA kinetics³  
                                         | Every 6–12 months: DRE⁴  
                                         | At 12 months: prostate rebiopsy                              |
| Years 2–4 of active surveillance      | Every 3–6 months: measure PSA²  
                                         | Throughout active surveillance: monitor PSA kinetics³  
                                         | Every 6–12 months: DRE⁴                              |
| Year 5 and every year thereafter until | Every 6 months: measure PSA²  
                                         | Throughout active surveillance: monitor PSA kinetics³  
                                         | Every 12 months: DRE⁴                              |
Optimal care pathway for men with prostate cancer
Prostate Cancer Optimal Care Pathway

Step 1  
Prevention and early detection

Prevention: The causes of prostate cancer are not fully understood and there is currently no clear prevention strategy.

Early detection  
Risk factors include:
• increasing age
• family history of prostate cancer
• certain dietary factors

Case finding: Men at higher risk (based on their family history) should be counselled regarding their risk. Annual digital rectal examination (DRE)/PSA testing should be considered.

Men in good health may consider tests for early detection after discussing the risks and benefits with their primary care provider.
Prostate Cancer Optimal Care Pathway

Step 2
Presentation, initial investigations and referral

Signs and symptoms
- The majority of men presenting with prostate cancer have no symptoms.
- Symptoms of locally advanced disease may include irritation on urination, obstructive urinary symptoms and/or blood in the urine.

Initial investigations include:
- DRE
- PSA level
- Measurement of free-to-total PSA ratio.

Assessments by the general practitioner should be completed within one week.

Referral: The patient should be referred to a urologist within six to 12 weeks (without symptoms) and earlier if symptomatic.

Communication – lead clinician¹ to:
- Explain to the patient/carer who they are being referred to and why
- Support the patient/carer while waiting for specialist appointments.

The significance of rising PSA (i.e. free-to-total PSA ratio), even within the age-adjusted normal range, should be recognised, as well as a PSA that is at the high end of the normal range in younger men.
Prostate Cancer Optimal Care Pathway

Step 2: Presentation, initial investigations and referral

This step outlines the process for establishing a diagnosis and appropriate referral. The types of investigation undertaken by the general or primary practitioner depend on many factors, including access to diagnostic tests and medical specialists and patient preferences.

2.1 Signs and symptoms

The majority of men presenting with prostate cancer have no symptoms.

A minority of men present with locally advanced disease. Symptoms and signs of locally advanced disease may include obstructive or irritative urinary symptoms or blood in the urine.

Only a small percentage of men present with metastatic disease; symptoms may include back pain, bone pain, weight loss and neurological symptoms, and/or symptoms of the primary cancer.

2.2 Assessments by the general or primary medical practitioner

Investigations prior to referral should include:

- DRE
- PSA level (Frydenberg 2007), recognising the effects of age on normal reference ranges.

An abnormal result should be discussed face to face with the patient, and information provided.

The significance of rising PSA, even within the age-adjusted normal range in an individual man, should be recognised, as well as a PSA that is at the high end of the normal range in younger men. Measurement of free-to-total PSA ratio may be helpful in assessing the clinical significance of an elevated PSA.
2.3 Referral
The patient should be referred to a urologist (Fellow of the Royal Australasian College of Surgeons (FRACS) or equivalent) who is affiliated with or has access to a multidisciplinary team (and multidisciplinary team meetings).

Referral for suspected prostate cancer should incorporate appropriate documentation sent with the patient including:

- a letter that includes important psychosocial history and relevant past history, family history, current medications and allergies
- results of current clinical investigations and abnormal results (DRE and/or PSA)
- results of all prior relevant investigations
- notification if an interpreter service is required.

If access is via online referral, a lack of a hard copy (of results) should not delay referral.

3.3.2 Responsibilities of individual team members
The general or primary medical practitioner who made the referral is responsible for the patient until care is passed to another practitioner.

The general or primary medical practitioner may play a number of roles in all stages of the cancer pathway including diagnosis, referral, treatment, coordination and continuity of care, as well providing information and support to the patient, their carer and family.
Prostate Cancer Optimal Care Pathway

Step 3
Diagnosis, staging and treatment planning

Implications of both a positive and negative biopsy result should be discussed with the patient before biopsy. A prostate biopsy should not be offered on the basis of serum PSA level alone.

Diagnosis and staging:
- prostate biopsy
- with or without prostate magnetic resonance imaging (MRI).

The use of staging investigations in men with clinically localised disease should be based on their risk of metastatic spread (Gleason score, clinical stage, PSA), and provisional treatment intent. Tests may include:
- DRE assessment
- Isotope bone scans
- Computed tomography (CT) scan and/or prostate MRI
- Interval reimaging (to determine the appropriate timing of androgen deprivation therapy (ADT).

Treatment planning: All newly diagnosed patients should be discussed by a multidisciplinary team before beginning treatment.

Research and clinical trials: Consider enrolment where available and appropriate.

Communication – lead clinician to:
- discuss a timeframe for diagnosis and treatment with the patient/carer
- explain the role of the multidisciplinary team in treatment planning and ongoing care
- provide appropriate information or refer to support services as required.

Offer advice on how to access support from prostate cancer peer support groups and groups for carers; visit www.prostate.org.au for local area listings.
Prostate Cancer Optimal Care Pathway

Step 4

Treatment:
Establish intent of treatment:
- curative
- anti-cancer therapy to improve quality of life and/ or longevity without expectation of cure
- symptom palliation.

If curative treatment is considered, men should be offered an opportunity for a second opinion in order to have a balanced view about the available treatment options.

Treatment of localised or locally advanced prostate cancer:
- **Watchful waiting:** some patients (for example, those with other health issues who are not expected to live more than 7 years) should be monitored and symptoms treated if they arise.
- **Active surveillance:** some men with low-risk prostate cancer should be regularly monitored for signs of disease progression so curative treatment can be initiated if necessary.
- **Surgery (radical prostatectomy):** may benefit some men with at least a 10-year life expectancy.

- Radiation therapy by external beam radiotherapy (EBRT) or brachytherapy +/- ADT: may benefit patients with at least a 10-year life expectancy.

Treatment of advanced prostate cancer:
- **ADT** is the standard treatment. The timing of starting ADT is often related to balancing the risk of side effects against the unwanted effects of the disease.
- For patients with metastatic disease, chemotherapy, second-generation anti-androgens, bisphosphonates and RANK ligand inhibitors may be of benefit.
Prostate Cancer Optimal Care Pathway

Step 5
Care after initial treatment and recovery

Cancer survivors should be provided with the following to guide care after initial treatment:

Treatment summary (provided to the patient, carer and general practitioner) outlining:
- diagnostic tests performed and results
- tumour characteristics
- type and date of treatment(s)
- interventions and treatment plans from other health professionals
- supportive care services provided.

Follow-up care plan (provide a copy to patient/carer and general practitioner) outlining:
- medical follow-up required (tests, ongoing surveillance)
- care plans for managing the late effects of treatment
- a process for rapid re-entry to medical services for suspected recurrence.

Communication – lead clinician to:
- explain the treatment summary and follow-up care plan to the patient/carer
- inform the patient/carer about late effects, secondary prevention and healthy living
- discuss the follow-up care plan with the patient’s general practitioner.
Prostate Cancer Optimal Care Pathway

Step 6
Managing recurrent, residual and metastatic disease

Detection: Most residual or recurrent disease will be detected by a rising PSA in asymptomatic men.

Treatment: Where possible, refer the patient to the original multidisciplinary team. Treatment will depend on the location and extent of disease, previous management and patient preferences.

Palliative care: Early referral to palliative care can improve quality of life and in some cases survival. Referral should be based on need, not prognosis.

Communication – lead clinician to:
- explain the treatment intent, likely outcomes and side effects to the patient/carer.
Prostate Cancer Optimal Care Pathway

Palliative care: Early referral to palliative care can improve quality of life and in some cases survival. Referral should be based on need, not prognosis.

Communication – lead clinician to:
- discuss treatment options with the patient/carer including the intent of treatment as well as the risks and benefits
- discuss advance care planning with the patient/carer where appropriate
- discuss the treatment plan with the patient’s general practitioner.


Step 7
End-of-life care

Palliative care: Consider referral to palliative care if not already involved. Ensure that an advance care plan is in place.

Communication – lead clinician to:
- be open about the prognosis and discuss palliative care options with the patient
- establish transition plans to ensure the patient’s needs and goals are addressed in the appropriate environment.
# Summary – Optimal Timeframes

<table>
<thead>
<tr>
<th>Care point</th>
<th>Timeframe</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.2 Assessments by the General Practitioner</td>
<td>To be completed within 1 week</td>
</tr>
<tr>
<td>2.3 Referral to specialist</td>
<td>• Men without symptoms should see a specialist within 6-12 weeks of an abnormal result being identified.</td>
</tr>
<tr>
<td></td>
<td>• Men with symptoms should see a specialist earlier, depending on the urgency of the symptoms (including psychological distress).</td>
</tr>
<tr>
<td>3.1 Diagnostic work-up</td>
<td>Investigations to be completed within 4 weeks</td>
</tr>
<tr>
<td>4.2.1 Treatment - Surgery</td>
<td>Within 3 months of diagnosis</td>
</tr>
<tr>
<td>4.2.2 Treatment – Chemotherapy and other drug therapy</td>
<td>Within 3 months of diagnosis</td>
</tr>
<tr>
<td>4.2.2 Treatment – Radiation therapy</td>
<td>Timely consultation with a medical oncologist in patients who are not responding to first line therapy.</td>
</tr>
</tbody>
</table>
The Early Detection of Prostate Cancer in General Practice: Supporting Patient Choice

SIX DECISION STEPS – TALK TO YOUR PATIENT ABOUT:

1. What is your main concern?
2. What is prostate cancer and what tests are there?
3. What is your risk?
4. What are the pros and cons of early detection?
5. What is most important to you?
6. Your decision.

**What is your risk?**

- Of 1000 men who are aged 50 years, 144 will be diagnosed with prostate cancer before the age of 80.
- Younger men have a smaller chance of a diagnosis than older men. But if they are diagnosed with prostate cancer, younger men are more likely to die prematurely from it. This is because there is more time for the cancer to progress and younger men are less likely to die of other causes.

*What is the chance of a diagnosis of prostate cancer within the next 10 years?*

- For a man aged 40: 1 in 1000
- For a man aged 50: 14 in 1000
- For a man aged 60: 48 in 1000
- For a man aged 70: 80 in 1000
- For a man aged 80: 102 in 1000

*Family history increases risk, for example, a man with a father or brother diagnosed has at least twice the risk of a diagnosis. The risk increase is highest in relatives of men diagnosed before age 60 years, and decreases with increasing age of the affected relative.*

**What is most important to you?**

**For: Is this like you?**

- I'm concerned that I might get prostate cancer.
- I want the best chance of finding it early if I do get it.
- I'm not interested in waiting for all the proof to be in.
- I want to do everything possible to reduce my risk of dying from prostate cancer.

**Against: Is this like you?**

- I think my chance of getting prostate cancer is low.
- I am not convinced about the effectiveness of testing.
- I am more concerned about avoiding treatment side-effects if there is no guarantee I would be reducing my risk of dying from prostate cancer.

The authors do not specifically recommend any treatment in this publication. Information on prostate disease is constantly being updated. We have made reasonable effort to ensure that information was current at the time of production (03/10/2007).
The Early Detection of Prostate Cancer in General Practice: Referral Guide for Prostate Testing

This information is provided with the view that if a man chooses to be tested, he hopes to have the cancer detected at an early stage so that treatment options have the chance for cure. Testing of men with life expectancy less than 10 years is not normally recommended [14,16]. If PSA testing is performed a DRE is also recommended.

### Normal ranges for PSA

<table>
<thead>
<tr>
<th>Age range</th>
<th>50th percentile (median)</th>
<th>95th Percentile (upper limit of normal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-49</td>
<td>0.85</td>
<td>2.0</td>
</tr>
<tr>
<td>50-59</td>
<td>0.85</td>
<td>3.0</td>
</tr>
<tr>
<td>60-69</td>
<td>1.30</td>
<td>4.0</td>
</tr>
<tr>
<td>70-79</td>
<td>1.04</td>
<td>5.5</td>
</tr>
</tbody>
</table>

Men whose PSA is above the 50th (median) but below the 95th percentile have been shown to be at higher long term risk of prostate cancer compared with those below the median [17,18].

**Normal rate of change (velocity).** PSA velocity is calculated from at least three PSA measurements over 12 to 18 months, with a higher rate suggestive of increased cancer risk [19]. A threshold of 0.75ng/ml/yr is frequently used as a threshold to predict cancer [19,20]. PSA velocity increases with age and a lower cutoff has been proposed for men less than 80 years of age [21].

**Percentage free PSA (free to total percentage or FTP) is lower when cancer is present and may be helpful to distinguish cancer from benign prostatic enlargement in men with intermediate total PSA ranges (2.0 to 10.0 ng/ml) [14]. Cancer is likely if FTP is below 10% and a low risk if FTP is over 25%.

**Accuracy of test**

The positive predictive value of cancer given abnormal result is about 30% [18,22]. The positive predictive value of combined abnormal PSA and DRE is about 38 - 60% [23-26].

### Non cancer contributors to increases in PSA [27]

1. Benign prostate enlargement - accounted for to some extent by using age-based reference ranges and percentage free-PSA (see left).
2. Ejaculation: both total PSA and % free PSA increase (can remain altered for 6-48 hours).
3. Urinary infection.
4. Urinary retention (48 hours after resolution, PSA decreased by 50%).
5. Prostatitis or sub-clinical prostate inflammation (can remain higher for at least 6 weeks following resolution).
6. Prostatic massage but probably not routine DRE (prudent to take blood prior to DRE).
7. Prostate needle biopsy.
8. Bicycle riding has been reported not to change the PSA level [23,29].
9. Different manufacturer assays may cause variation (up to 10%).

*Other investigations to consider: MSU, Electrolytes, Creatinine*

**Consider referral if:**

- PSA exceeds upper or lower limit of normal for age range (95th percentile see table)
- PSA rate of change from a normal base is high
- DRE indicates nodularity or hard prostate

**Consider follow-up if:**

- PSA is in upper ranges of normal for age (exceeds median)
- Patient has a family history of prostate cancer
- Patient requests testing for the purpose of early detection

Recommended follow up intervals for the detection of early stage cancer may vary depending on the result of the PSA test [22,26-30]. Medicare Benefits Schedule for PSA as of August 2007, one patient episode in a 12 month period: refer to www.health.gov.au/mbsonline.

The authors do not specifically recommend any treatment in this publication. Information on prostate disease is constantly being updated. We have made reasonable effort to ensure that information was current at the time of production (03/10/2007).
Prostate Cancer Risk Assessment

PSA Reference Ranges

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>MEDIAN (µg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20–29</td>
<td>0.7</td>
</tr>
<tr>
<td>30–39</td>
<td>0.76</td>
</tr>
<tr>
<td>40–44</td>
<td>0.8</td>
</tr>
<tr>
<td>45–49</td>
<td>0.86</td>
</tr>
<tr>
<td>50–54</td>
<td>0.96</td>
</tr>
<tr>
<td>55–59</td>
<td>1.1</td>
</tr>
<tr>
<td>60–64</td>
<td>1.2</td>
</tr>
<tr>
<td>65–69</td>
<td>1.3</td>
</tr>
<tr>
<td>70–74</td>
<td>1.4</td>
</tr>
<tr>
<td>75–79</td>
<td>1.5</td>
</tr>
<tr>
<td>80+</td>
<td>1.6</td>
</tr>
</tbody>
</table>

- Below the Lower Reference Limit (LRL)
- PSA reference interval (95% of the population)
- The median is the PSA value at junction of green and lime bands
- Above the Upper Reference Limit (URL)
- Below average risk
- Above average risk
- Increased risk

PSA (µg/L)
Digital Rectal Examination (DRE)

- Increased firmness, hardness, nodularity, irregularity, asymmetry, cragginess

Sensitivity of DRE in detecting Prostate cancer

- GP: 26.5%
- Specialist Urologist: 61.8%

One in four men with a normal PSA have an abnormal DRE due to Prostate cancer

Health professionals need to be trained to do DRE properly if they are to competently assess Prostate cancer risk
Prostate Cancer Risk Assessment

Who Should be referred to a Urologist?

- **Age-specific PSA Elevated**
- **DRE Abnormal**
- **or Both**
- **PSA Velocity**
  - PSA rising at greater than 0.5ng/ml/year is suspicious for cancer
  - PSA doubling time
    - <2 years – high risk
    - <5 years – intermediate risk
    - > 5 years low risk
- **Free/Total PSA Ratio** – can help to distinguish non-cancer from cancer for PSA in the range 2-10ng/ml. A FT ratio <11% is suspicious for cancer (a higher level does not exclude cancer)
- **Prostate Health Index (phi) > 45**
# Prostate Cancer Risk Assessment

## Individualized Risk Assessment of Prostate Cancer

**PCPTRC 2.0**

<table>
<thead>
<tr>
<th>Enter Your Information</th>
<th>PCPTRC 2.0 and Adjusted Risk Calculators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race</td>
<td>PCPTRC 2.0</td>
</tr>
<tr>
<td>Age</td>
<td>%freePSA</td>
</tr>
<tr>
<td>PSA Level</td>
<td>Download the R Code</td>
</tr>
<tr>
<td>ng/ml</td>
<td></td>
</tr>
<tr>
<td>Family History of Prostate Cancer</td>
<td>PCPTRC 1.0 and Adjusted Risk Calculators</td>
</tr>
<tr>
<td></td>
<td>BMI</td>
</tr>
<tr>
<td></td>
<td>PCA3</td>
</tr>
<tr>
<td></td>
<td>Finasteride</td>
</tr>
<tr>
<td></td>
<td>%freePSA</td>
</tr>
<tr>
<td></td>
<td>[2]proPSA</td>
</tr>
<tr>
<td></td>
<td>%freePSA and [2]proPSA</td>
</tr>
<tr>
<td></td>
<td>Prostate Volume and Number of Biopsy Cores</td>
</tr>
<tr>
<td></td>
<td>AUA Symptom Score</td>
</tr>
<tr>
<td></td>
<td>Finasteride with Volume</td>
</tr>
<tr>
<td></td>
<td>Finasteride with AUA Symptom Score</td>
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<tr>
<td></td>
<td>Download the R Code</td>
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</tbody>
</table>

Multiparametric-MRI (mp-MRI) Risk Stratification

Prostate mp-MRI combines

1. high resolution T2 weighted Images (T2WI) which detect zonal anatomy, extracapsular extension, NVB, SV & other local staging.

2. functional MRI techniques – diffusion weighted imaging (DWI) and MR Spectroscopy add specificity to lesion characterisation, while dynamic contrast enhanced MRI (DCE-MRI) has a high sensitivity in cancer detection.

Dual reporting is required.

The combination of different MRI modalities gives more accurate assessment of anatomy, tissue density and blood supply.
Multiparametric-MRI (mp-MRI) Risk Stratification

A PI-RADS score 1-5 is given to every abnormal lesion.

- PI-RADS 1 = Clinically significant disease is **highly unlikely** to be present
- PI-RADS 2 = Clinically significant cancer is **unlikely** to be present
- PI-RADS 3 = Clinically significant cancer is **equivocal**
- PI-RADS 4 = Clinically significant cancer is **likely** to be present
- PI-RADS 5 = Clinically significant cancer is **highly likely** to be present.
Multiparametric-MRI (mp-MRI) for Risk Stratification

Advantages

• Detects lesions ≥ 7mm, or Gleason grade 4 or 5

• Low Risk cancers – reassure that active surveillance is appropriate, helps plan nerve sparing surgery

• Intermediate and high risk - improved detection of extracapsular extension, SV involvement, regional lymphadenopathy and bone involvement

• mp-MRI targeted biopsies may lead to
  – fewer biopsies, with fewer cores at each biopsy
  – reduced detection of clinically insignificant disease
  – better representation of disease burden "cancer core length, Gleason score"
Multiparametric-MRI Prostate

Multiparametric-MRI (mp-MRI) for Risk Stratification

Disadvantages

- MRI contraindications, claustrophobia
- Reporting – mpMRI is highly technique and operator dependent. Dual reporting by 2 Uro-Radiologists
- Cost - not currently reimbursed by Medicare or private health funds. This significantly adds to cost of Prostate cancer risk assessment
- No prospective randomised trials to assess the role of mp-MRI in Prostate cancer screening

Multiparametric-MRI is should not be considered as definitive, but rather part of a comprehensive assessment.

Prostate biopsy (TRUS or TPBx) is still needed to confirm cancer histologically and to assess cancer volume and Gleason score (Grade Group).
PSMA PET-CT scan

Ga$^{68}$ labelled Prostate-specific Membrane Antigen (PSMA) PET-CT

Very sensitive imaging modality which can detect small volume recurrent prostate cancer or metastatic disease.

Promising, still under evaluation.

No Medicare rebate, availability is limited in Australia and worldwide.
PSMA PET-CT scan

Indications

• PSA rise on follow-up after prostatectomy or other definitive treatment (higher pickup when PSA >0.2ng/ml)

• Not used in initial staging of newly diagnosed men – yet
What type of Prostate Biopsy?

Trans-Rectal (TRUS) vs Trans-Perineal Ultrasound-guided Biopsy

**Trans-Rectal**
- 14-16 cores
- Inadequate sampling of anterior prostate
- Sepsis 1-2% (ESBL)
- Retention <1%
- Bleeding mild

**Trans-Perineal**
- 20 areas sampled with multiple cores
- mp-MRI fusion
- Sepsis almost 0%
- Retention 2-5%
- Bleeding increased, pelvic haematoma
- Erectile dysfunction
- Peri-prostatic scarring
- Anaesthetic Risk
- Increased cost
Prostate Cancer Risk Assessment

Transperineal Biopsy Template

1. Right Lateral
2. Right Medial Anterior Apex
3. Right Medial Anterior Base
4. Right Medial Posterior Apex
5. Right Medial Posterior Base
6. Right Parasagittal Anterior Apex
7. Right Parasagittal Anterior Base
8. Right Parasagittal Posterior Apex
9. Right Parasagittal Posterior Base
10. Midline Posterior Apex
11. Midline Posterior Base
12. Left Parasagittal Anterior Apex
13. Left Parasagittal Anterior Base
14. Left Parasagittal Posterior Apex
15. Left Parasagittal Posterior Base
16. Left Medial Anterior Apex
17. Left Medial Anterior Base
18. Left Medial Posterior Apex
19. Left Medial Posterior Base
20. Left Lateral
# Prostate Cancer Risk Stratification

<table>
<thead>
<tr>
<th>Low Risk</th>
<th>Intermediate Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 – T2b</td>
<td>T2c – T3a</td>
<td>T3b – T4</td>
</tr>
<tr>
<td>Gleason &lt; 7</td>
<td>Gleason 7</td>
<td>Gleason &gt; 7</td>
</tr>
<tr>
<td>PSA &lt; 10</td>
<td>PSA 10 - 20</td>
<td>PSA &gt; 20</td>
</tr>
</tbody>
</table>

D’Amico 1998
Prostate Cancer Risk Stratification

- Death
- Symptoms
- Cancer Size
- Abnormal cell
- Fast
- Slow
- Very Slow
- Non-progressive
- Time
- Death from other causes
The Decision – Informed Choice

Patient Factors

- Does the patient want treatment?
- What is his life expectancy, and his expected quality of life?
- Active surveillance – can he live with cancer diagnosis and no treatment/delayed treatment?
- What quality of life is he prepared to sacrifice to be cured of his cancer (continence, sexual function, bowel dysfunction, time off work)?
The Cancer

- Is this Prostate cancer life threatening or likely to cause significant morbidity?
- Is this Prostate cancer curable with the treatment options available?

Treatment Options for this Man

- What potentially curative treatment options are available?
  - Clinical factors
  - Increased risk of side effects in this man (LUTS, rectal toxicity, sexual dysfunction)
  - Access to services (eg. geography, family support, travel)
  - Cost – treatment, transport and accommodation, time off work
Treatment of Localised CaP

Treatment options

Active Surveillance/Watchful waiting

Radical Prostatectomy
- Open Retropubic, Perineal, Laparoscopic, Robotically-Assisted RP

Radiotherapy
- Intensity Modulated External Beam (IMRT)
  - +/- Neo-adjuvant LHRH to downsize
  - +/- Adjuvant LHRH for 2-3 years (survival advantage)
- Brachytherapy
  - Low Dose Rate Permanent Seeds (I^{125})
  - High Dose Rate + EBRT

Hormone Therapy
- LHRH (eg Goserelin, Leuprorelin)
- Antiandrogen (steroidal or non-steroidal)
Treatment of Localised CaP

“No Treatment...Yet”

Active surveillance – for men who would benefit from treatment but where the cancer is too small to recommend active treatment.
   – Close monitoring
   – change in PSA, size or aggressiveness (which requires repeat biopsy at defined intervals)
   – If the cancer is found to progress, then definitive treatment with surgery or radiotherapy is offered.
   – Currently around 25-30% of men newly diagnosed with Prostate cancer in Australia are commenced on Active Surveillance.

Watchful waiting is the no treatment option for elderly men who are not likely to benefit from definitive treatment.
   – Observation of PSA and symptoms, no repeat biopsy.
Treatment of Localised CaP

Radical Prostatectomy - History

1906 – first Radical Prostatectomy at Johns Hopkins University

Early 1980’s - Dr Patrick Walsh et al published anatomical studies on pelvic venous and nerve anatomy.

The Walsh Radical Prostatectomy (or open Radical Prostatectomy) revolutionised the surgical technique and dramatically reduced blood loss and surgical morbidity.

1990’s–now - refinements in technique, including "nerve sparing" Radical Prostatectomy
Open Radical Prostatectomy

Open Radical Prostatectomy - Technique

• Retropubic approach
• +/- Pelvic Lymph Node Dissection
• Dorsal Venous complex ligated and divided
• +/- Nerve sparing prostate dissection
• Urethra transected, prostate mobilised, Bladder neck divided
• Vesico-urethral Anastamosis
Open Radical Prostatectomy - Pathology
Open Radical Prostatectomy

Recovery of Continence

- Continent
- Occasionally incontinent
- Severely incontinent

N = 1499, 1298, 953
Victorian Radical Prostatectomy Register 1995-2000
Open Radical Prostatectomy

Recovery of Erections Postoperatively (normal preoperative)

N = 717, 586, 422
Victorian Radical Prostatectomy Register 1995-2000
RCT: Open Radical Prostatectomy vs Active Surveillance

“The Scandinavian Trial”

795 men (mean age 65) randomised to active surveillance or Radical Prostatectomy

At 10 years follow-up the Radical Prostatectomy group had:
- 40% reduction in progression to metastatic disease
- 16% reduction of overall death rate

In addition men under 65 years had:
- Improved cancer-specific survival in surgical group (8.5% die of CAP vs. 19% in ww group)
- Lower chance of local disease progression requiring treatment for local symptoms of bleeding and obstruction in surgical group.

Bill-Axelson NEJM 2005
Conclusions:

In men < 65 years with 10 years follow-up, Radical Prostatectomy will
1. saves lives,
2. reduces complications of locally advanced cancer, and
3. reduces the rates of development of metastatic cancer
Robotic-assisted Radical Prostatectomy
Robot-assisted Radical Prostatectomy (RARP) - da Vinci™ Technique

- Console surgeon uses 3D HD images to drive computer simulation to manipulate the robotic arms
- Table-side surgeon inserts the laparoscope and x 4-5 laparoscopic ports for the robotic arms
- “Endowrist” instruments provide precise control with increased range of motion and improved dexterity
- The prostate is removed through the large port site
- Operative time 2½-6 hours
- Hospital stay 1-3 days, patient home with urethral catheter for 7-14 days
Robotic-assisted Radical Prostatectomy (RARP) highlights the concerns surrounding the increasing costs of Healthcare.

In Australia, RARP adds
- $AUD 3,000 to the cost of a Radical Prostatectomy (consumable costs, operating room time)
- additional $400 to $4,800 per case in capital costs and maintenance of the da Vinci Robot

Health Administrators are increasingly analysing the cost/benefit of new therapies to ensure that they are cost effective and improve QALY’s.
Controversy - Robotic-Assisted Prostatectomy

a “pseudo-innovation—a technology that increases costs without improving patients’ health”

a “fake innovation”

Dr Ezekiel Emanuel
Medical Oncologist and former White House Advisor

New York Times  May 2012
RCT: Radical Prostatectomy – Open vs RARP

THE LANCET

Robot-assisted laparoscopic prostatectomy versus open radical retropubic prostatectomy: early outcomes from a randomised controlled phase 3 study

John W Yaxley, FRACS, Geoffrey D Coughlin, FRACS, Prof Suzanne K Chambers, PhD, Stefano Occhipinti, PhD, Hema Samaratunga, FRCPath, Leah Zajdlewicz, MOrgPsy, Nigel Duglinson, FRACS, Prof Rob Carter, PhD, Scott Williams, MBBS, Diane J Payton, FRCPA, Joanna Perry-Keene, FRCPA, Prof Martin F Lavin, PhD, Prof Robert A Gardiner, AM MD

Published Online: 26 July 2016

Yaxley, J  Lancet Online July 26, 2016
RCT: Radical Prostatectomy – Open vs RARP

Open Retropubic RP vs RARP Randomised Trial (Brisbane, Australia)

• 326 men randomised to each treatment, 163 in each group.
• 151 underwent open retropubic RP, 157 underwent RARP

Results
• Postoperative complications - open 14 (9%) vs RARP 6 (4%) (p=0.052)
• Positive surgical margins – open 15 (10%) vs RARP 23 (15%) (NS)

• Urinary function scores did not differ at 6 and 12 weeks postop
• Sexual function scores did not differ at 6 and 12 weeks postop

Conclusion
• Similar functional outcomes at 12 weeks. Longer term follow-up needed.

Yaxley, J  Lancet Online July 26, 2016
Intensity Modulated Radiotherapy (IMRT)

Radiotherapy can be accurately focused onto the Prostate, minimising radiation toxicity to the adjacent bladder and bowel

- 78Gy in 39 fractions
- Fiducial (gold) seeds are inserted into the prostate (using TRUS) for targeting
- 5 treatments/wk = 8 weeks
- Neoadjuvant LHRH agonist given for 3-6 months prior to Radiotherapy to downsize intermediate to high risk cancers and reduce radiotherapy field, potentially minimising side effects to bladder and bowel
Low Dose Rate (LDR) Brachytherapy

Radioactive seeds are implanted trans-perineally into the prostate using a predetermined Radiotherapy dose plan.

Indications/Exclusions

- Men with localised (T1-2) Prostate Cancer with:
  - PSA < 10
  - Gleason ≤ 7 (3+4)
  - 10 year life expectancy

- Mild symptoms, prostate volume < 50cc, no previous TURP

Results

- 90% 15 year survival in Seattle, USA (equivalent to RP in select patients)
LDR Brachytherapy Seed Implantation

Permanent $^{125}$I seeds are implanted into the prostate trans-perineally by a Urologist and Radiation Oncologist.

$I^{125}$ seeds deliver a high dose of photons to a small, precise volume of prostate around the seed.

$I^{125}$ seeds decay with a T½ of 60 days.

Patients are radioactive and radiation safety precautions must be taken.

This treatment has been available at St John of God Bendigo for 11 years.
Low Dose Rate Brachytherapy

Urethral catheter in the bladder to visualize urethra and bladder base

Ultrasound probe in rectum for needle guidance

18 F needle for seed placement

Perineal template
Low Dose Rate Brachytherapy
Prostate Cancer - Conclusions

Lifetime Risk

- “Microscopic” Prostate cancer  
  - many of these cancers will be low risk.  
  - 30%

- “Clinical” Prostate cancer  
  - 10%

- Dying of Prostate cancer  
  - 4.1%

The Challenge

“For a patient with Prostate cancer, if treatment for cure is necessary, is it possible? If possible, is it necessary?”  
Whitmore 1970’s

or to put it another way,

“The challenge is to find men with significant disease who are going to benefit from diagnosis and treatment”.
"Treatment or no treatment decisions can be made once a cancer is found, but not knowing about it in the first place surely burns bridges"

Dr Joseph Smith, J Urology Editorial 2009
Androgen Deficiency

ANDROGEN DEFICIENCY IN THE AGING MALE
Androgen Deficiency - Late-Onset Hypogonadism (LOH)

• Since antiquity, the biological and clinical effects of testosterone and its deficiency were known. (eg loss of Qi or Chi in Chinese Medicine)

• Organotherapies – bulls testicles, tiger penis, deer horn etc.

• Phytotherapies – 1st Century Rome
  
  • Leeks and water of boiled asparagus - to treat impotence
  
  • Garlic and coriander taken with neat wine – good aphrodisiac
Androgen Deficiency

Androgen deficiency is primarily a clinical diagnosis, supported by consistent biochemical findings of repeatedly low serum testosterone levels.

Causes
- organic pathology of the H-P-T axis
- functional problem related to ageing (Late Onset Hypogonadism).

Diagnosis of LOH can be difficult as the symptoms and signs are non-specific and there is no evidence-based, universally agreed pathological cut-off level for “normal” testosterone.
Androgen Deficiency

PBS Authority Restrictions

Androgen replacement therapy (ART) is recommended for symptomatic androgen deficiency syndromes.

Contraindications - breast cancer, prostate cancer (diagnosed or suspected by abnormality of the PSA or DRE), untreated sleep apnoea or uncontrolled cardiac failure.

ART was previously supported by the PBS without the need for specialist consultation. In April 2015 PBS criteria changed. Patients now need to be seen (or have appointment booked with) a specialist prior to PBS Authority approval:

• Paediatrician for children
• Endocrinologist, Urologist or member of the Australian Chapter of Sexual Health Medicine for adults
Androgen Deficiency

Causes - Organic Pathology

Partial/Transient

- acute illness
- chronic illness (ESRF, COPD, HIV, DM)

Primary (elevated FSH/LH)

- testicular damage from trauma, infection, chemo/radiotherapy
- Klinefelter's syndrome, cryptorchidism

Secondary (FSH/LH low or normal)

- androgen deprivation therapy for Prostate cancer
- anabolic steroids (exogenous testosterone)
- pituitary tumour, surgery, radiation, trauma, infiltration (sarcoidosis, haemochromatosis)
- hyperprolactinaemia (tumour, drug side effect)
- morbid obesity/metabolic syndrome
- depression
- Cushing's syndrome
- alcohol
Androgen Deficiency

Investigating Men with Suspected Androgen Deficiency

History and Examination
• reduced libido, decreased spontaneous erections, breast discomfort, loss of body hair/reduced shaving
• incomplete or delayed sexual development (if hypogonadism occurs before or during puberty), small testes, infertility, osteoporosis/pathological fractures.

Biochemistry
• Initial total Testosterone (fasting, morning due to diurnal variation, higher levels in morning, food reduces testosterone by as much as 25%). No generally agreed lower limit of normal, but for PBS Authority <6nmol/L.
• Second test (morning, fasting), total and free testosterone, SHBG, FSH/LH and prolactin

Referral to a specialist is required for PBS authority.

Abnormal levels
• Testosterone < 6nmol/L
• LH > 1.5 times upper limit of normal range for Primary Androgen Deficiency
Late-Onset Hypogonadism (LOH) & the PBS

- Late-onset hypogonadism, or “Male Menopause” occurs in men over the age of 40 years.

- LOH is usually due to functional (and potentially reversible) causes such as obesity and depression. The diagnosis may be difficult.

- There are no long-term randomised controlled trials in men with LOH to show a proven benefit (i.e. fracture reduction, improved functional morbidity or mortality) from androgen replacement in this group of men.

- The Testosterone level required for PBS authority approval has been reduced from 8nmol/L to <6nmol/L for these men. There is no “Grandfather” clause.

- Many men with borderline or low testosterone levels may feel symptomatically better on testosterone replacement, but do not have any organic pathology and do not fulfil the new criteria for PBS authority.
Reassessing Men already on Testosterone

All previous testosterone levels are needed. If two previous testosterone levels were <6nmol/L, the specialist can seek PBS authority and the replacement can continue uninterrupted. The GP can manage the patient's future testosterone treatment.

If there is inadequate documentation of previous biochemical levels, or if they do not fulfil the criteria (<6nmol/L) the patient will need to stop the androgen replacement. The testosterone levels will need to be reassessed once they have returned to pre-treatment levels. If the patient has recurrent symptoms and testosterone levels <6nmol/L on repeated testing, the patient would qualify for treatment under the new PBS criteria.

Sometimes low testosterone levels will have spontaneously improved, and the patient will no longer need androgen replacement therapy.

Some patients will want to remain on testosterone on a private prescription, without PBS subsidy.
Androgen Deficiency

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