Prostate Cancer

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Outline

• Incidence, prevalence, risk factors
• Diagnostic pathways
• Grading & staging
• NICE guidance
• Treatment options
• Advances?

Incidence

Latest figures, for UK:
• 47,300 diagnosed (2013) – 13% of all cancer cases
• Now commonest cancer in men (was 3rd in 1990)
• Lifetime risk for men: 1 in 8

Male Cancers

Prostate Cancer: The Numbers
Incidence

<table>
<thead>
<tr>
<th>Age</th>
<th>20-29</th>
<th>30-39</th>
<th>40-49</th>
<th>50-59</th>
<th>60-68</th>
<th>70-79</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>8</td>
<td>28</td>
<td>39</td>
<td>53</td>
<td>66</td>
<td>80</td>
</tr>
</tbody>
</table>

Age of diagnosis:
- Peak age: 75-79
- ~65% diagnosed under 75
- ~25% diagnosed under 65
- Only 1% under 50

Incidence by Age

Latest figures, for UK:

- Peak age of diagnosis: 75-79
  - ~65% diagnosed under 75
  - ~25% diagnosed under 65
  - Only 1% under 50

Incidence by deprivation

Latest figures, for UK:

- >11,000 deaths / year (2014)
- Approx 1/3 with prostate cancer die from it

Prevalence

330,000 men predicted to be living in UK with a diagnosis of prostate cancer

= 1/3 of men living with and after cancer in the UK

Mortality

Latest figures, for UK:

- >11,000 deaths / year (2014)
- Approx 1/3 with prostate cancer die from it
Male Cancer Deaths

Mortality

- Like many other cancers, mortality rates higher in UK than European average
- Difference greater for prostate cancer than most

Survival

Latest figures, for England:

- 1 year survival: 94%
- 5 year survival: 84%
- 10 year survival: 80% (predicted)

Risk factors

- Age & ethnicity
- Family history / genetic factors:
  - Approx 7% linked to genes / family history
  - ~3x risk if brother
  - ~2x risk if father
  - ~2x risk if 2nd-degree relative
  - Increases with younger diagnosis & more relatives
  - Up to 5x higher in men with BRCA2 mutation

5-yr Relative Survival by stage

~75% deaths in men 75y and over
1% under 55y
Risk factors

Some evidence:
- Obesity
  - ↑risk aggressive prostate cancer, & death
- Smoking, alcohol
- Physical activity ↓ risk

Presentation

• PSA: Screening?
• Case finding:
  - Family history
  - Ethnicity risk
  - Patient choice / “well man clinic”
• LUTS
• Bleeding
• Systemic / Metastatic

Diagnostic Pathways

Digital Rectal Examination

- Size: Aid to risk stratification
- Feel: Soft/Firm/Nodular
- Most prostate cancer (approx ¾) in peripheral zone
Digital Rectal Examination

- 50% abnormal DREs associated with cancer
  - Most advanced at least locally
- Abnormal DRE with normal PSA → 30% cancer

Is it time to abandon the digital rectal examination? Lessons from the PLCO Cancer Screening Trial and peer-reviewed literature

- 2016 paper
- Abnormal DRE with normal PSA:
  - Only 2% had clinically significant prostate cancer

NICE guidance

- Consider PSA & DRE to assess for CaP in men with:
  - Any LUTS
  - ED
  - Visible haematuria
- 2 week referral if:
  - Prostate feels malignant O/E
  - PSA above age-specific level

Prostate biopsy
Prostate biopsy

Study of symptoms after biopsy:
- 2% reported no symptoms

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Frequency (All)</th>
<th>Frequency (moderate or severe only)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>44%</td>
<td>7%</td>
</tr>
<tr>
<td>Haematospermia</td>
<td>90%</td>
<td>25%</td>
</tr>
<tr>
<td>Haematuria</td>
<td>66%</td>
<td>6%</td>
</tr>
<tr>
<td>Rectal bleeding</td>
<td>37%</td>
<td>2%</td>
</tr>
<tr>
<td>Fever</td>
<td>20%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Prostate biopsy

- Other risks:
  - Septicaemia (1% admitted, infection rates ↑)
  - Urinary retention
  - Chance of missing a cancer (approx 25%)

Risk of cancer with –ve biopsy slightly higher if:
- Certain histological features
- Abnormal DRE

May consider MRI, template biopsy...

Template biopsy

- Biopsy needle to take samples from the prostate
- Ultrasound probe to locate the prostate
- Template to aid accurate placement of biopsy needles

Grading

- Gleason Score
  - Score: 2 scores added together, “X + Y”:
    - (Most common cell pattern) + (Highest grade pattern), e.g. Gleason 3 + 4 = 7
  - Consensus: Report as score between 5 & 10
  - Gleason 5 and 6 = low risk
Gleason effect on **survival** after surgery

TNM Staging

**Imaging**

- NICE 2014 considered evidence for MRI pre-biopsy: not yet, but increasing interest

**PROMIS study**

- MRI & then TRUS-biopsy, compared to accurate reference (template biopsy) in men with ↑PSA
  - MRI better sensitivity (93% vs 48%)
  - MRI better NPV (89% vs 74%)
  - MRI as triage test would avoid biopsy in 27% (without impairing detection of clinically significant Ca)

**Treatment of localised cancer**

- Options:
  - Watchful waiting
  - Active surveillance
  - Radical prostatectomy
  - External beam radiotherapy (EBRT)
  - Brachytherapy
  - High intensity focused ultrasound (HIFU)
  - Cryotherapy

- To help choose, **risk stratification** is essential
Risk stratification

Based on recurrence risk after definitive treatment:

<table>
<thead>
<tr>
<th>RISK</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>T1−T2a</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>10−20</td>
<td>7</td>
<td>T2b−T2c</td>
</tr>
<tr>
<td>High risk</td>
<td>&gt; 20</td>
<td>8−10</td>
<td>T3−T4</td>
</tr>
</tbody>
</table>

Low risk localised cancer

- **Active surveillance** = NICE 1st-line recommendation

Active surveillance

- Recommend protocol of:
  - MRI
  - Re-biopsy at 12 months
  - Regular monitoring of PSA & DRE (shared care?)
  - MRI and/or re-biopsy if any concerns

Active surveillance

- Addresses **overdetection & overtreatment**
- **Avoids or delays** treatment morbidity
- Maintains QoL
- Reduces healthcare spending?

Intermediate and high risk localised cancer

- **↑ anxiety?**
- Risks under-treatment: cancer may progress
- Later treatment may entail ↑ morbidity
- Uncertain long-term (>10 yrs) natural history

- **Radical prostatectomy or radiotherapy:**
  - 1st line
Radical prostatectomy

• What to expect:
  – Remove prostate & seminal vesicles, +/- lymph nodes
  – Open, laparoscopic, robotic

• Operation:
  – Prostate removed, urethra joined around catheter
  – Nerve-sparing if possible: 1 or both bundles

• Advantages:
  – Aims to remove whole tumour
  – Get histology, grading
  – Easy to quickly measure success:
    • PSA <0.1 6-8 weeks post-op
  – If PSA ↑, may have radiotherapy / hormone therapy

• Disadvantages:
  – Hospital inpatient stay
  – Urinary problems: usually return to normal in 3-6 mths
  – ED (potency rates range from 30-86%)
    • Can improve over time
  – Penile shortening
  – Infertility (anejaculation)

Radical prostatectomy

• Risks:
  – Blood loss / transfusion
  – Bowel injury
  – Thrombosis
  – Wound infection

Radical radiotherapy for localised prostate cancer

To whole prostate, +/- tissue just outside, LNs
Radical radiotherapy for localised prostate cancer

2 main types:
1. 3D-conformal: computer mapping
2. Intensity modulated: strengths of beams varied, usually lower risk side effects

Radical radiotherapy

NICE:
- 6 months of Androgen Deprivation Therapy (ADT) before, during or after
- High risk: consider extending ADT for 3 years

Radical radiotherapy

Advantages:
- Can continue many normal activities
- Painless
- Unfit for surgery?
- Short treatment sessions, 10-20 mins
- Can develop support network with other patients

Radical radiotherapy

Disadvantages:
- Hospital 5 days/week for several weeks
- Bowel, urinary & erection problems
- Fatigue
- Delay until know if successful
- Salvage surgery after radiotherapy not easy

Radical radiotherapy

Sexual function:
- Can get painful or reduced ejaculation
- Erectile dysfunction:
  - Less common than surgery, can be slower recovery
  - Can be a delayed effect, appearing up to 2yrs later

Patient Choice

- "Which one’s best Doc?"
- No definitive answer
- Proponents for different approaches
ProtecT Study

- 1999-2009
- Clinically localised cancer
- Randomised to AS, surgery, radiotherapy
- Approx 550 in each arm

ProtecT Study

- No significant difference in:
  - Prostate cancer deaths
  - Deaths from any cause
- Higher rates in active surveillance (AS) group for:
  - Metastases
  - Disease progression
- Lower rates for side effects with AS

Prostatectomy or Radiotherapy

**Latest UK figures:**

- **Radical prostatectomy (2014):** 6651 men
  - 13% open
  - 27% laparoscopic
  - 60% robotic-assisted
- **Radiotherapy (2012):** 8644 men
  - 3074 RT alone
  - 5210 RT + hormone therapy

Brachytherapy for localised prostate cancer

Source of radiation **inserted** into the prostate:

1. Permanent / low dose
2. Temporary / high dose

Permanent Seed Brachytherapy

- More common form
- More for low-risk localised CaP, sometimes others
- Tiny radioactive seeds
- Continuous radiation over 8-10 months
Permanent Seed Brachytherapy

Brachytherapy

Advantages:
- Short hospital stay
- Focused radiation, fewer side effects if given alone
- Quick recovery

Brachytherapy

Disadvantages:
- Need GA
- Urinary, bowel, erection problems
- Can be uncomfortable, especially if > 1 treatment
- Takes time to know if successful

Other active treatments for localised prostate cancer

- High-intensity focused ultrasound
- Cryotherapy
  - Both recommended only in context of clinical trials

Watchful Waiting

- VERY DIFFERENT to active surveillance
- No curative intent
- Usually elderly or frail
- Aims to avoid any treatment for as long as possible
- Likely delayed hormone therapy, if any

Watchful Waiting

- Wait for evidence of significant disease progression:
  - PSA rising significantly
  - Bone pain
  - Obstructive LUTS
- Should have clear protocol from secondary care
Locally advanced prostate cancer

• NICE: can treat most with radical curative intent:
  – if they wish & fit enough
• Radiotherapy + hormone therapy = main treatment

Locally advanced prostate cancer

• Prostatectomy - depending on extent
• Some may choose hormone therapy alone
• Watchful waiting for others

Relapse after radical treatment

• Hormonal therapy may be offered:
  – PSA doubling time < 3 months, or
  – symptomatic local progression, or
  – metastases

Hormone Therapy

• Localised or locally advanced cancer:
  – Neo-adjuvant therapy
  – Adjuvant therapy
  – Recurrence
  • Metastatic cancer

Hormone Therapy

• Most commonly LHRH analogues
  – Zoladex (goserelin): 1 or 3-monthly
  – Prostap (leuprorelin): 1 or 3-monthly
  – Decapeptyl (triptorelin): 1, 3 or 6-monthly
• Also LHRH antagonists (e.g. degarelix - Firmagon)
• Bilateral orchidectomy: likely try injections first

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• Anti-androgen: bicalutamide
Hormone Therapy

- Initial **tumour ‘flare’** with LHRH analogues:
  - Can cause bone pain, urinary tract obstruction
  - Rarely spinal cord compression
- Manage with **anti-androgen**:
  - Cyproterone acetate,
  - Bicalutamide

Metastatic Prostate Cancer

- Most commonly to **bone**, LNs
  - Less to lungs, liver, brain... anywhere
- 5 year survival 30%
- Early advanced care planning encouraged

Metastatic Prostate Cancer

Possible problems:
- Pain
- Fractures (metastases, osteoporosis)
- Spinal cord compression
- Urinary symptoms: local spread
- Bowel symptoms (radiotherapy, analgesics, immobility)
- Anaemia
- Hypercalcaemia
- Poor appetite

Metastatic Prostate Cancer

Treatment:
- Long term **LHRH agonists**, or orchidectomy
- Alternative: **bicalutamide** 150mg daily
  Pros: better sexual function
  Cons: decreased overall survival, gynaecomastia
  • Stop if still poor sexual function

Metastatic Prostate Cancer

Painful metastases:
- Analgesics / NSAIDs
- Palliative radiotherapy (also for lymphoedema)
- Bisphosphonates
- Strontium-89
Hormone-refractory disease

- PSA rising despite hormone therapy
- MRI if known extensive spinal mets & spinal-related symptoms

2nd line hormone therapy:
- Can add anti-androgen (‘maximum blockade’)
- Stopping anti-androgen can also lower PSA
- Steroids: decrease adrenal androgens
  - May help appetite, energy levels, pain

Earlier chemotherapy?

STAMPEDE trial:
- Men with metastatic (60%) or high-risk L.A. cancer
- “Hormone-naïve”
- Early docetaxel + ADT, vs ADT alone:
  - Overall, 10 months ↑survival (77 vs 67 months)
  - For metastatic: 22 months ↑survival (65 vs 43 months)

Hormone-refractory disease

- Abiraterone & Enzalutamide:
  - Novel types of hormone therapy, oral

Newer treatments

- Radium-223
- Cabazitaxel
  - Both NICE approved, 2016
- Therapeutic Vaccines

Resources