Prostate Cancer

Dr Paula Wells
Consultant Clinical Oncologist
The Facts

In UK:
Prostate cancer most common cancer in men
Second commonest cause of cancer death in men
Prostate cancer rates have tripled in 40 years
75% cases of prostate cancer over 65 years @ presentation
9/10 deaths from prostate cancer in men > 65 years

In 2010:
40975 men diagnosed with prostate cancer (112 per day)
10721 deaths from prostate cancer (29 per day)
2005-9 81.4% men in England survived their cancer > 5 yrs
Lifetime risk of developing prostate cancer is 1:8
10 most common causes of cancer death – Males 2010

- Lung
- Prostate
- Bowel
- Oesophagus
- Pancreas
- Bladder
- Stomach
- Leukaemia
- Kidney
- Non-Hodgkin Lymphoma
- Other Sites
Survival over Time – 5year
Survival over Time – 10 year
Aetiology

Age

Low incidence under 50yrs
Aetiology

**Family History**
First degree relative increases risk by 120-150%
Highest risk when brother affected
When mother has breast cancer risk of prostate in son 19 - 24%

Breast cancer susceptibility gene BRCA2 – 7 x risk in men < 65yrs
5-9% prostate cancer linked to family history or genetic factors

**Ethnicity**
Increased in black men
Higher numbers of younger patients and diagnosed 3-5 years earlier than white men

**Height**
Increase in aggressive or fatal prostate cancer 12% for each 10cm above male average.
Aetiology

Insulin like growth factor 1 (IGF-1)
Men with high levels of IGF-1 38-83% increased risk

Previous cancers associated increased risk of prostate cancer
Renal cell carcinoma – 69%
Bladder cancer 14 -151%
Melanoma 15 - 50%
Lung Adenocarcinoma – 56%

Radiation

REDUCED prostate cancer risk in men with Diabetes
Symptoms and Diagnosis

LUTS

Dysuria            rare for prostate cancer
Haematospermia     rare for prostate cancer

Symptoms not specific to prostate cancer

BUT

These is addition to abnormal DRE and raised PSA for age should lead to referral

PSA vs Age

3 ng/ml or less is in normal range normal for a man under 60 years old
4 ng/ml or less is normal for a man aged 60 to 69
5 ng/ml or less is normal if you are aged over 70.

PSA not cancer specific
Prostate Cancer Screening

*Prostate Lung Colorectal Ovary (PLCO) 2009 76,000 men*
*PSA yearly for six years*
No survival benefit to screening @ PSA 4.0ng/ml @ 10 years

*European Randomised Screening for Prostate Cancer (ERSPC)*
*182,000 men NEJM 2012*
20% reduction in risk from Prostate Cancer death but high risk over diagnosis
PSA cut off 3.0ng/ml and screening interval four yearly

**Overall**
To prevent 1 death from prostate cancer over 11 years, 1055 men had to be screened with 37 cancers being detected
Management Algorithm

Assessment of risk – Roach formula
Estimated risk of lymph node involvement = \( \frac{2}{3} \) PSA + \([\text{Gleason score} - 6] \times 10\)
(For radical RT to prostate + SV should be less than 30%)

Biological Age
Hereditary
Co-morbidities
Patient choice
Very Low Risk Prostate Cancer

T1a-2a Gleason 3+3 adenocarcinoma pPSA < 10

Active surveillance
Radical Prostatectomy
Brachytherapy
Radical Radiotherapy (EBRT) alone
Very low risk Prostate Cancer

T1a
Disease specific progression – 5% @ 5 years
BUT ~ 50% progression at 10 years
Therefore offer therapy if life expectancy >15 years

T1b
Progression after 5 years

T1c
Up to 30% progression but look at other factors PSA dt, core positivity

T2a
30-35% progression @ 5 years
Active Surveillance Protocol

T1c to T2a
Gleason score 3+3 and PSA <10ng/ml
Or
Gleason 3+4 and PSA < 15 in men > 70y

FU median 8 years, OS 85%, DSS and met S 99%
PSA DT 7 years (42% >10years, 22% < 3years)
33% patients went on to have radical therapy:
22% PSA DT < 3 years
5% Gleason score progression at re biopsy
10% patient preference

Choo, Klotz et al 2001
## Outcome of Deferred Treatment
Prostate Cancer vs. Tumour Grade

% of patients (95% CI) surviving at 5 & 10 years.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Disease-specific survival</th>
<th>5 years (%)</th>
<th>10 years (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>98 (96-99)</td>
<td>87 (81-91)</td>
</tr>
<tr>
<td>Grade 1</td>
<td></td>
<td>97 (93-98)</td>
<td>87 (80-92)</td>
</tr>
<tr>
<td>Grade 2</td>
<td></td>
<td>67 (51-79)</td>
<td>34 (19-50)</td>
</tr>
<tr>
<td>Grade 3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Metastasis-free survival |                           | 93 (90-95)  | 81 (75-86)   |
| Grade 1                 |                           | 84 (79-89)  | 58 (49-66)   |
| Grade 2                 |                           | 51 (36-64)  | 26 (13-41)   |
| Grade 3                 |                           |             |              |
### 15-year risk of dying from Prostate Cancer vs. Gleason score @ diagnosis
*(localised disease 55-74 years)*

<table>
<thead>
<tr>
<th>Gleason score</th>
<th>Risk of cancer death*</th>
<th>(%) Cancer-specific mortality † (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-4</td>
<td>4-7</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>6-11</td>
<td>14</td>
</tr>
<tr>
<td>6</td>
<td>18-30</td>
<td>44</td>
</tr>
<tr>
<td>7</td>
<td>42-70</td>
<td>76</td>
</tr>
<tr>
<td>8-10</td>
<td>60-87</td>
<td>93</td>
</tr>
</tbody>
</table>

* The figures on the risk of cancer death differ for different age groups and represent the true risk.
Outcome of Scandinavian Prostate Cancer Group Study (SPCG-4)@ 12 years follow-up (patients randomised between 1989 and 1999)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>DSS % (n)</th>
<th>Relative Risk</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RP (n 347)</td>
<td>12.5 (43)</td>
<td>0.65 (0.2-11.1)</td>
<td>0.03</td>
</tr>
<tr>
<td>WW (n 348)</td>
<td>17.9 (68)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(MPD – metastatic progressive disease)

Prostate Cancer Intervention Versus Observation Trial: VA/NCI/AHRQ Cooperative Studies Program #407 (PIVOT) 1994-2002 - ongoing analysis
Indications

- **Low & intermediate risk localised** Prostate cancer
  (cT1b-T2 and Gleason score 2-7 and PSA< 20) and a life expectancy > 10 years.  

Optional

- T1a disease and a life expectancy > 15 years or Gleason score 7.  
- Selected patients with **low-volume high-risk localised** Prostate Cancer
  (cT3a or Gleason score 8-10 or PSA >20).  
- **Highly selected patients with very high-risk localised** Prostate Cancer
  (cT3b-T4 N0 or any T N1) in the context of multimodality treatment.

Recommendations

- Short-term (three months) neo-adjuvant therapy with LHRH analogues is **not**
  recommended in the treatment of stage T1-T2 disease.  
- Nerve-sparing surgery may be attempted in pre-operatively potent patients
  with low risk for extra-capsular disease
  (T1c, Gleason score < 7 and PSA < 10 ng/mL or see Partin tables/nomograms).  
- Unilateral nerve-sparing procedures are an option in stage T2a disease
# Complications of Radical Prostatectomy

<table>
<thead>
<tr>
<th>Complication</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peri-operative death</td>
<td>0.0-2.1</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>1.0-11.5</td>
</tr>
<tr>
<td>Rectal injury</td>
<td>0.0-5.4</td>
</tr>
<tr>
<td>Deep venous thrombosis</td>
<td>0.0-8.3</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>0.8-7.7</td>
</tr>
<tr>
<td>Lymphocele</td>
<td>1.0-3.0</td>
</tr>
<tr>
<td>Urine leak, fistula</td>
<td>0.3-15.4</td>
</tr>
<tr>
<td>Slight stress incontinence</td>
<td>4.0-50.0</td>
</tr>
<tr>
<td>Severe stress incontinence</td>
<td>0.0-15.4</td>
</tr>
<tr>
<td>Impotence</td>
<td>29.0-100.0</td>
</tr>
<tr>
<td>Bladder neck obstruction</td>
<td>0.5-14.6</td>
</tr>
<tr>
<td>Ureteral obstruction</td>
<td>0.0-0.7</td>
</tr>
<tr>
<td>Urethral stricture</td>
<td>2.0-9.0</td>
</tr>
</tbody>
</table>
## Results of Organ Confined Prostatectomy

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Mean FU (Mo)</th>
<th>5-yr PSA-free S (%)</th>
<th>10-yr PSA-free S (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Han (2001)</td>
<td>2404</td>
<td>75*</td>
<td>84</td>
</tr>
<tr>
<td>Catalona (1994)</td>
<td>925</td>
<td>28</td>
<td>78</td>
</tr>
<tr>
<td>Hull (2002)</td>
<td>1000</td>
<td>53</td>
<td>–</td>
</tr>
<tr>
<td>Trapasso (1994)</td>
<td>601</td>
<td>34</td>
<td>69</td>
</tr>
<tr>
<td>Zincke (1994)</td>
<td>3170</td>
<td>60</td>
<td>70</td>
</tr>
</tbody>
</table>
Radical EBRT

MD Anderson 2006
305 Stage T1-3 pPSA ~ 10ng/ml
70 vs 78 Gy
Increased risk of biochemical failure @ 70Gy

PROG 95-09 (2005)
395 T1b-T2b (75% Gl <= 6, pPSA <= 15)
Proton boost 18.8 Gy vs 28.8Gy + EBRT 50.4Gy
Increased biochemical control for higher dose arm

In practice – 74Gy is recommended
1980s

The Rectangular Era
1990s

The Conformal Era

Blocks/MLC
Intensity Modulation (IMRT)
Non-uniform fluence
Forward Planning

Start with some beams
Adjust beam properties to achieve an *acceptable* dose distribution

- energy
- number of beams
- direction
- weight
- wedges
- shielding
Inverse Planning

Outline PTVs and OARs
Set dose limits for PTV and OARs
Select energy, number of beams, directions
Iteratively calculate intensity modulated beams
Inverse Planning

Forward planning optimises the weights of a few beams.

Inverse planning optimises the weight of thousands of beamlets for each treatment field.
3D-CRT: What can it do?

Conventional 3 field plan

95 % isodose
IMRT: What can it do?

IMRT plan

95 % isodose
Prostate PTV and OAR
Prostate PTV and OAR
Prostate Movement Over an 8 Minute Period
Target verification using KV imaging
Gold seeds - IGRT
Gold seeds - IGRT
Gold seeds - IGRT
Prostate EBRT – IMRT plan
Colour wash image - sagittal
Colour wash image - coronal
Radiotherapy Overview

In daily practice, a minimum dose of > 74Gy is recommended with short-term androgen deprivation therapy (ADT) (based on the results of a phase III RCT).

Higher Dose RT provide a significant increase in 5-year freedom from clinical or biochemical failure for patients in an intermediate-risk group:

- Dutch Trial: 68Gy with 78Gy
- MRC RT01 study: 64Gy with 74Gy
- MD Anderson study especially in high risk group
Where we are now?


MRC study 64Gy vs 74Gy + Neo HT 11% increase biochemical DFS
Neoadjuvant HT - 13% increase in OS (D’Amico 2008)

Conventional or Hypofractionated High Dose Intensity Modulated Radiotherapy for Prostate cancer - CHHiP

Dose escalation / hypofractionation
Alpha/beta ? ~ 1.5Gy for prostate cancer
### Toxicity of EBRT – EORTC 22863 (Ataman 2004)

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 2</th>
<th></th>
<th>Grade 3</th>
<th></th>
<th>Grade 4</th>
<th></th>
<th>Any significant toxicity (≥ grade 2)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Cystitis</td>
<td>18</td>
<td>4.7</td>
<td>2</td>
<td>0.5</td>
<td>0</td>
<td>0</td>
<td>20</td>
<td>5.3</td>
</tr>
<tr>
<td>Haematuria</td>
<td>18</td>
<td>4.7</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>18</td>
<td>4.7</td>
</tr>
<tr>
<td>Urinary stricture</td>
<td>18</td>
<td>4.7</td>
<td>5</td>
<td>1.3</td>
<td>4</td>
<td>1</td>
<td>27</td>
<td>7.1</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>18</td>
<td>4.7</td>
<td>2</td>
<td>0.5</td>
<td>0</td>
<td>0</td>
<td>20</td>
<td>5.3</td>
</tr>
<tr>
<td>Overall GU toxicity</td>
<td>47</td>
<td>12.4</td>
<td>9</td>
<td>2.3</td>
<td>4†</td>
<td>1†</td>
<td>60</td>
<td>15.9</td>
</tr>
<tr>
<td>Proctitis</td>
<td>31</td>
<td>8.2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>31</td>
<td>8.2</td>
</tr>
<tr>
<td>Chronic diarrhoea</td>
<td>14</td>
<td>3.7</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>14</td>
<td>3.7</td>
</tr>
<tr>
<td>Small bowel obstruction</td>
<td>1</td>
<td>0.2</td>
<td>1</td>
<td>0.2</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0.5</td>
</tr>
<tr>
<td>Overall GI toxicity</td>
<td>36</td>
<td>9.5</td>
<td>1</td>
<td>0.2</td>
<td>0</td>
<td>0</td>
<td>37</td>
<td>9.8</td>
</tr>
<tr>
<td>Leg oedema</td>
<td>6</td>
<td>1.5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>1.5</td>
</tr>
<tr>
<td>Overall toxicity*</td>
<td>72</td>
<td>19.0</td>
<td>10</td>
<td>2.7</td>
<td>4</td>
<td>1</td>
<td>86</td>
<td>22.8</td>
</tr>
<tr>
<td>Treatment</td>
<td>BRFS (5 yrs)</td>
<td>Complications</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------</td>
<td>--------------</td>
<td>--------------------------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salvage Surgery</td>
<td>44-65%</td>
<td>Incontinence 40%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stricture 25%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cryotherapy</td>
<td>58%</td>
<td>Incontinence 15%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fistula 10% rectal and perineal pain 35%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIFU</td>
<td>10-50%</td>
<td>Stricture 11%, rectal fistula up to 66%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brachytherapy</td>
<td>34-75% (LDR)</td>
<td>Incontinence 6%, GU (G3-4) 17%, 89% (2 yrs for HDR) 89%, GI 7%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Prostate Brachytherapy

Treatment of early-stage prostate cancer by permanent implant of Iodine seeds

Low dose rate

Bulk of dose delivered within year ($T_{1/2}$ 59.4 days)

Low risk: T1c-T2a, PSA<10, prostate vol<50cc
i.e. low risk of extra-capsular spread

Established treatment option in UK & US
**Brachytherapy: results**

**US**
- Seattle (late 1980s)
- Stock & Stone (1990) – 96% 10yr DFS (low risk)
- Potters (1992) – 93% 12yr DFS

**UK**
- Leeds (1995) DFS and OS (85% and 95% @ 10yrs)
- Guildford (1999)
- Guy’s & St Thomas’ (2003)
- Barts (2008)
Iodine-125 seeds

Emissions: 27-35 keV photons (γ and X rays)
Half value layer: 0.02 mm lead
1.7 mm tissue
Half-life: 59.4 days
Typical AKS: 0.533 μGyh-1 @1m
Size: 4.5mm x 0.8mm
Number used: 60 to 100 per implant
Sealed-sources - no radiation contamination from seeds
Implant Technique

Single-stage interactive dose feedback ('dynamic')
Day case; GA
Patient in extended Lithotomy position
Trans-rectal ultrasound probe
Needles implanted

Brachytherapy Grid

Needles

U/S probe
Implanting seeds

- Grid
- Seed cartridge
- Mick applicator
- Stilette
Image capture & contouring
Producing the plan

Automatic source placement
Source activity; seed number

Run optimisation routine, user-defined dose rules (constraints)*:
100% prostate + margin vol to be above 100% prescribed dose
75% prostate + margin vol to be below 200% prescribed dose
90% urethra vol to be below 140% prescribed dose
95% rectum surface to be below 150% prescribed dose
50% of prostate+margin vol to be below 150%

* Potters et al Brachytherapy 2 2003 & GEC Estro Guidelines 2007
Quality alerts

\[ D_{90} = \text{dose received by 90\% of the prostate must be greater than 100\% of prescription dose i.e. dose coverage} \]

\[ V_{200} = \text{volume of prostate receiving more than 200\% of prescription dose must be less than 30\% i.e. plan not too hot} \]
Late effects of Brachytherapy

Urinary retention 1.5-22% (SBH 1/110)
Post implant TURP – up to 8.6%
Incontinence 0-19%
Chronic urinary morbidity in up to 20%
Gd 2-3 proctitis 5-21%
ED up to 40%
Cyberknife

Cyberknife is a frameless robotic radiosurgery system

Three main elements:

Radiation is produced from a small linear accelerator.

Has a robotic arm which allows the energy to be directed at any part of the body from any direction.

Image guidance system: X-ray imaging cameras to obtain instantaneous x-ray images.
Intermediate Risk Prostate Cancer

cT2b-T2c (T3a) or Gleason score 7 or PSA 10-20 Roach score >15-30% risk SV involvement

Prostatectomy +/- RT (RADICALS trial)
EBRT + Neoadjuvant hormone therapy
(Hormone therapy)
(AS)
TTP T2 disease 6-10 years
T2b (> half lobe) – T2c 70% progression @ 5 years

Cochrane review
Neoadjuvant hormone therapy + RP no improvement in OS DFS
BUT improves local pathological variables eg + margins and organ confined rates
Adjuvant HT + RP – trend to OS but stat significant DFS

RADICALS trial
Management of Advanced Disease

- LHRHa (eg Zoladex)
- Bicalutamide (Casodex)
- Dexamethasone
- Docetaxel (Taxotere)
- Stilboestrol
- Strontium
Endocrine Basis of Prostate Cancer
Testosterone response to LHRH agonist vs antagonist

*p < 0.001 degarelix (both doses) versus leuprorelin
LHRH agonist vs Antiandrogen

Quality of life analysis of the effect of treatment with bicalutamide 150 mg or castration at 12 months in M1 patients. Reproduced
10-year Survival in the 27 Randomised Trials of MAB Versus Monotherapy

- Androgen suppression only
- Androgen suppression + antiandrogen

8000 prostate cancer patients in 27 trials of antiandrogen (nilutamide, flutamide, or cyproterone acetate)

Proportion alive (%)

Time since randomisation (years)

Treatment better by 0.7% (SE 1.1)
Logrank 2p > 0.1

Absolute difference 1.8% (SE 1.3)

25.4%
23.6%
5.5%
6.2%
# Continuous vs Intermittent Hormone therapy

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>Setting</th>
<th>Treatment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tunn et al AUA 2007 (abstract only)</td>
<td>16</td>
<td>Rising PSA after RP Multi-centre phase III (RELAPSE trial)</td>
<td>Leuprolide + cyproterone cover</td>
<td>Similar progression to CRPC, improved QoL in intermittent arm</td>
</tr>
<tr>
<td>Miller et al ASCO 2007 (abstract only)</td>
<td>33</td>
<td>N+ M+ relapse post RP Multi-centre phase III</td>
<td>Goserelin + bicalutamide (over 50% time off Rx)</td>
<td>Similar time to progression, improved QoL</td>
</tr>
<tr>
<td>De Silva et al ASCO 2006 (abstract only)</td>
<td>62</td>
<td>T3-4 N+ M+</td>
<td>Triptorelin + cyproterone</td>
<td>Similar time to progression, improved QoL</td>
</tr>
</tbody>
</table>
Management of Advanced Disease

- LHRHa (eg Zoladex)
- Bicalutamide (Casodex)
- Dexamethasone
- Docetaxel (Taxotere)
- Stilboestrol
- Strontium
Conclusions

Significant treatment options now open to all patient groups

Different challenges in management depending on stage

Aggressive therapy where appropriate but increasing use of AS in early stage low risk cancer internationally

Advanced disease patients have two thirds of lifetime in hormone refractory phase