Prostate and testicular cancer.

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Gresham College 2020.
Prostate and testicular cancer.

- **Prostate cancer** very common disease of older men.
- Most people with it will not die of it.
- Possible to live with it as a chronic condition.
- **Testicular cancer** an uncommon cancer of younger men.
- Often can be cured with surgery.
- Very good outcomes normal.

Rembrandt self-portraits.
Prostate cancer is a common condition of age.

- In older men who die of unrelated cause, prostate cancer cells frequently found.
- Up to 50-60% of those in their 90s.
- In one study of male organ donors who had of sudden deaths 0.5% in <50 yrs old;
- 23% 50-59; 35% 60-69, 46% ≥70 age groups. *(Yin et al 2008)*
- This talk on prostate cancers significant enough to be diagnosed.
- Many of these will cause no symptoms and require no or minimal treatment.
Prostate cancer rates are very low below 50 years old, peak late 70s.
Prostate cancer, UK. (CRUK/ONS).

• Around 47,000 cases registered in the UK a year.
• Around 26% of cancers in men.
• Overall mortality a combination of incidence (how common) and survival.

• The key difficulty is removing, killing or controlling the cancer whilst minimising damage to the person whose cancer it is.
The prostate gland.

- Normally about the size of a chestnut.
- Its function is to produce seminal fluid, and has muscles to ejaculate.
- Hormone-like substance spermine mostly ensures sperm cells can move rapidly.
- Enzymes, including protein PSA which makes semen thinner to allow swimming.
- Converts testosterone to biologically active form, DHT (dihydrotestosterone).
- Gets larger in older age—benign prostatic hyperplasia. This can cause urinary symptoms.
Symptoms and signs that *might* be prostate cancer.

- Symptoms- a minority:
  - needing to pee frequently, inc. at night.
  - needing to rush to the toilet to pee.
  - difficulty in starting to pee (hesitancy).
  - straining or taking a long time while peeing.
  - weak flow.
  - feeling bladder has not emptied fully.
  - blood in urine or semen.
- In most men these symptoms are **not** cancer.
- Prostate cancer generally grows very slowly.
Many men diagnosed who do not have symptoms.

- Routine digital exam by a doctor.
- Routine or diagnostic PSA test.
- PSA is raised in prostate cancer, but also by multiple other causes. Include:
  - BPH
  - Urinary/prostate infection
  - Recent ejaculation
  - Physical pressure

PSA bound to substrate. EAS/Wiki
Next stage is usually imaging and possibly biopsy.

- MRI scan.
- Transrectal ultrasound scan (TRUS).
- Transrectal ultrasound guided (TRUS) biopsy done under local anaesthetic.
- Transperineal (template or targeted) biopsy under general or local anaesthetic.
Stage, grade and type of cancers.

**Stage**: size and degree of spread. Prostate generally Stage 1-4.

**Grade**: appearance of the cells. The more different from normal cells the higher the grade. ‘undifferentiated’. Gleason score.

**Type**: Several types in one organ, usually from the cell they arise from.

US National Cancer Institute
Type of cancer of the prostate.

• >95% adenocarcinoma.
• Adenocarcinoma is cancer that forms in mucus-secreting glands.

• The remainder are all rare:
  Small-cell tumours (1%).
  Intralobular acinar carcinomas.
  Ductal carcinomas.
  Clear cell carcinomas.
  Mucinous carcinomas.
Tests to stage.

- If biopsies show it is cancer, men may have additional staging tests.
- Mainly to check whether it has spread, and if so where.
- MRI
- CT (sometime PET CT for recurrence).
- Plain X-ray of bones.
- Ultrasound of abdomen.

PET CT. Rauscher, Isabel; Maurer, Tobias; Fendler, Wolfgang P.; Sommer, Wieland H.; Schwaiger, Markus; Eiber, Matthias
Various staging systems. Most common is TNM.

- TNM (Tumour-Nodes-Metastases) system.
- The **T stage** shows how far the cancer has spread in and around the prostate. T1-T4.
  - T1 can’t be felt or seen, only seen in biopsy.
  - T2 within the prostate.
  - T3 broken through the prostate wall.
  - T4 spread to local organs.
- The **N stage** shows whether the cancer has spread to the lymph nodes.
- The **M stage** shows whether the cancer has spread (metastasised) to other parts of the body.

CRUK/Prostate Cancer UK
Stage 4 and metastases.

- Stage 4 prostate cancer is any spread, whether local (T4) or nodes or metastases.
- Metastases when there is distant spread.
- Most common sites:
  - Lymph nodes
  - Bone (ribs, spine, pelvis)
- Can also go to lungs, liver, brain but much less common.
- Rarely other sites.
Bone metastases from prostate.
Osteosclerotic.

James Heilman/Wiki XR and CT
Except for Stage 4 survival is very good.

- Most men are diagnosed Stages 1-3.
- 5 year cancer-specific survival is essentially 100% for Stages 1-2 and 95% for Stage 3.
- 5 year survival currently 49% Stage 4. 88% survival at a year.

Stage at diagnosis, and 5 year survival. UK data. (CRUK)
Survival steadily rising.

- Ten year survival overall 1971-2011 (CRUK).
- Some change in diagnosis so some is artefact, but major improvements, which are continuing.
- Treatment less invasive, fewer side effects over time.
- Many men need no treatment at all, just watchful waiting.
Screening for prostate cancer?

- Current prostate cancer screening is with PSA blood test.
- Systematic review of 341,342 men in trials found relative risk 1 (no difference) for mortality.
- Increases number of unnecessary biopsies and treatment.
- Screening not worthwhile.

*Ilic et al 2013 Cochrane*
Prostate screening- a graphical representation.

Harding Centre for Risk Literacy / Cochrane.

How many men died from prostate cancer? 7 7
How many men died from any cause? 210 210
How many men without prostate cancer experienced false alarms and unnecessarily had tissue samples removed (biopsy)? - 160
How many men with non-progressive prostate cancer were unnecessarily diagnosed or treated? - 20
Remaining men

*E.g. treatments that include removal of the prostate gland (prostatectomy) or radiation therapy which can lead to incontinence and impotence.

Last update: November 2017
www.harding-center.mpg.de/en/fact-boxes
Clear evidence watchful waiting is often the best policy in early disease. But not always.

- Prostatectomy vs radiotherapy vs active watching, prostate cancer over 10 years no difference (R). Hamdy et al NEJM 2016.
- Slightly lower disease progression, more side effects active groups.
- At 23 years, a mean of 2.9 extra years of life were gained with radical prostatectomy. Bill-Axelson NEJM 2018.
- If very early disease. May remain indolent.
- If likely lifespan <10 years.
For those who wish to, there are tools to help understand the risks and benefits of treatment to help discussions with your doctor.
Surgery- prostatectomy.

• Generally considered if cancer within the prostate, especially if fast-growing or younger men.
• Generally radical prostatectomy. Remove prostate and seminal vesicles +/- lymph nodes.
• Nerve sparing where possible.
• Can be open, laparoscopic (keyhole) or robot-assisted.
• Main risks incontinence, erectile dysfunction (minority).
Surgery- transurethral resection.

• Transurethral resection of prostate (TURP) is generally used for benign prostatic hyperplasia.

• It can be used as part of symptom control in prostate cancer- but will not be curative.
External beam radiotherapy.

- Radiotherapy damages and kills cancer cells, healthy cells usually recover.
- May be used to treat cancer confined to the prostate; cancer that has spread; to alleviate symptoms.
- Radiotherapy over 100 years old. Modern radiotherapy much more accurate.
- Image on R compares conventional radiotherapy compared to isodosimetry by IMRT.
- Recent advances include fewer, higher doses.

prostate-cancer-radiotherapy.org.uk;
Prostate cancer centre.
Radiotherapy: brachytherapy.

- Brachytherapy means radiation emitting implants placed into the prostate.
- Low dose rate (LDR) in the form of permanent seeds.
- High dose rate (HDR) temporary implants.
- Less scatter to other tissues.
- May be combined with external beam.
Side effects of radiotherapy. Radiotherapy only damages the tissue it passes through.

Temporary include:
- Tiredness.
- Diarrhoea.
- Urinary frequency or obstruction.
- Pubic hair loss, skin soreness.

Long-term (minority) can include:
- Urinary frequency, flow reduced or incontinence.
- Diarrhoea.
- Erectile dysfunction.
Surgery v radiotherapy v watchful wait side effects.
ProtecT trial, NEJM 2016. Self-reported, n 1643.

Urinary incontinence.

Sexual quality of life.
Radium-223 or Strontium-89

- Used for bone metastases which are not under hormone treatment control.
- Weakly radioactive $\alpha$-emitting (Radium) or $\beta$-emitting (Strontium) drugs injected into the vein.
- Taken up into bone like calcium.
- Concentrates in areas of bone damaged by prostate cancer.
- Kills cancer cells locally.
Hormone therapy for prostate cancer.

• Most prostate cancer cells are driven by testosterone: hormone-dependent.
• Therefore if testosterone is removed they shrink or die.

Broadly two indications:
• As a temporary adjunct to other treatment like radiotherapy to shrink the tumour.
• Long term suppression of advanced cancer or cancer that has recurred.
• Long-term use becomes less effective over a number of years (‘castration-resistant’).
Hormone therapy treatment options.

- **Switch off the production of testosterone in the testes by preventing the brain signalling production.**
  - Injections of luteinizing hormone releasing hormone (LHRH) agonist. Block release of LH by pituitary gland.

- **Block testosterone reaching cancer cells- anti-androgen tablets.**
  - Often given at the time of starting treatment to prevent hormone surge.

- **Remove testes (orchidectomy).**
Active watching, surgery, radiotherapy, hormone treatment, chemotherapy, novel therapies. Depends on stage of disease.

<table>
<thead>
<tr>
<th></th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
<th>Stage 4</th>
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<tbody>
<tr>
<td>Surgery</td>
<td>11%</td>
<td>28%</td>
<td>23%</td>
<td>3%</td>
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<tr>
<td>Radiotherapy</td>
<td>22%</td>
<td>35%</td>
<td>53%</td>
<td>28%</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>&lt;1%</td>
<td>1%</td>
<td>2%</td>
<td>9%</td>
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</tbody>
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% of men who had treatment 12-15 months after diagnosis.

National Cancer Registration & Analysis Service / CRUK
Cytotoxic chemotherapy mechanisms.

- The basic mechanisms of conventional chemotherapy simple.
- Kill any cell that is dividing- cancer cells more sensitive and slower to recover.
- Good effect depends on the cancer. Rapidly dividing = more effective.
Chemotherapy usually only in advanced cancer.

• Most common chemotherapy docetaxel, and sometimes cabazitaxel, with steroids to reduce the risk of reaction.

• Both taxanes; the class was originally derived from the bark of Pacific Yew.

• Inhibit cellular mitosis and division. Dividing cancer cells die (apoptosis).

• Side effects mainly because of effects on other rapidly dividing cells- e.g. bone marrow (infection, bleeding), hair follicles, gut. Usually temporary.
Novel therapies, mainly in trials.

Include:

• High intensity focal ultrasound (HIFU). Kills cancer cells by heating.
• Cryotherapy. Freezing cancer cells.
• Proton beam therapy- a novel form of radiotherapy.
• Immunotherapy. Includes checkpoint inhibitors and a therapeutic vaccine.
• The single biggest advance would being able to predict which cancers will progress.

PC3 prostate cancer cells. Wiki.
Non-modifiable risk factors for prostate cancer other than age.

- Inverse relationship with deprivation (higher in less deprived).
- Genetic and familial may explain 5-9%.
- White males 96.0-99.9/100,000.
- Asian heritage males lower, 28.7-60.6.
- African and Afro-Caribbean heritage males higher, 120.8-247.9/100,000.
- Up to 5x higher in men with BRCA2.
- Higher with Lynch syndrome.
Family history, lifestyle.

• If father has prostate cancer 2x as likely to develop the disease; if a brother around 3x; if >2 relatives nearly 4x.

• Strongest link to early prostate cancer.

• Risk higher if family members diagnosed age <65.

• Genomewide association studies identified >100 common variants that account for approximately 33% of excess familial prostate cancer risk.

• Obesity not associated with higher rates but possibly with more aggressive cancer.

• Some conditions associated with lower risk: include diabetes, HIV and Parkinson’s.
Testicular cancer.

• A rare disease of younger men.

• 98% survive 10 or more years.

• Around 2300 cases a year in the UK.

• <100 deaths/year UK.
Testicular cancer.

- ~1% of cancers in men.
- Peak incidence in 30s.
- Very rare after 60s.
- More common in white men, and higher SES.
- <100 deaths/year UK.
Usually diagnosed at an early stage; men finding a lump. Survival has improved from 69% in 1970s to 98% now.
Diagnosis is usually by ultrasound and blood test.

- Most swellings are not cancer. But they should be checked.

- Ultrasound helps tell if solid or fluid-filled and where it is.

- Blood markers:
  - alpha feta protein (AFP)
  - human chorionic gonadotrophin (HCG)
  - lactate dehydrogenase (LDH)

Courtesy Brendan Cullinane, Radiopaedia
The mainstay of treatment is orchidectomy.

- Removing the testis with early cancer is usually curative.
- Men can have a completely normal life, including professional, romantic and sexual life, have children.
Stage and type define further treatment.

Stage. May include CT scan

• Stage 0/1 confined to testis.
• Stage 2 spread to local lymph nodes.
• Stage 3 more distant spread.
• High blood test markers may imply spread.

Type.

• Seminoma and nonseminoma.
• Seminoma types of testicular cancer more sensitive to radiotherapy, chemotherapy and less prone to distant metastases.
Seminoma

- Arise from the seminiferous tubules of the testes where spermatozoa are created (top).

- Seminomas usually diagnosed aged 15-35, a few years later than other germ cell tumours.
Non-seminoma

Mixed germ cell tumours. Some combination of:

• teratoma
• embryonal carcinoma
• choriocarcinoma
• yolk sac tumours

• Treatment is slightly more complicated.

Drevinskaite et al 2019
Typical treatments. All have orchidectomy.

- **Stage 1.** Usually just surgery- curative. Chemotherapy only if cancer has a high risk of coming back.
- **Stage 2.** **Seminoma** further treatment depends on the stage of the cancer. Early Stage 2 radiotherapy, later chemotherapy.
- **Non-seminoma.** Chemotherapy.
- **Stage 3.** **Seminoma.** Chemotherapy.
- **Non-seminoma** Chemotherapy +/- abdominal surgery to remove nodes or lung surgery.
Radiotherapy.

- For seminomas that have spread to the lymph glands of the abdomen.
- 3-4 weeks, sometimes shorter.
- Common temporary side effects: tiredness, diarrhoea, sore skin, occasional nausea.
- May be temporary damage to sperm; man advised not to father children for a year.
Chemotherapy for testicular cancer.

- Typical drugs for seminoma **carboplatin**.
- Typical chemotherapy drugs **BEP**; bleomycin, etoposide and cisplatin.
- **Bleomycin** derived in 1966 from the bacteria *Streptomyces verticillus*.
- **Etoposide** (1966). Originally derived from rhizome (type of root) of wild mandrake.
- **Cisplatin** discovered in 1845; **carboplatin** same class. Cancer-fighting properties 1965 after finding that using platinum electrodes inhibited *E. coli* growth.
- Other drugs for relapse or advanced disease.
Chemotherapy continues to improve.

• The study illustrated at right was reported earlier this month. One cycle rather than two probably as good for cancer, fewer side effects.

• As outcomes are already good for the great majority, much of the emphasis of research is on reducing side effects further.
Risk factors for testicular cancer.

- Undescended testicle at puberty. Correcting this reduces risk.
- Family history: if father had testicular cancer around 4x times more likely to develop it, with a brother who had testicular cancer are around 8x.
- Mumps orchitis.
- Previous testicular cancer.
- Inguinal hernia.
- White males (and tall males) higher risk.

National Cancer Institute
Potts disease of the scrotum.
An historically important, now unknown, disease.

• Squamous cell carcinoma of the scrotum seen in chimney sweeps. Boys as young as 4 working.

• Sir Percival Pott C 1775: “... they are treated with great brutality ... thrust up narrow and sometimes hot chimneys, where they are bruised burned and almost suffocated; and when they get to puberty they become ... liable to a most noisome, painful and fatal disease.”

• First occupational cancer identified.

• Chimney Sweepers Act 1788; children must be 8, with parents consent. No really effective Act until 1875 (after The Water Babies). Strong concern not to interfere with trade.
Prostate and testicular cancer.

• **Prostate cancer** very common disease of older men.
• The great majority of people with it will not die of it. Many unaware.
• Possible to live with it as a chronic condition.
• Hormone treatment important.
• **Testicular cancer** an uncommon cancer of younger men.
• Often can be cured with surgery.
• Very good outcomes normal.
• **Penile cancer** very rare (600/yr), will get even rarer with HPV vaccination (60%).