1. Screening, Early Diagnosis and Surgical Management of Prostate Cancer

Mr Alwin Tan (Urological Surgeon)

Diagnosis Consideration

- Fhx, Ethnicity and Agent Orange exposure
- DRE
- PSA
- Ultrasound
- MRI: ?50% of patients before bx
- Biopsy: transrectal vs transperineal
- Once diagnosis confirm: CT, BS
- ?PSMA Pet scan
- MRI does not replace the finger: 1 in 6 prostate cancer diagnosed have low PSA but picked up as irregularity on DRE

Gleason Score – The Prognosis

- Gleason score is from 1 – 5
- Gleason Sum = major gleason score + 2nd major gleason score
- +2 – 10 (majority 6 – 10)
- Carries the prognostic factor

Staging the Cancer

- Bone scan: esp. with symptom or PSA >10
- CT scan: look for lymph nodes (diagnosis based on size)
- MRI: soft tissue
- Endo rectal MRI: not specific enough

PSMA Pet Scan

- 1% false positive
- PSA >0.2
- Also picks up nodes and bone mets.

Victorian Prostate Cancer Registry: On Low Risk Prostate Cancer, Gleason 6

- 42% of men are diagnosed in Victoria with low risk prostate cancer Gleason 6 is managed with active surveillance
- A large proportion of the remaining have robotic surgery

Active Surveillance

- Postpone immediate therapy
- Definite treatment in place if progression
- Not like the old watchful waiting (for symptomatic or metastatic)

Arguments for:

- Prostate cancer not clinically significant yet
- Reliable parameter: clinical + pathological + imaging to help distinguish that less chance of progression and spread
- All treatments have some side effects
- Time and surveillance will pick out those than need to reclassify as higher risk
- ?psychological burden

Evidence

- Autopsy studies
- Epidemiological studies
- Prostate Bx trials

Guidelines for selection not universal: NCNN

- Fhx and ethnicity and agent orange exposure
- T1c or T2a clinically
- Gleason 6 – less than 3 cores +ve – less than 50% at core
- PSA 6 or less & PSA density < 0.15ng/ml/g
- MRI – small or not visible
- Repeat bx in 6-12 months
- Individual preferences
- ?PSA pet scan individual cases

Surveillance strategy – still in progress

- PSA change 3-6 monthly
- Repeat bx under 1 year and after that 2 – 4 years
- Up to 28% have higher grade missed

6 Shades of Prostate Cancer Based on Criteria

- Local therapy: new or relapse
- Gleason score – 6 vs. 7 vs. 8-10
- PSA <10, 10-20 vs. 20
- Digital rectal normal vs. nodule vs. mass
- % biopsy <50% vs. more at core
- Imaging ECE, SV, nodes, bones
- GOAL: get the best treatment for your stage

Shade 1 = low risk

- No previous therapy
- Small nodule or no nodule
- Gleason 6 and PSA <10
- Scan shows no ECE
- Monitor because:
  - Higher grade missed
  - New cancer develop

Shade 2 – Intermediate Risk

- No previous surgery
- Grade 7
- PSA 10-20
- Unilateral node
- Scan: no ECE

Shade 2 – 2 Groups

- Low risk
- Gleason 3+4 = 7
- % bx <50%
- Only one intermediate risk
- Management
- Active surveillance
- Seed implant – Brachytherapy
- IMRT
- Focal therapy
- Surgery
- ?Hormone therapy

Shade 2 – High Risk

- High risk
- Gleason 4+3 = 7
- Over 50% cores %
- 2 or more intermediate risk
- Scan –ve
- Options:
  - Surgery (but may get +ve margin)
  - IMRT
  - HDR

Shade 3: High Risk

- No previous treatment
- Gleason 8, 9, 10 or PSA >20
- ECE, SVI or node mets
- Options:
  - Surgery +/- consolidation XRT
  - IMRT -& anti androgen
  - ?Chemotherapy

Shade 4: Previous Local Treatment Rising PSA

- Good marker of relapse
- Find the location: now good imaging
  - Prostate region
  - Pelvic lymph node
  - Bones
- PSA doubling time
- Options:
  - Local: cryo? Hifu?
  - Radiotherapy
  - ?Add hormone

Shade 5 mets

- Radical surgery or chemo XRT

Surgery vs. Seeds

- J.Clinical Onc 29:362.2010
- Seeds implants shows better:
  - Urinary function
  - Sexual function
  - Overall satisfaction
- No difference in bowel function
- At 12 years out: equivalent or better "cure rate"

Seeds & Brachytherapy

- Now 13 years on the Mornington Peninsula

Advantage

- Day procedure
- High preservation of erection
- High preservation in ability to climax
- In cancer G6 and single core small Gleason 7: cancer free as good if not better than surgery
- Incontinence rare
- Back at work within 3 days
- Radioactive for 63 days

Beware

- No colonoscopy or Bx without contacting the radiation oncologist or the surgeon
- Biopsy can lead to FISTULA formation
- 1 patient out of 513 did not do that

Cancer Recurrance at 13 year follow up

- 5 patients in 825 cases
- 2% stricture
- 1% bladder irritation

Surgery: Radical Prostatectomy

Principles

- Save the nerve (neurovascular preservation)
- Preserve the external sphincter
- Preserve the bladder neck

If considered organ confined (T1 – T2): radical prostatectomy a choice

- Aim:
  - Preserve the nerves
  - Preserve the urethra
  - Preserve the bladder neck
- Risk:
  - Impotence risk 30-60%
  - Incontinence: 1-3% still uses pad at the end of 12 months
  - Home with IDC for 1-2 weeks

Penile Rehabilitation

- Start Viagra, Levitra or Cialis early
- Start at low dose
- Important to get patient to understand initially is micro vessels induction and erection may not happen till 6-12 months

Gel in Space & Gold

Advantage

- Temporary separation between rectum and prostate
- Day procedure
- Single needle insertion during gold seeds insertion
- Reduce radiation dose to rectum

Symptoms

- Minimal but may get some rectal symptoms
- Grade 1 at worst
- Gel absorbed over 3-6 months: need to keep bowel loose with Metamucil etc.
- Personal series of 30 with 15 completing 12 months follow up

Botox to Bladder

- Via a cystoscope
- Day procedure
- Now covered by PBS from September 2015
- Good for irritable bladder: mainly OAB (both neurogenic and non-neurogenic) and post radiation
- Can go into retention (so must be able to ISC if cannot avoid)

Green Light Laser

Where do we use it?

- Benign prostate for outlet obstruction
- Prostate cancer patient with obstructive issues: pre-brachytherapy and pre-external beam radiotherapy
- Post-radiotherapy: bladder neck stricture and radiation induced bleeding (beware of Xaroleta)

Advantages

- No need to stop any anti coagulation
- Small instrument compared to Gyrus or traditional TURP
- Almost no bleeding
- Most go home after one night (unless over 80yo)
- Must take it easy for 4 weeks (reactionary bleed especially on blood anticoagulation)

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2. Latest Improvements in Radiation Therapy for Prostate Cancer – Impact of New Technologies

Dr David Blakey (Radiation Oncologist)

CASE

- 51yo male, no significant prior health issues
- Screening PSA: 4.2
- DRE T1c
- Estimated prostate volume 19cc (renal tract US)
- TRUS-guided prostate biopsy = Gleason 3+3=6 Ca in 1 of 12 cores
- MRI: no abnormality detected ("active surveillance advised")
- Staging CT/bone scan: clear
- Urinary flow rate: peak 28ml/sec, mean 16ml/sec, res volume 90ml

Options

1. Active surveillance
2. Surgical prostatectomy
3. Prostatic IMRT with IG
4. LDR brachytherapy

MBS LDR Brachy

Requirements

- Prostate: radioactive seed implantation of, radiation oncology component, using transrectal ultrasound guidance, for localized prostatic malignancy at clinical stages T1 (clinically unapparent) or T2 (tumour confined within prostate)
- Gleason score ≤ 7
- PSA ≤ 10ng/ml (at the time of diagnosis)
- Procedure must be performed at an approved site in association with a urologist

Indications

- Histologically proven low to intermediate risk prostate cancer
- Clinical stage T1c-T2NX or N0M0 (UICC 1997)
- Pre-treatment PSA <10ng/ml
- Gleason score ≤ 7
- Ideally a prostate volume ≤ 50cc assuming no pubic arch interference
- Fit for general or spinal anaesthetic
- Life expectancy > 10 years
- Urinary function is satisfactory (e.g. urinary flow > 15ml/sec, IPSS <10)

Contra-indications

- Previous TURP (patients with minimal volume loss from previous TURP may still be considered if satisfactory dosimetry can be achieved)
- Higher risk patients with PSA > 10ng/ml and Gleason score > 7 are not suitable for permanent seed brachytherapy alone
- No contraindications on cystoscopy – no median lobe etc.

Brachy Process

1. Volume study
2. Implant (prescribed dose + 145Gy to PTV, using Iodine 125 seeds)
3. Post-implant dosimetry (CT scan)

Side Effects

- Short term: occur during or within a few weeks of finishing radiotherapy (usually temporary)
- Perineal bruising and swelling
- AUR
- Urinary frequency/dysuria
- Rectal urgency

- Long term side effects: may be permanent
- Urethral stricture
- Obstructive urinary symptoms
- Urinary incontinence
- Impotence
- Prostato-rectal fistulas (rare)
- Rectal bleeding (rare)

PSA Response:

- 12/13: 0.25
- 3/14: 0.25
- 9/14: 0.54
- 3/15: 0.36
- 9/15: 0.18
- 3/16: 0.16

CASE

- 64yo
- PSA 17.4
- TRUS prostate biopsy: Gleason 5+9 = 4 in every core
- Staging CT/bone scan clear
- Commenced GnRH agonist, continued for 2.5yrs
- Prostatic IMRT July-Sept 2010 (78Gy in 29 fractions)

PSA Response

- 03/11: 0.03
- 04/12: <0.03
- 03/13: <0.03
- 04/14: 0.26
- 01/15: 1.24
- 07/15: 3.08
- 04/16: 8.69

CASE

- 65yo fit man
- PSA 02/15: 6.2
- TRUS prostate biopsy: Gleason 3+4=7 malignancy
- 20.6.16 robotic prostatectomy
- Path: multifocal Gleason 4+3=7 prostate cancer, with extra-prostatic extension/+ve surgical margin R apex. SV/bilat nodes –ve

PSA Response

- 08/15: 0.03
- 10/15: 0.05
- 01/16: 0.08

Adjuvant Prostate Bed RT

- Post radical prostatectomy for adenocarcinoma prostate
- One of the following adverse pathological features:
    - Extraprostatic extension (pT3a, pT4)
    - Seminal vesicle invasion (pT3b)
    - Positive resection margins
- No evidence of lymph node or distant metastases
- Undetectable PSA
- ECOG 0-2
- Ideally within 4 months of radical prostatectomy

Salvage Prostate Bed RT

- Previous radical prostatectomy for adenocarcinoma prostate
- A persistently elevated PSA >6wks post radical prostatectomy (including elevations in the ultrasensitive range)
- A rising PSA from previously undetectably level
    - ***Note:* it is important to demonstrate a progression in the PSA from undetectable levels, particularly in the ultrasensitive range. PSA should be performed by the same laboratory)**
    - No evidence of distant metastatic disease
    - ECOG 0-2

3. What's New in Metastatic Prostate Cancer?

A/Prof Vinod Ganju (Medical Oncologist & Clinical Haematologist)

CASE

- 66yo male
- Presented to his GP with 2yr of LUTS
- PR = large hard prostate, bilateral involvement
- PSA 153
- Ref to an urologist
- CT and bone scan = large prostate, fatty change in the liver, no mets

Diagnosis & Staging

- MRI pelvis = 100ml prostate vol.
- Normal <30ml
- PSMA PET = LAPC, involving both lobes and seminal vesical, no LN or distal mets
- TRUS Bx: 8/8 cores positive for Gleason 9 adenoca
- Stage T3b N0 M0 (stage 3)
- LAPC locally advanced prostate ca

History

- FHx: nil for cancer
- PHx: morbid obesity (wt 151 kg, 161cm, BMI 55)
- Abdo liposuction, complicated by infection, slow healing
- NIDDM, HbA1c = 7.5%
- HT
- Hypercholesterolemia
- Depression in the past
- OA
- SHx: divorced, lives alone, in contact with his daughter
- IT consultant, self-employed, works part-time
- Ref to Meridith Studdert prostate care RN for counselling and support

Management

- TURP: major improvement in his LUTS
- PSA 61
- Considered for a clinical trial (ENZARAD) but found to be ineligible
- 5/15: ADT (Zoladex and Cosudex)
- 7/15: PSA nadir 16

- 11/15: PSA 33 while on ADT
- Chemotherapy (based on 2 trials)
    - STAMPEDE
    - GETUG 15
- Docetaxel chemotherapy for 6 cycles
- Dexamethasone premed given
- Required insulin on day 1
- Input from GP re. oral hypoglycemic and monitoring
- Main side effect was lethargy
- Completed chemotherapy 6 wks ago
- Awaiting cystoscopy
- Plan for radical radiotherapy to the prostate
- IMRT
- 70-78 Gy

Important side effects of Docetaxel chemotherapy

- Febrile neutropenia, septicaemia
- Lethargy
- Diarrhoea or constipation
- Nausea
- Myalgia
- Mouth ulcers
- Hair loss

Prostate Cancer Systemic Therapies: Historical Overview

- Orchiectomy alone
- Lutenizing hormone-releasing hormone (LH-RH) agonists:
    - May be associated with tumor flare when used alone
    - Initial concomitant use of antiandrogens should be considered in the presence of:
        - Liver pain
        - Ureteral obstruction
        - Impending spinal cord compression
- Leuprolide plus flutamide
    - The addition of antiandrogen to leuprolide has not been clearly shown in a meta-analysis to improve survival

- Estrogens (diethylstilbestrol [DES], chlorotrianisene, ethinyl estradiol, conjugated estrogens-USP and DES-diphosphate).
    - DES is no longer commercially available
- Immediate versus deferred hormonal therapy
- LH-RH agonists or antiandrogens
- Maximal androgen blockade (MAB)
- Continuous versus intermittent hormonal therapy
- Hormonal treatments added to external-beam radiation therapy (EBRT)
- Chemotherapy for hormone-resistant prostate cancer
- Bisphosphonates
- Bisphosphonates and decreasing risk of bone metastases
- Abiraterone acetate is an inhibitor of androgen biosynthesis that works by blocking cytochrome P450c17 (*CYP17*)
- Enzalutamide: an androgen-receptor signaling inhibitor
    - Has been shown to increase OS and QOL in men with metastatic prostate cancer that has progressed despite ADT
- Denosumab: a monoclonal antibody that inhibits osteoclast function
- Radiopharmaceutical therapy
- Immunotherapy

STAMPEDE

- Large, randomized, multiarm, multistage trial
- Ongoing since 2005
- Standard of care: androgen deprivation therapy with or without external beam radiation therapy
- Compares SOC **vs** SOC plus docetaxel **vs** SOC plus zoledronic acid **vs** SOC plus both agents
- Men with high-risk locally advanced or metastatic prostate cancer who are hormone therapy naïve
- Primary end point: OS
- Secondary endpoints:
    - Failure-free survival (FFS)
        - Prostate-specific antigen (PSA)
        - Local lymph node failure
        - Distant metastases
        - Prostate cancer death
    - Toxicity
    - Quality of life
    - Cost-effectiveness

Conclusions

- Cytotoxic Chemotherapy i.e. Docetaxel may benefit some patients be given earlier in the course of the disease
- It may be useful additional treatment in some patients with aggressive locally advanced disease
- Chemotherapy appears to confer greater benefit when given earlier rather than the previous approach of the “end of the line therapy”.