PROSTATE CANCER

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The diagnostic pathway, e.g. TRUS and biopsy, bone scan, MRI etc
- Gleason scoring and clinical staging
- Treatment options in early prostate cancer
- Treatment options in advanced prostate cancer

Presentation

- Screening
- Case Finding:
  - Family History
  - Racial Risk Groups
  - Well man check/pt choice
- LUTS
- Bleeding
- Systemic/Metastatic

DRE: “if you don’t put your finger in it, you might put your foot in it!”
- Size → risk stratification aid
- Soft/Firm/Nodular
- Other diagnoses:
  - Most prostate cancer in peripheral zone
  - 50% abnormal DREs associated with CAP
  - Only 40% cancers diagnosed by DRE are T1-2
  - “Normal” PSA + abnormal DRE → 30% chance cancer

Chance of Cancer

<table>
<thead>
<tr>
<th>PSA</th>
<th>4-10</th>
<th>&gt;10</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRE normal</td>
<td>27%</td>
<td>&gt;50%</td>
</tr>
<tr>
<td>DRE abnormal</td>
<td>45%</td>
<td>&gt;75%</td>
</tr>
</tbody>
</table>

The diagnostic pathway

- TRUS and biopsy
  - 12 cores
  - Antibiotics, local anaesthetic
  - Bleeding, sepsis 2→5%, retention
- Trans-perineal template/sector biopsy
  - 24-32 cores, can be 60-80
  - General anaesthetic
- Bone scan
  - Intermediate and high risk
- MRI
The diagnostic pathway

- MRI
- TRUS and biopsy
  - 12 cores
  - Antibiotics, local anaesthetic
  - Bleeding, sepsis 2->5%, retention
- Trans-perineal template/sector biopsy
  - 24-32 cores, can be 60-80
  - General anaesthetic
- Bone scan/PSMA or CHOLINE PET SCAN
  - Intermediate and high risk

Why is a diagnostic MRI useful?

- Goals:
  - Prevent unnecessary biopsies: large BPH, Stone
  - (1) To optimize treatment selection
    - Active surveillance
    - Focal therapy
    - Radical prostatectomy
    - Radiation or systemic therapy
  - (2) To optimize both cancer control (negative surgical margins) and recovery of sexual function (tailored approach to nerve sparing) in men undergoing open and robotic prostatectomy

MRI has become much better

- Multiparametric approaches
  - Diffusion Weighted MRI
    - short acquisition times
    - no need for intravenous administration of contrast medium
    - ability to study diffusion of water molecules that indirectly reflects tissue cellularity
  - Endorectal Coil
  - MRSI (magnetic resonance spectroscopy imaging).
  - Dynamic contrast-enhanced MRI (DCE-MRI)
- 1.5T -> 3T

Tailoring Nerve Sparing Based on MRI (1)

- 53 year old male
  - PSA 9.5
  - TRUS Bx
  - Gleason Score 3+3=6 in 5% of Sample on the right
- Path: T3a
  - Gleason 4+3
  - T2 weighted image
    - Irregular capsule
  - Perfusion
  - Diffusion

MRI restaging of low risk prostate cancer

- 55 y.o. man with PSA 7.4 nm/ml
eT3c. Gleason 6 (3+3) in 5% of 1/6 cores. Deferred therapy recommended pending MRI and repeat biopsy.
- MRI: large anterior TZ cancer.
- Treatment: RP.
**Bone Scan**

- Gleason Primary Pattern ≥ 4
- PSA >20
- Clinical T3 disease
- Bone symptoms
- Clarify with  
  - MRI/CT/  
  - plain x-ray or biopsy
- PET/CT arriving

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**Gleason grading and clinical staging**

- Dr. Donald Gleason, pathologist from 1960s.
- Grade most common tumour pattern, and a second grade to next most common pattern.
- The two grades are added together to get a Gleason Score (3+3, 4+5)
- Tertiary patterns added
- ASAP
- HG PIN

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**Pre-malignant or perimalignant**

- HG PIN  
  - Prostatic Intra-epithelial neoplasia  
  - Benign/normal acini and ducts lined with cytologically atypical cells  
  - Precursor for intermediate/high grade cancer  
  - 27-30% cancer on re-biopsy
- ASAP  
  - Atypical small acinar proliferation  
  - Suspicious for cancer  
  - Acini small with cytologically abnormal cells  
  - Basement membrane intact  
  - 40-46% cancer on re-biopsy

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**Evaluation of the (primary) tumour**

- T1: tumour present, but not detectable clinically or with imaging  
  - T1a: less than 5% of TURP  
  - T1b: greater than 5% of TURP  
  - T1c: needle biopsy performed due to an elevated serum PSA
- T2: the tumour can be palpated, but has not spread outside the prostate  
  - T2a: ≤ half of one lobe  
  - T2b: >more than half of one lobe  
  - T2c: both lobes
- T3: the tumour has spread through the prostatic capsule  
  - T3a: spread through the capsule on one or both sides  
  - T3b: invaded one or both seminal vesicles
- T4: the tumour has invaded other nearby structures
  - N1: there has been spread to the regional lymph nodes
  - M1: there is distant metastasis  
  - M1a: spread to lymph nodes beyond the regional ones  
  - M1b: spread to bone  
  - M1c: spread to other sites (regardless of bone involvement)

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**Prostate Cancer Staging**

- T2: Tumor is confined within one or both lobes of the prostate  
  - T2a: Tumor involves one lobe  
  - T2b: Tumor involves both lobes
- T3: Tumor extends through capsule  
  - T3a: Tumor extends on one or both sides  
  - T3b: Tumor invades seminal vesicle

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**Treatment options for Localised disease**
Risk of death from prostate cancer or other causes after RP by Gleason grade in the RP specimen for men age 60-69

From Eggener S et al. Cancer-specific mortality after RP: a collaborative study (n=23,910)

D’Amico Risk Stratification

- Low Risk
  - PSA <10, clinical stage T1c, Gleason ≤6
- Intermediate Risk
  - PSA 10-20, clinical stage T2a-c, Gleason ≥7 (3+4, 4+3)
- High Risk
  - PSA >20, clinical stage T3, Gleason ≥ 8 (4+4, 4+5, 3+5)

Table 1: Risk stratification criteria for men with localized prostate cancer. Men with clinical stage T3c, T4, or Gleason 9+ are not eligible for active surveillance (see page 10).

<table>
<thead>
<tr>
<th>Risk Stratification</th>
<th>PSA (ng/ml)</th>
<th>Gleason score</th>
<th>Clinical stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>&lt; 10</td>
<td>≤6</td>
<td>T1c</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>10-20</td>
<td>≥7 (3+4, 4+3)</td>
<td>T2a-c</td>
</tr>
<tr>
<td>High risk</td>
<td>&gt; 20</td>
<td>≥8 (4+4, 4+5</td>
<td>T3</td>
</tr>
</tbody>
</table>

Active Surveillance: NICE Guidance

Advantages
- Avoids (or postpones) side effects of therapy
- Retains quality of life
- Maintains normal activities and work schedule
- Minimizes over-treatment of indolent cancers

Disadvantages
- Risks under treatment - Cancer may progress and become incurable before it is treated
- Later treatment may entail greater morbidity
- Increases anxiety of living with untreated cancer
- Requires frequent assessments, repeat biopsies with uncertain side effects
- Uncertain long-term (> 10 yrs) natural history of cancer

Active Surveillance - Actuarial Probability of Remaining on AS

- Two-year: 91%
- Five-year: 75%

Eggener et al. J Urol, 2009

NICE 2008 Guidance

Localised prostate cancer

Table 2 Treatment and management options for men with localised prostate cancer.

<table>
<thead>
<tr>
<th>Key:</th>
<th>Preferred treatment</th>
<th>Treatment option</th>
<th>Not recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watchful waiting</td>
<td>Low risk</td>
<td>Intermediate risk</td>
<td>High risk</td>
</tr>
<tr>
<td>Active surveillance</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Prostatectomy</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Brachytherapy</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Conformal radiotherapy</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Cryotherapy</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>High-intensity focused ultrasound</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

* Offer if there is a realistic prospect of long-term disease control
† Conformal radiotherapy should be given at a minimum dose of 74 Gy (at a maximum of 2 Gy per fraction)
‡ Unless as part of a clinical trial comparing one with established interventions.
**Guy’s Active Surveillance Protocol**

- Suitable: low risk, low volume, T1c, ≤2/12 cores Gleason 3+3, <50% core involvement.
- MRI and TP Biopsy at Entry
- PSA 6 monthly
- Repeat MRI annually
- Re biopsy 12-18/12 with TPBx
- 2nd Re-biopsy 3-5 years
- Stop AS if upgraded, Up-staged, up- volume, pt choice/anxiety

**AS Protocol**

<table>
<thead>
<tr>
<th>Timing</th>
<th>Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>At enrolment in active surveillance</td>
<td>Multimetric MRI if not previously performed</td>
</tr>
<tr>
<td>Year 1 of active surveillance</td>
<td>Every 3-4 months measure PSA&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Work 2-4 of active surveillance</td>
<td>Every 3-4 months measure PSA&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Year 5 and every year thereafter until active surveillance ends</td>
<td>Every 6 months measure PSA&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**LDR Brachytherapy**

- Low/Intermediate risk
- IPSS <15
- FR/RV
- Small gland <80mls
- No prev pelvic DXT

**Dynamic Inverse plan low dose brachytherapy**

- Single session
- No catheter
- Day case
- Safe with minimal side effect profile
- Bad for basal disease, high risk?, significant LUTS, very large prostates, caution in younger patients.
- Difficult to do after TURP

**Randomized trial of RP v. WW**

Surgical treatment reduced the risk of metastasis (HR 0.65) and death from prostate cancer (HR 0.65): significantly.

- Cancer control- Margins and PSA
- Continence
- Potency
- Complications
- Return to normal activity/ general wellbeing- quality of life

Cancers with extra prostatic extension may not be pathologically confined but are often "confined" within the surgical specimen, are "clinically organ confined" and are often curable.

Survival after surgery for prostate cancer

- 12,677 men treated at 4 institutions (MSKCC, Baylor, Cleveland Clinic and U. Michigan, with RP in the PSA era (1987-2005)
- Neither PSA velocity nor BMI added to the accuracy of the prediction model.
- Only 17% had a predicted 15-year PCSM rate >5% and 4% had a probability >30%.

Open radical prostatectomy

- Gold standard
- Is it MORBID??
  - Mortality <1%
  - Blood transfusion 20-30%
  - Complications 9-30%
  - Hospital stay 6-4 days
  - Incontinence <10%
  - Erectile dysfunction 14-44%

Dual Console Da Vinci Si HD

Judge et al. BJU 2007
Catalona et al. J Urol 2004
Walsh et al. Urology 2000
Graefen et al Eur Urol 2006
Prostate cancer: diagnosis and treatment

- Commissioners of urology services should consider providing robotic surgery to treat localised prostate cancer. [new 2014]

Cost Effectiveness

- QALY (quality adjusted years) threshold for NHS/NICE £30,000, for 10 year timespan.
- Incremental cost per QUALY for RARP <£30,000
- Provided number procedures/year >150.
- When 100/yr £47,822
- When 50/yr >£66,000

BAUS Audit 2014

- Median no of cases/consultant: 32 (range 1 - 157)
- Median no of cases/centre: 85 (range 1 - 250)
- Transfusion rate was 2.7% - 5,174 of the entries recorded whether there had been adverse events. The total post-operative complication rate was 9.5% (491 / 5174).
- Of these 491 cases, 364 recorded the Clavien Grade:
  - ≥3 = 1.6%

Positive surgical margins: RALP Vs LRP

Urinary continence: RARP Vs RRP
12-mo continence rate


Urinary continence: RARP Vs LRP
12-mo continence rate


Potency recovery: RARP Vs RRP
12-mo potency rate


Potency recovery: RARP Vs LRP
12-mo potency rate


T2 Margins

pT2 Margins by Technique
Approach specific or surgeon specific?

Case volume is Key

The robot is here to stay

MIS:
- Less blood loss/transfusion
- Less pain
- Earlier Discharge
- Faster return to work
- Better oncological and functional results

Choose your surgeon wisely

Radical Prostatectomy

External-beam radiotherapy
- Outpatient procedure
- 20-30 minutes of treatment
- 5 days a week for 6-7 weeks
- Neo-adjuvant hormones 3/12
- Intensity-modulated radiotherapy (IMRT), high doses of radiation precisely shaped to the individual patient's prostate
- Proton Beam

Locally advanced prostate cancer
- External Beam Radiotherapy
  - neoadjuvant and concurrent LHRHa therapy for 3-6 months
  - adjuvant LHRH therapy for a minimum of 2 years if Gleason ≥ 8
  - pelvic radiotherapy for men with > 15% risk of pelvic lymph node involvement
- Radical Prostatectomy if very young.
- As part of multimodal therapy

Metastatic prostate cancer
- LHRH therapy (Prostap, Zoladex)
- Options
  - bilateral orchidectomy as an alternative
  - monotherapy with bicalutamide (150 mg) if the man hopes to retain sexual function and is willing to accept gynaecomastia and reduced survival
  - LHRH antagonist
  - intermittent androgen withdrawal
- Maximum androgen blockade if fails

Side effects of ADT
- Decreased libido and erectile dysfunction
- Hot flushes
- Gynaecomastia
- Loss of muscle and an increase in body fat
- Osteoporosis
- An increased risk of developing type 2 diabetes
- An increased risk of developing or worsening coronary heart disease
Docetaxel chemotherapy
- if Karnofsky score is ≥ 60%
- PS 0/1
- 10 planned cycles
- Corticosteroid as a third-line therapy after androgen withdrawal and MAB
- Bisphosphonates to prevent or reduce the complications of bone metastases.
- New agents: abiraterone and enzalutamide
- Immunotherapy: sipuleucel-T, Provenge.
  - vaccine is made by isolating dendritic cells
  - reinjected into the patient three times, at intervals of two weeks.

If you are the kind of person who doesn't wear a seat belt, (smokes) nor goes regularly to the dentist or your family doctor for a check-up and are not worried about dying from prostate cancer, do not undergo PSA testing.

On the other hand if you are a healthy man age >40 who does not want to die from prostate cancer, early PSA testing can save your life.

Immediate:
- Bleeding
- Infection
- Rectal/Bowel injury
- Anastomotic Stricture
- Recurrence
  - Salvage DXT, Radicals, WW
- Incontinence
  - PFE, Advance sling, AUS
- Erectile dysfunction
  - PDE5, vacuum pump, MUSE, Caverject

Urinary Symptoms
- Dysuria, bladder irritation, frequency, urgency

Bowel symptoms
- Rectal irritation or discomfort
- Diarrhoea and bleeding

Erectile dysfunction: gradually over 6–12/12

Second tumours
- slightly higher risk of developing rectal or bladder cancer

Difficult salvage options