Metro North Hospital and Health Service *Putting people first*

Cancer Preceptorship for General Practitioners 2018

Prostate Cancer

Screening and Surveillance

Dr Robyn Cheuk, Senior Radiation Oncologist, Cancer Care Services, RBWH

PSA and Prostate Cancer

- Prostate cancer is an important health issue in Australia
  - Second most commonly diagnosed cancer in Australian men (after skin cancer)
  - Second most common cause of cancer death in Australian men (after lung cancer)
  - Australia has one of the highest incidence rates of prostate cancer in the world (119.2 per 100,000 men, age-standardized) partly due to widespread PSA testing (not as per Australian guidelines for screening)
  - In 2018, estimated 17,729 men will be diagnosed with prostate cancer

PSA (Prostate Specific Antigen)

- PSA is a glycoprotein produced by the prostate gland
  - Free PSA
  - Bound PSA
  - Total PSA = free and bound PSA, measured as the standard PSA test
- There is a range of values for PSA regarded as normal which can vary with age
- PSA values are used for
  - Screening for prostate cancer in men not known to have prostate cancer
  - Surveillance after diagnosis
  - Surveillance after treatment
  - Monitoring response during treatment

PSA Screening for Prostate Cancer remains controversial

- PSA levels are not specific for prostate cancer (specificity range 6 – 66%)
    - > 4ng/mL positive predictive value of 30%
    - <4 ng/mL negative predictive value of 85% (ie 15% will have prostate cancer)
- PSA levels do not indicate the level of aggressiveness of a prostate cancer
- Requires a prostate biopsy to establish diagnosis which has morbidity (with >15% false positive result over 10 year screening period)
- Risk of over diagnosis estimated from 23% - 67% in US and European screening trials (i.e. when prostate cancer would not have become symptomatic in patient's lifetime so treatment would result in harm with no benefit, risk is highest in men >70)

PSA Screening for Prostate Cancer remains controversial

- Risk of overtreatment and associated morbidity and reduction in quality of life:
  - Infection, bleeding and pain with biopsy
  - Urinary incontinence, erectile dysfunction and bowel problems associated with treatment
    - Prostatectomy – 1 in 5 long term incontinence needing pads, 2 in 3 erectile dysfunction
    - XRT - >50% erectile dysfunction, 1 in 6 have long term bowel symptoms including urgency and faecal incontinence
- The benefit of population-wide PSA testing in avoiding death from prostate cancer is only modest
  - 1.3 fewer prostate cancer deaths per 1000 men between 55-69 y screened over 13 years
  - Prevent 3 cases of metastatic prostate cancer per 1000 men aged between 55-69 y screened
  - No benefit seen in men 70 y and older

PSA Screening and Surveillance Australian Guidelines (Cancer Council Australia 2016)

- Men aged 50 – 69 y (average risk of prostate cancer)
  - Discuss the benefits and harms of testing and who decide to undergo regular testing for prostate cancer, offer PSA testing every 2 years from age 50 to age 69, and offer further investigation if total PSA is greater than 3.0 ng/mL
- Men 70 years or older
  - Discuss the benefits and harms of testing (the harms of PSA testing likely to be greater than the benefits in this age group) ie. cease screening
- Not useful to screen men < 40 y age
- Men 40 - 50 y could be screened after appropriate counselling of risks v benefits especially if at increased risk e.g. if FH for prostate cancer, could offer testing from 40 y of age
- Since any mortality benefit from early diagnosis of prostate cancer due to PSA testing is seen after 6–7 years from testing, PSA testing is not recommended for men who have < 7 year life expectancy

  - Due for revision in 2019
  - Medicare rebate for multiparametric prostate MRI from 1 July 2018 – could reduce the number of men subjected to biopsies and guide more targeted biopsies for those with a significant lesion on imaging (rebate only if referred by urologist)
  - NSW 45 and Up Study analysis found that significant men >70 y and <50 y are being tested

USPTF Recommendations 2018

JAMA. 2018;319(18):1901–1913. doi:10.1001/jama.2018.3710
Published May 8, 2018

USPTF Recommendations 2018

Screening for Prostate Cancer

Population

ADULT MEN
Without symptoms of prostate cancer

USPSTF recommendation grade

C

Men aged 55 to 69 years
Recommendation depends on the patient's situation.

D

Men aged 70 years or older
Not recommended

C = recommends selective use, based on clinical judgement and patient preference, moderate certainty that net benefit is small
D = recommends against this, moderate to high certainty that this has no net benefit or that harms outweighs benefits

USPTF Recommendations 2018

Population	Men aged 55 to 69 y	Men 70 y and older
Recommendation	The decision to be screened for prostate cancer should be an individual one. Grade: C	Do not screen for prostate cancer. Grade: D

Informed Decision Making	Before deciding whether to be screened, men aged 55 to 69 years should have an opportunity to discuss the potential benefits and harms of screening with their clinician and to incorporate their values and preferences in the decision. Screening offers a small potential benefit of reducing the chance of death from prostate cancer in some men. However, many men will experience potential harms of screening, including false-positive results that require additional testing and possible prostate biopsy; overdiagnosis and overtreatment; and treatment complications, such as incontinence and erectile dysfunction. Harms are greater for men 70 years and older. In determining whether this service is appropriate in individual cases, patients and clinicians should consider the balance of benefits and harms on the basis of family history, race/ethnicity, comorbid medical conditions, patient values about the benefits and harms of screening and treatment-specific outcomes, and other health needs. Clinicians should not screen men who do not express a preference for screening and should not routinely screen men 70 years and older.
Risk Assessment	Older age, African American race, and family history of prostate cancer are the most important risk factors for prostate cancer.
Screening Tests	Screening for prostate cancer begins with a test that measures the amount of prostate-specific antigen (PSA) protein in the blood. An elevated PSA level may be caused by prostate cancer but can also be caused by other conditions, including an enlarged prostate (benign prostatic hyperplasia) and inflammation of the prostate (prostatitis). Some men without prostate cancer may therefore have false-positive results. Men with a positive PSA test result may undergo a transrectal ultrasound-guided core-needle biopsy of the prostate to diagnose prostate cancer.
Treatments	The 3 most common treatment options for men with screen-detected, localized prostate cancer are surgical removal of the prostate gland (radical prostatectomy), radiation therapy (external-beam radiation therapy, proton beam therapy, or brachytherapy), and active surveillance.

For a summary of the evidence systematically reviewed in making this recommendation, the full recommendation statement, and supporting documents, please go to https://www.uspreventiveservicestaskforce.org.

To reduce over diagnosis – lower age at which to stop screening, increase interval to 2-4 years instead of annually, higher PSA levels to trigger biopsy

Recommendations of Others

- The American Academy of Family Physicians and the Canadian Task Force on Preventive Health Care recommend against PSA-based screening for prostate cancer.
- The American College of Physicians recommends that clinicians discuss the benefits and harms of screening with men aged 50 to 69 years and only recommends screening for men who prioritize screening and have a life expectancy of more than 10 to 15 years.
- The American Urological Association recommends that men aged 55 to 69 years with a life expectancy of more than 10 to 15 years be informed of the benefits and harms of screening and engage in shared decision making with their clinicians, taking into account each man's values and preferences.
  - To reduce the harms of screening, the screening interval should be 2 or more years.
  - Decisions about screening, including potentially starting screening before age 55 years, should be individual ones for African American men and men with a family history of prostate cancer.
- The American Cancer Society adopted detailed screening recommendations in 2016 that highlight the importance of shared decision making and the need for informed discussion of the uncertainties, risks, and potential benefits of screening.
  - Discuss screening beginning at age 50 years and earlier for African American men and men with a father or brother with a history of prostate cancer before age 65 years

Low Risk Prostate Cancer

- GPs are in a position to present to men with favourable risk prostate cancer (Gleason 6 or lower, PSA < 10 ng/mL, T1-T2a disease, ISUP 1) with management options, balancing benefits and harms of the options
  - Active surveillance
  - Surgery (radical prostatectomy)
  - Radiotherapy
    - External beam
    - Brachytherapy (low dose rate/seed brachytherapy)

Surveillance

- Conservative management for prostate cancer consists of two very different strategies:

  - **Watchful Waiting** or observation - without curative intent, less intensive follow-up, relying on a change of symptoms to decide if treatment is needed.

  - **Active Surveillance** or expectant management - a postponement of immediate therapy with serial testing for disease progression to offer selective delayed treatment with curative intent

Active Surveillance

- Avoid unnecessary treatment of men with indolent prostate cancer (approx. 25% of new diagnoses) and treat only those who show signs of disease progression by close follow-up of patients diagnosed with low-risk prostate cancer, the risk of death due to prostate cancer over the next 10 years would be low, and would probably be no greater than if they were to choose immediate definitive treatment

- Offer active surveillance to men with prostate cancer if all the following criteria are met:
  - PSA ≤ 10 ng/mL
  - clinical stage T1-2a
  - Gleason score 6 or less

Active Surveillance

- Monitor PSA every 3 months, and a physical examination, including digital rectal examination, every 6 months
- Definitive treatment is offered at a time when disease progression is detected and cure is deemed possible or if the patient prefers to proceed to intervention
- For men aged less than 60 years, consider offering active surveillance based on the above criteria, provided that the man understands that treatment in these circumstances may be delayed rather than avoided
- If the man strongly prefers active surveillance, offer repeat biopsy to ensure that disease classification is accurate within 6–12 months of starting an active surveillance protocol and every 2-5 years (or MRI)

Active Surveillance

- Victorian study of Active Surveillance – only 1 in 4 had follow-up as per recommended protocol
  - Risks of repeated biopsies (or could mpMRI replace some of these)
  - Costs
  - Psychological distress
- Editorial review suggests that patients having active surveillance present an opportunity for GPs to offer a holistic approach, treating co-morbidities, enhancing QOL, active engagement of the patient

Watchful Waiting

- Not a curative option

- Reasons for undertaking watchful waiting include the following:

  - Disease is advanced and is incurable with local treatments
  - The patient's life expectancy is limited and prostate cancer is unlikely to cause significant problems in his lifetime
  - The patient chooses this option – some men may elect to undertake a program of watchful waiting rather than proceed with any of the localised disease management options with curative intent.

Watchful Waiting

- For men with potentially curable prostate cancer who are considering watchful waiting, advise that the risk of developing more advanced prostate cancer and dying from it is higher with watchful waiting than with immediate definitive treatment
  - If there is no evidence of significant disease progression (as indicated by 3–4 monthly PSA levels over 1 year and absence of relevant symptoms), continue monitoring by 6-monthly PSA levels
  - If there is evidence of significant disease progression (that is, relevant symptoms and/or rapidly-rising PSA level), refer to a member of the treating team (urologist, medical oncologist or radiation oncologist) for review.
- For men whose prostate cancer is advanced and is not curable
  - If no treatment is offered or accepted, monitor clinically and by PSA testing and reconsider androgen deprivation therapy if any of the following occur:
    - symptomatic local disease progression
    - symptomatic or proven metastasis
    - a PSA doubling time of < 3 months, based on at least three measurements over a minimum of 6 months (this should warrant consideration of further clinical investigations).

PSA surveillance after initial treatment

- There are no randomized trials that define the optimal surveillance strategy following definitive therapy for localized prostate cancer. The mainstay of follow-up in all patients is prostate-specific antigen (PSA) testing and clinical evaluation.
  - For men who have undergone definitive therapy for localized disease – suggest monitor PSA every 6 to 12 months for five years and then annually thereafter, routine imaging is not indicated in the absence of symptoms or a rising serum PSA
  - In patients with metastatic prostate cancer, surveillance should be geared toward the detection of progressive disease and the side effects of long-term androgen deprivation therapy. A physician visit and serum PSA level every three to six months is reasonable.

PSA surveillance after initial treatment

- **Surgery** – All prostate tissue is removed during a successful radical prostatectomy. Thus, any detectable PSA in the serum using the standard immunoassay (> 0.1 ng/mL) theoretically indicates remaining prostate tissue and presumably represents persistent or recurrent disease.
- **Radiation therapy** – The definition of a biochemical failure following RT is more complicated since there is benign prostate tissue remaining after RT.
  - The American Society for Radiation Oncology (ASTRO) has established guidelines to define PSA recurrence following RT. In the 2005 Phoenix criteria, a PSA rise of 2 ng/mL or more above the nadir PSA is considered the standard definition for biochemical failure after external beam RT.
  - The interpretation of an increase in serum PSA following RT is further complicated by the observation that serum PSA levels can fluctuate significantly after RT (particularly brachytherapy) before returning toward the post treatment nadir. Thus, increases in PSA must be interpreted with caution, and they do not necessarily indicate recurrence.

Salvage

- Treatment options are dictated by whether the recurrence is local or systemic and whether the initial treatment was surgery or radiation.
- Following radical prostatectomy – For men with a local recurrence following radical prostatectomy, RT may be a reasonable option for salvage therapy when there is no evidence of distant metastases. Salvage RT is most successful when the disease burden is low and when the relapse-free interval is 12 months or longer.
- Following prostate RT (external beam or seed brachytherapy) — Radical prostatectomy or ablation – Nano knife, cryotherapy, HIFU, HDR brachytherapy +/- androgen deprivation therapy.
- Distant metastases — For men with distant metastases and for those with a local recurrence who are not candidates for salvage therapy because of age or comorbidity, systemic treatment may be indicated. However, the optimal timing of such treatment is uncertain since treatment-related side effects can adversely affect QOL.

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