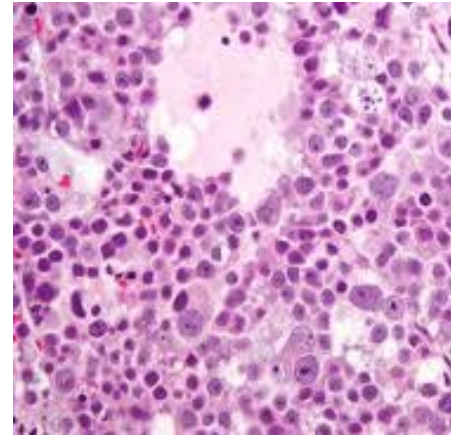
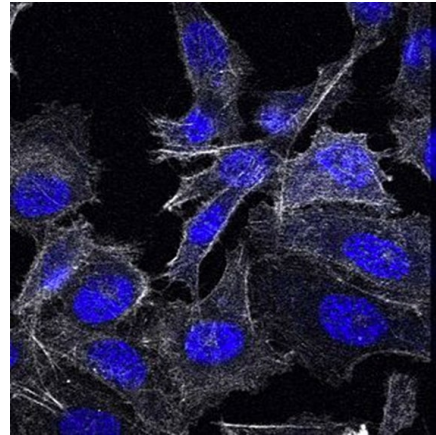


Prostate and testicular cancer.



Christopher Whitty
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.



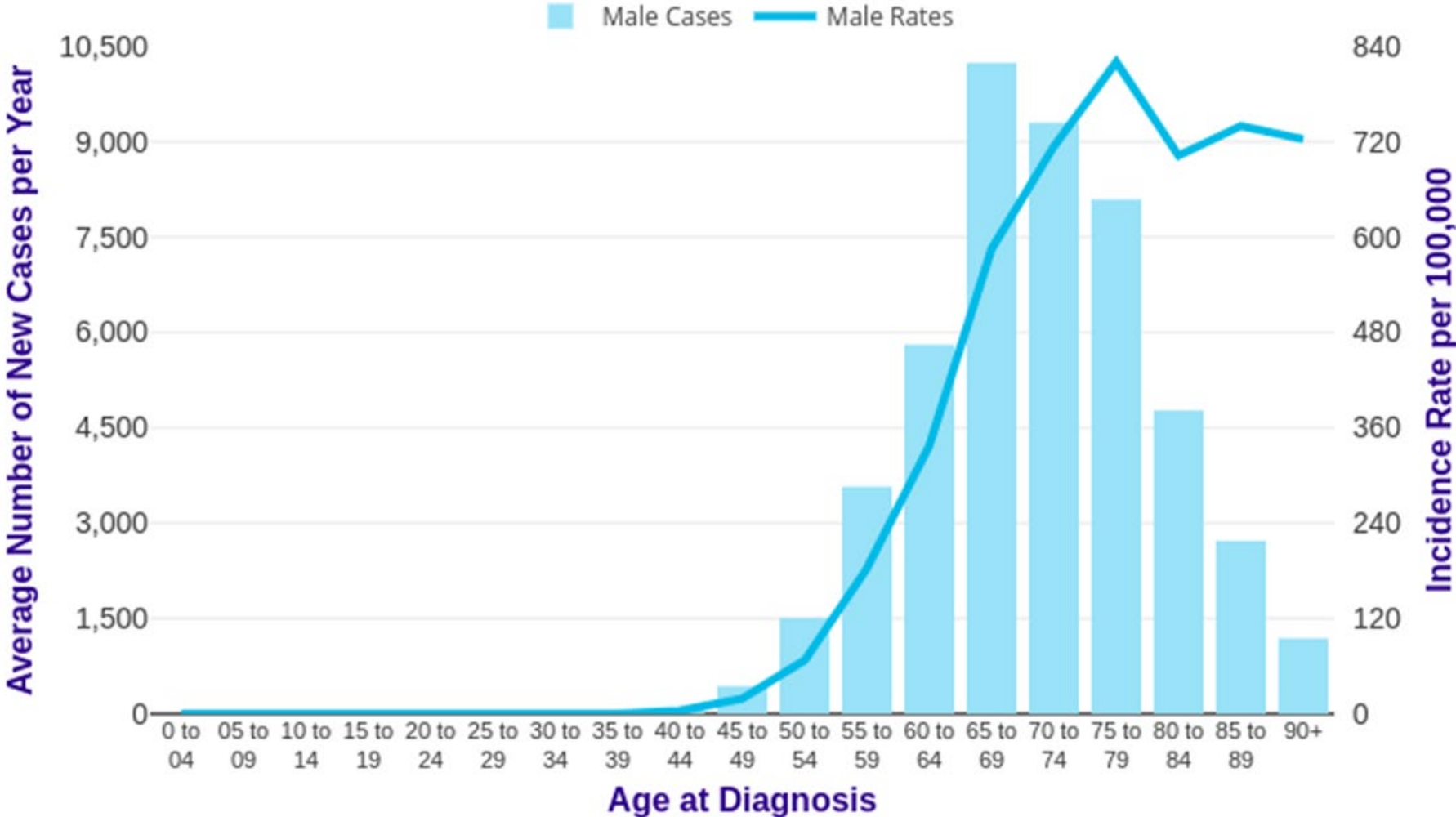
Rembrandt self-portraits.

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.

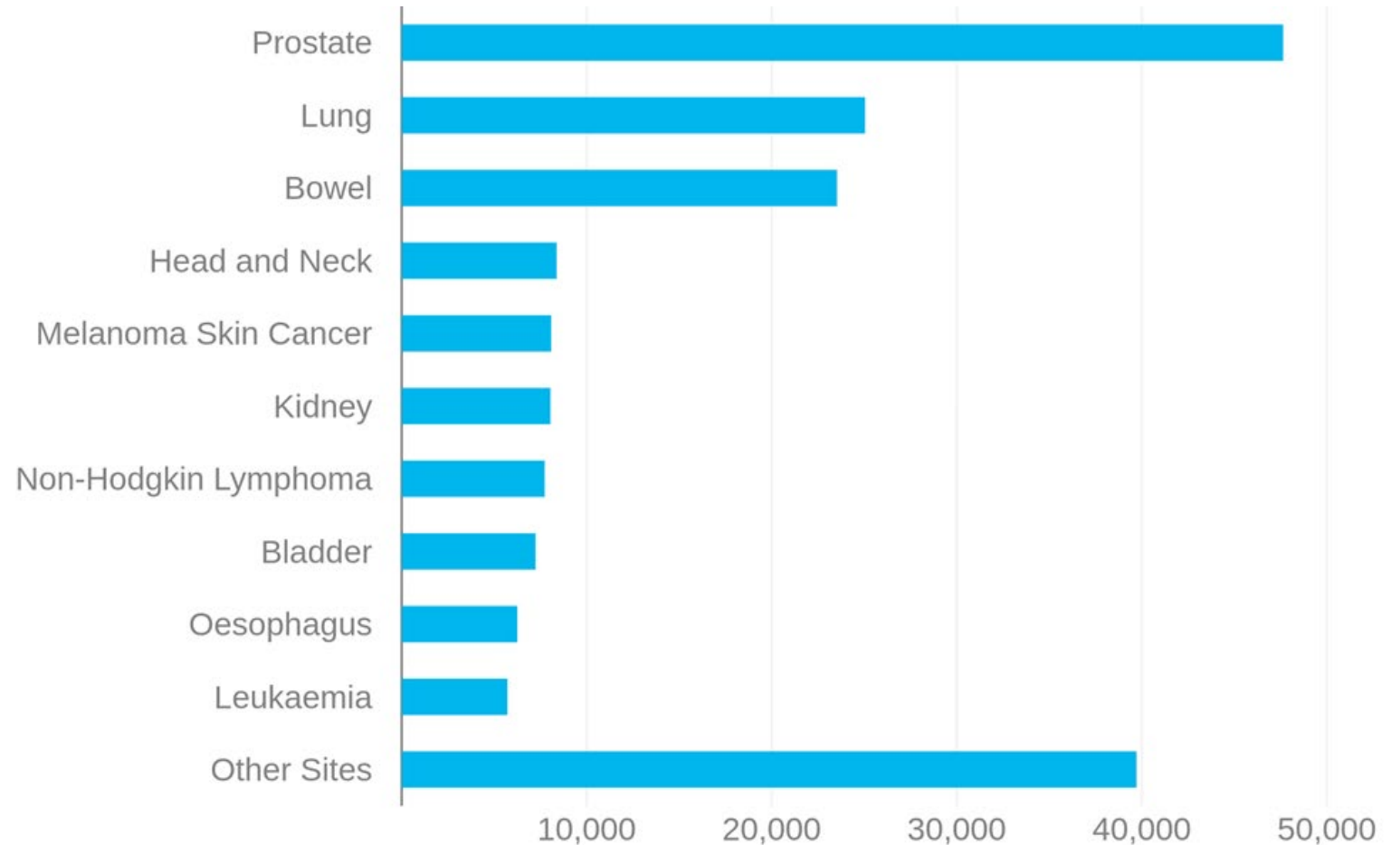
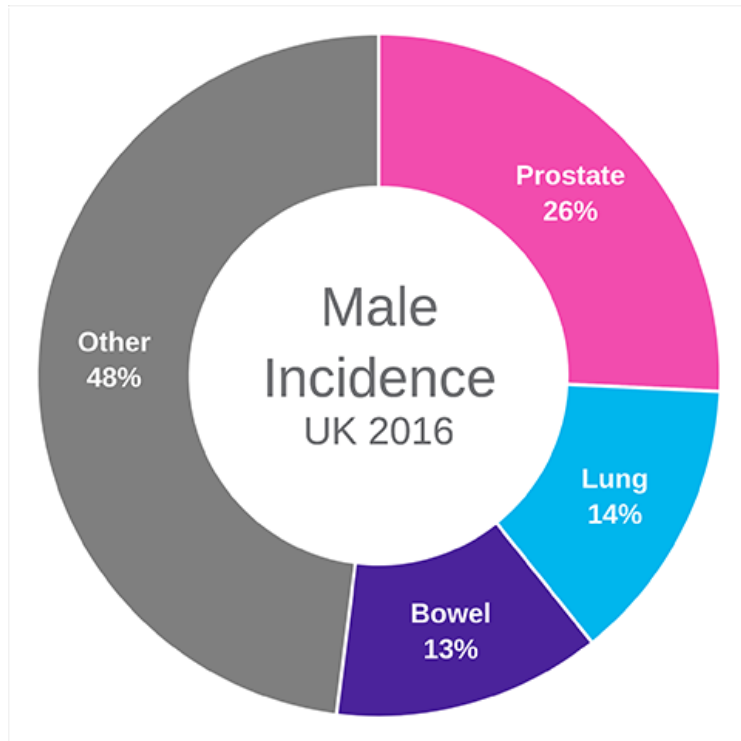


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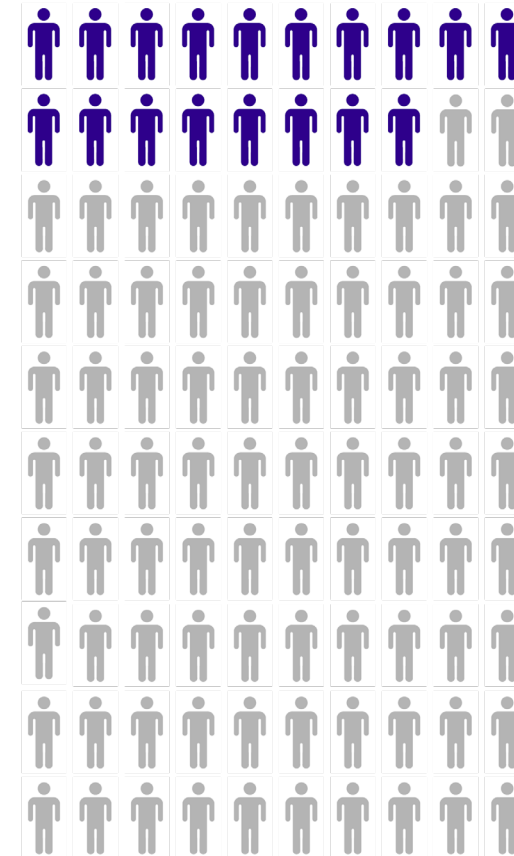
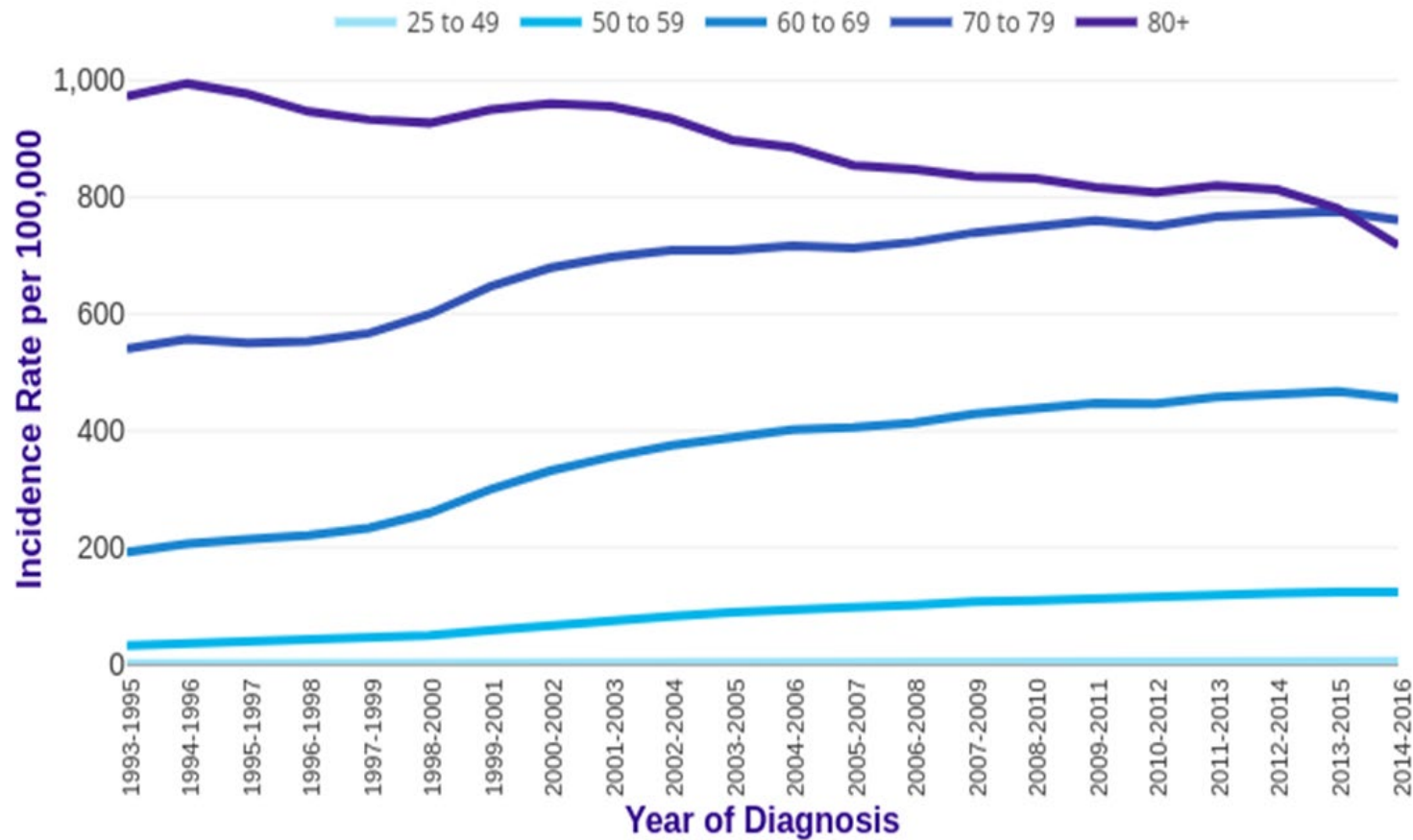
70

Prostate cancer, UK. (CRUK/ONS).

- Around 47,000 cases registered in the UK a year.
- Around 26% of cancers in men.



Around a 16% lifetime risk for UK men born after 1960.
 Increase in diagnosed incidence in men 60-79. Data 1993-2016.



CRUK



Will develop prostate cancer

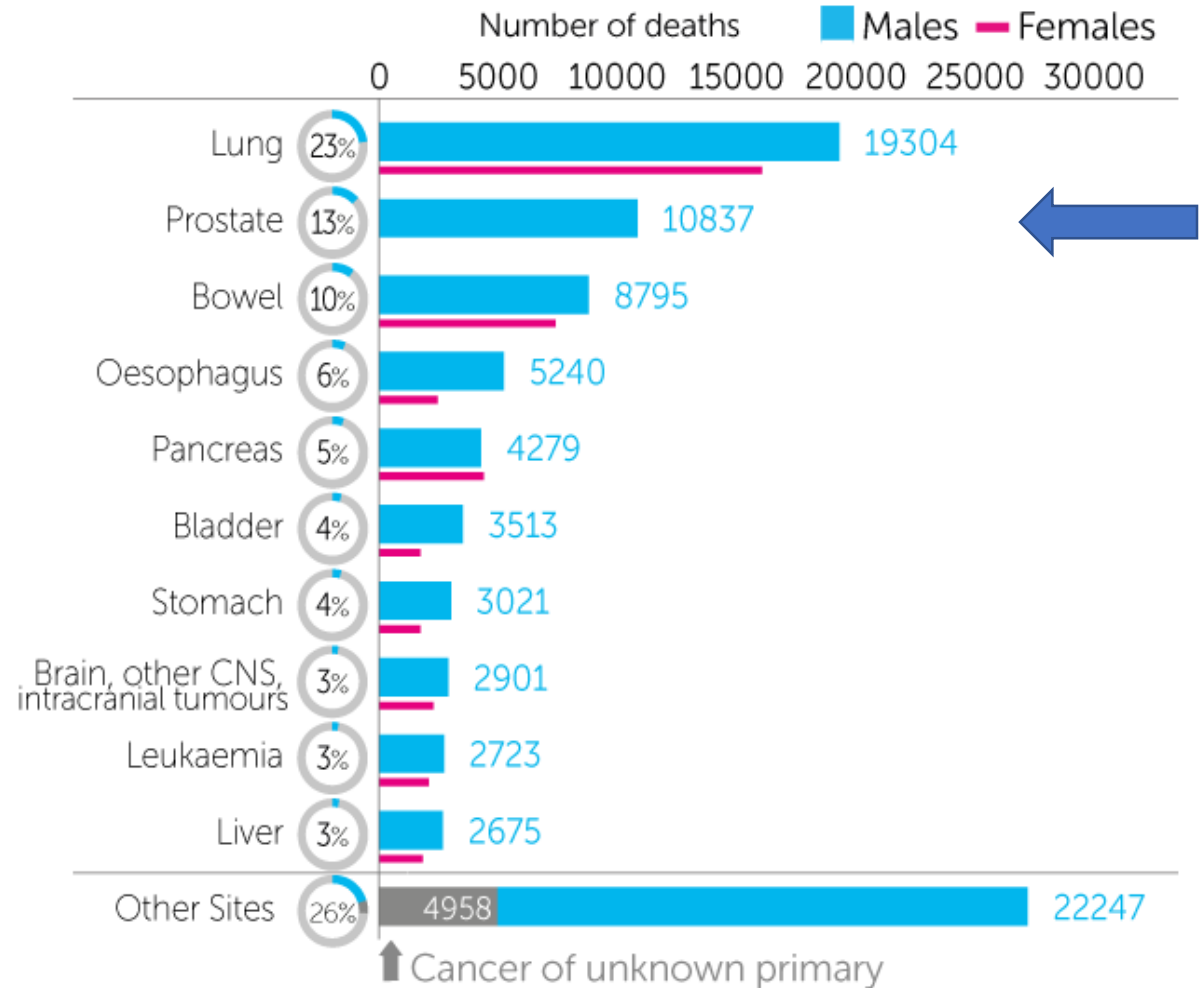


Will not develop prostate cancer

Cancers: UK mortality

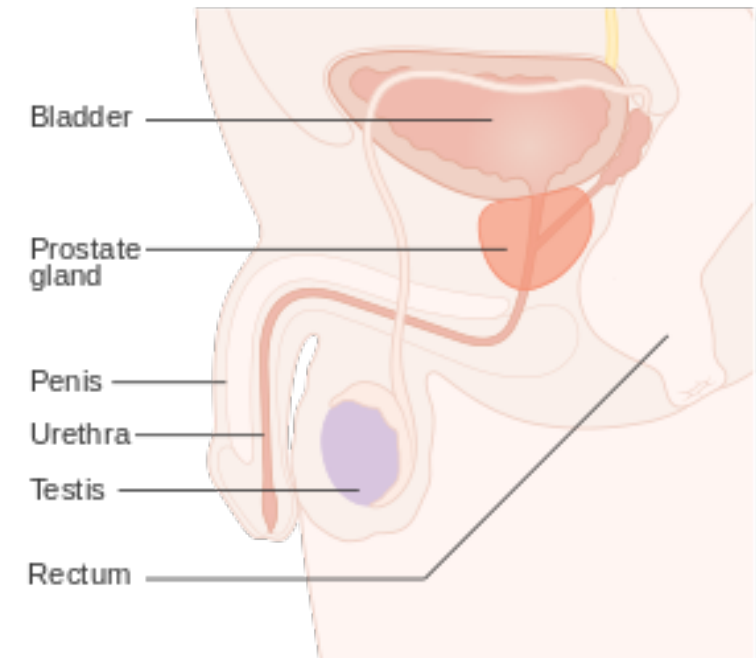
(CRUK 2014: males)

- 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.



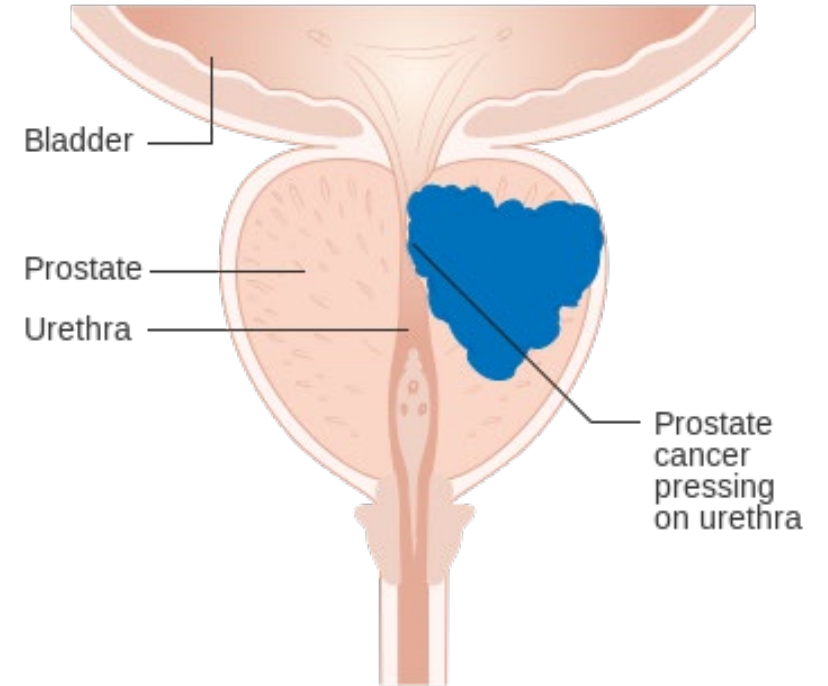
The prostate gland.

- 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.



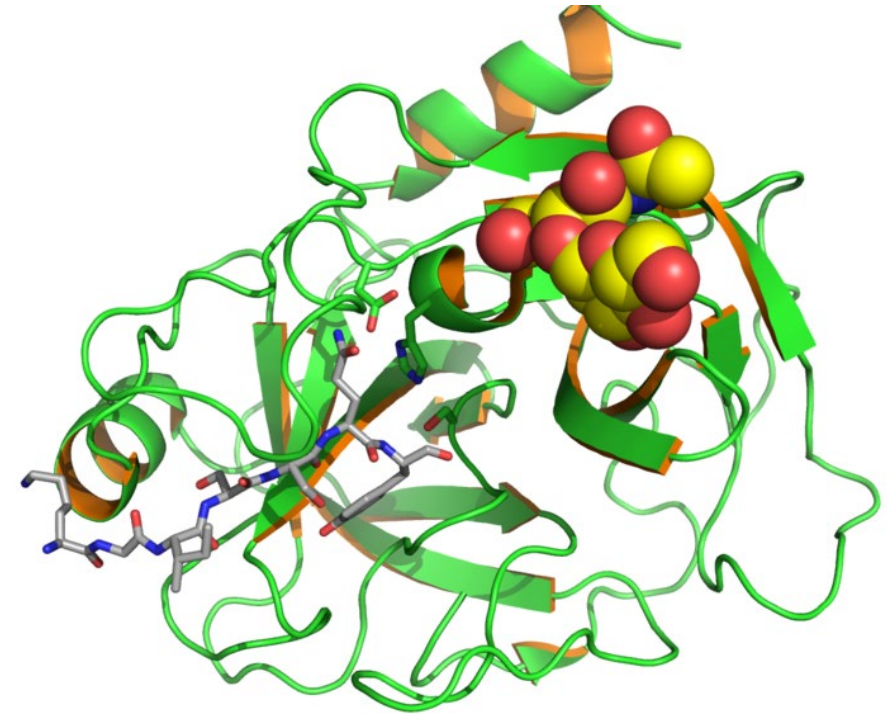
Symptoms and signs that *might* be prostate cancer.

- 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.

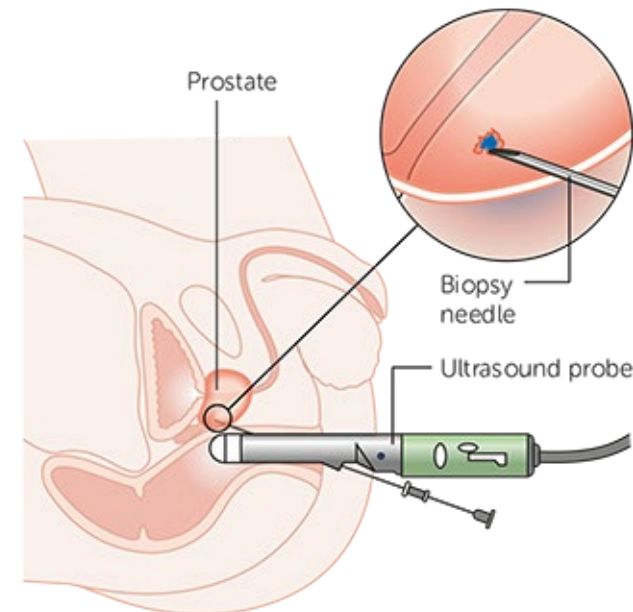
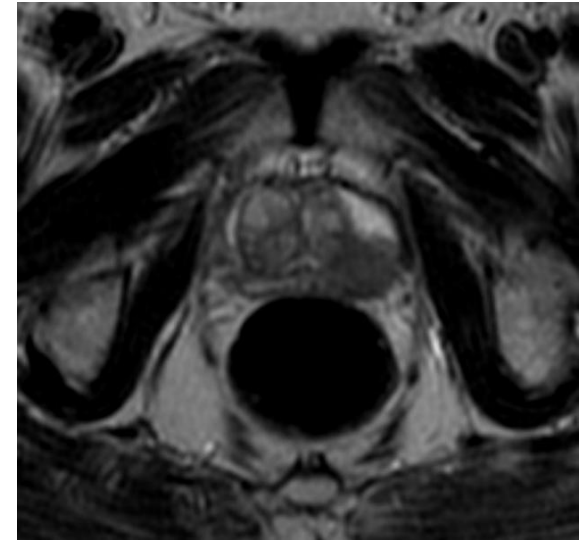
- Routine digital exam by a doctor.
- Routine or diagnostic PSA test.
- PSA is raised in prostate cancer, but also by multiple other causes. Include:
 - BPH
 - Urinary/prostate infection
 - Recent ejaculation
 - Physical pressure



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.



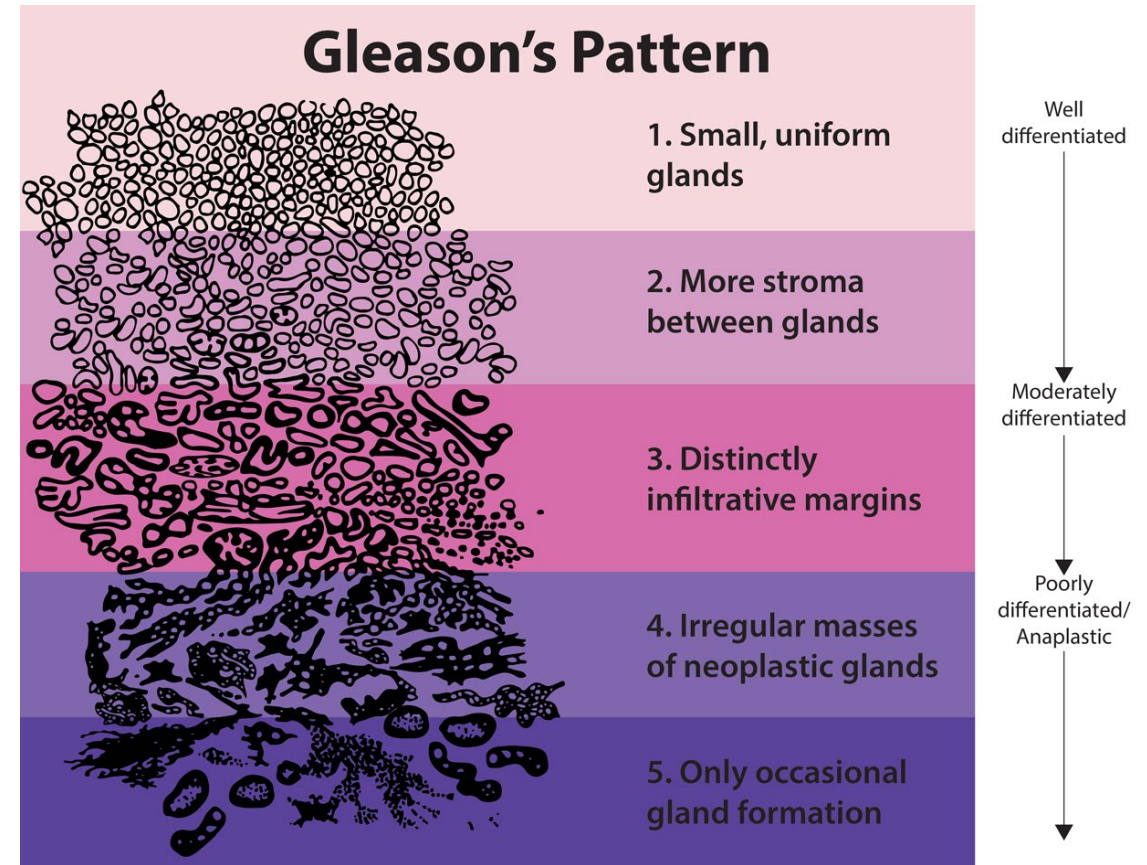
Roberto Schubert,
Radiopaedia/
CRUK

Stage, grade and type of cancers.

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

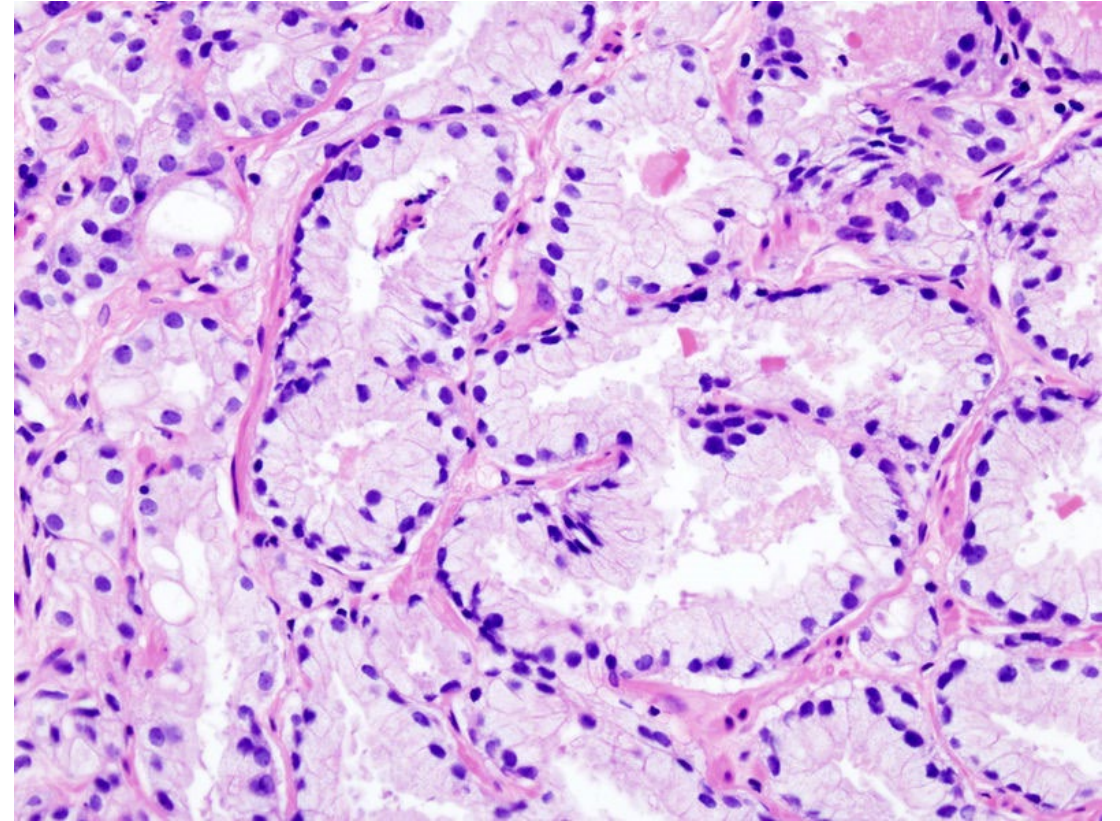
Grade: appearance of the cells.
The more different from normal cells
the higher the grade.
'undifferentiated'. Gleason score.

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



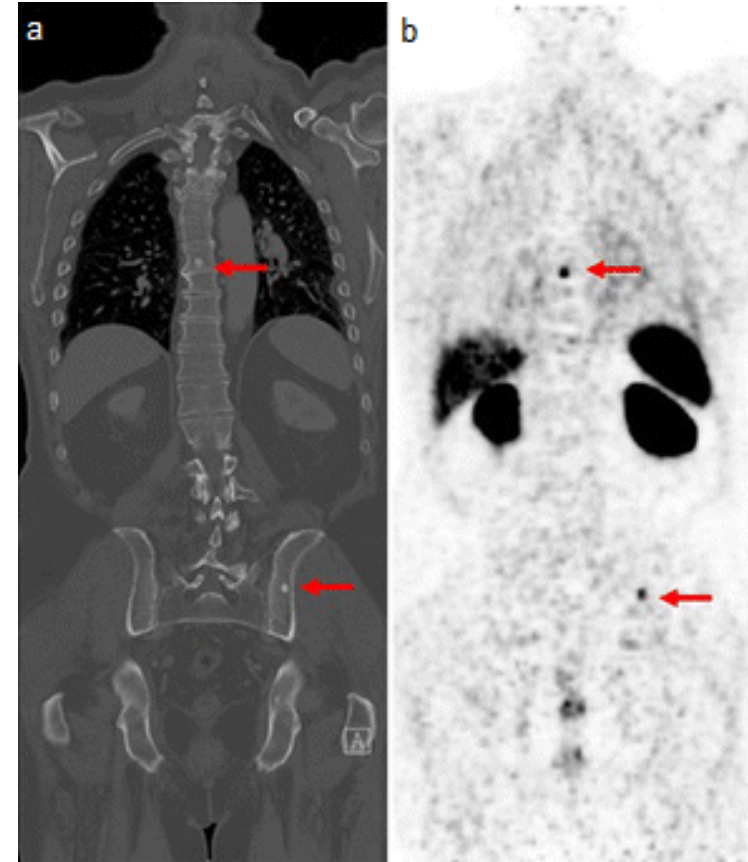
Type of cancer of the prostate.

- >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.

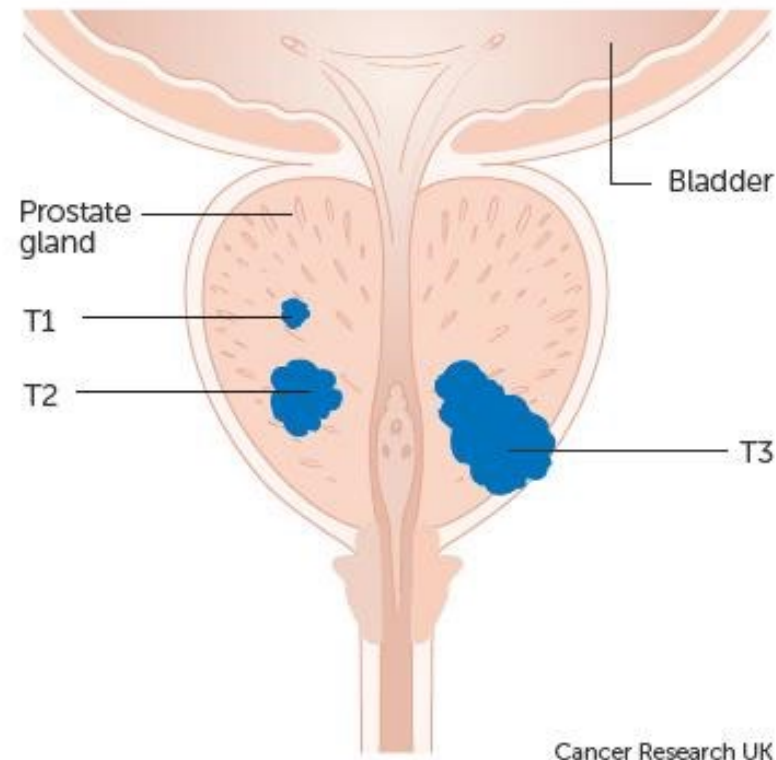
- If biopsies show it is cancer, men may have additional staging tests.
- Mainly to check whether it has spread, and if so where.
- MRI
- CT (sometime PET CT for recurrence).
- Plain X-ray of bones.
- Ultrasound of abdomen.



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.



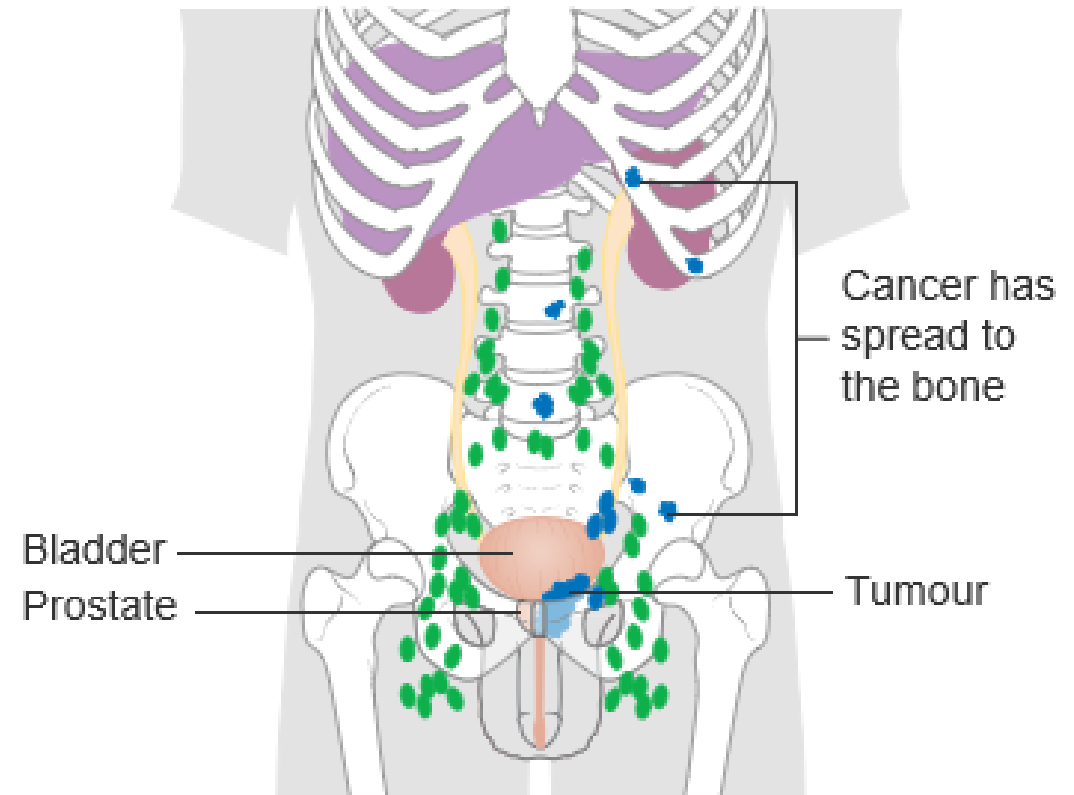
Stage 4 and metastases.

- Stage 4 prostate cancer is any spread, whether local (T4) or nodes or metastases.
- Metastases when there is distant spread.
- Most common sites:

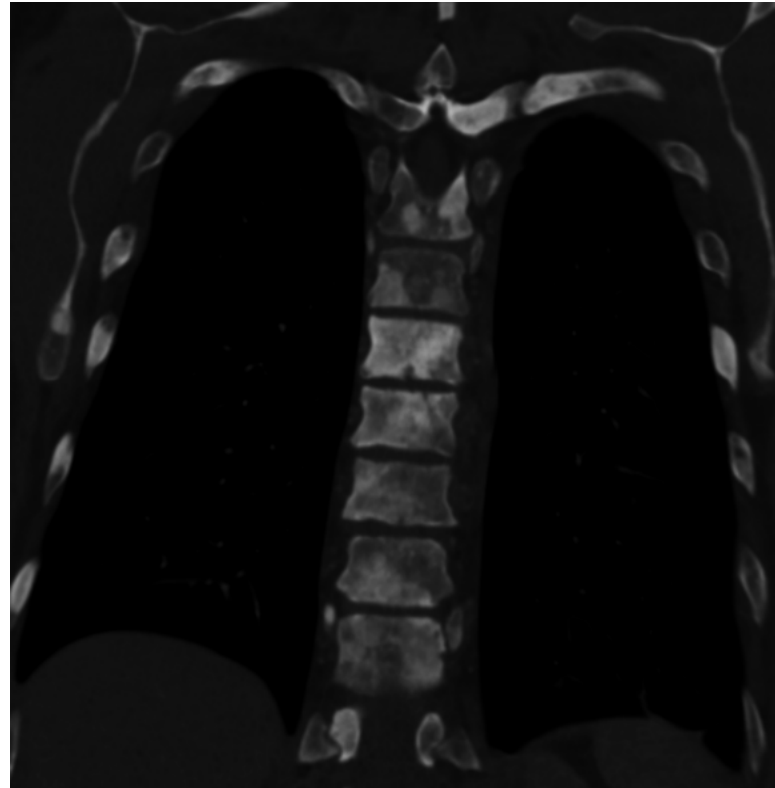
Lymph nodes

Bone (ribs, spine, pelvis)

- Can also go to lungs, liver, brain but much less common.
- Rarely other sites.

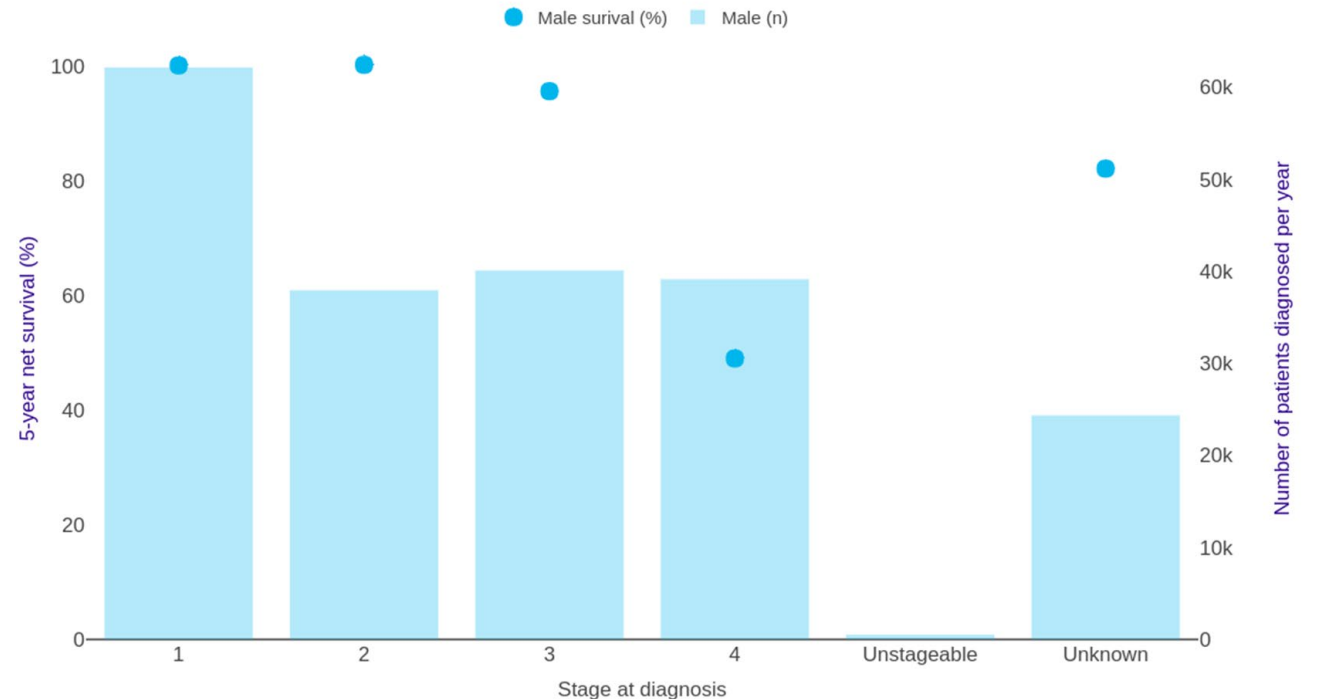


Bone metastases from prostate.
Osteosclerotic.



Except for Stage 4 survival is very good.

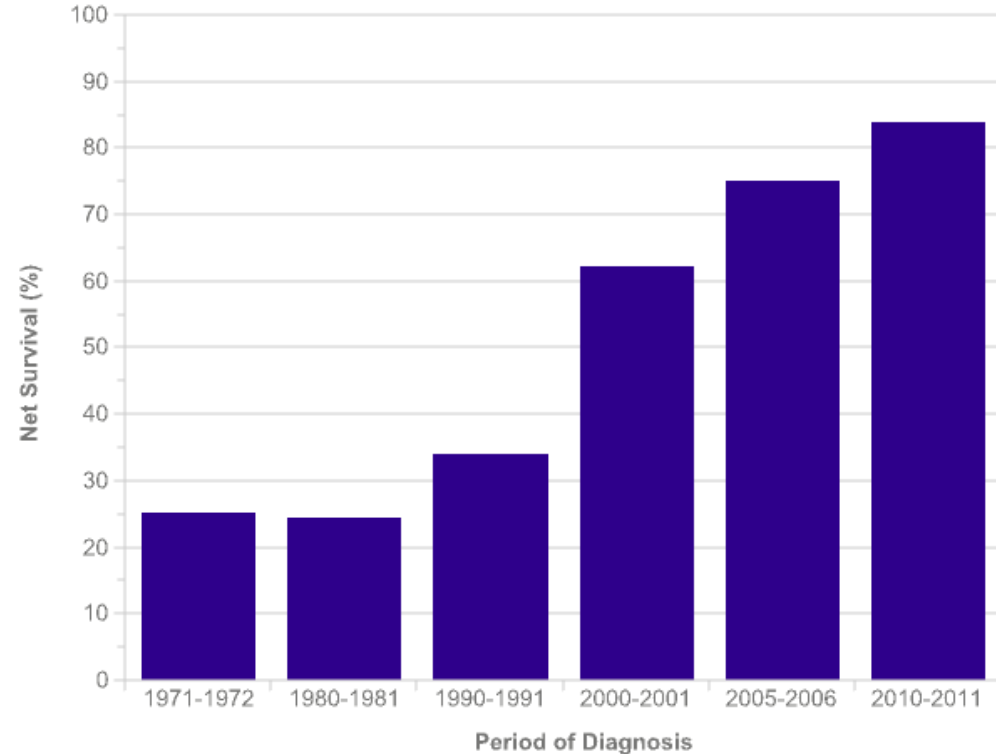
- Most men are diagnosed Stages 1-3.
- 5 year cancer-specific survival is essentially 100% for Stages 1-2 and 95% for Stage 3.
- 5 year survival currently 49% Stage 4. 88% survival at a year.



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

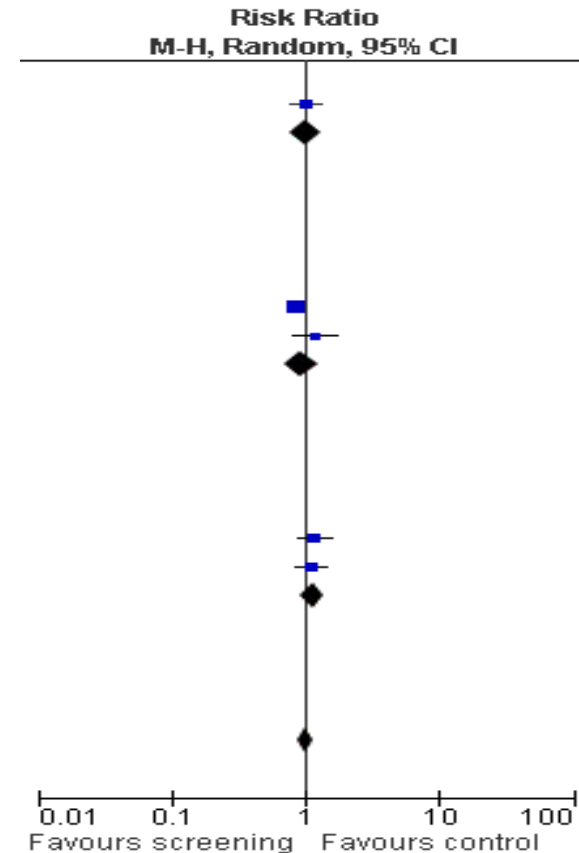
Survival steadily rising.

- 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?

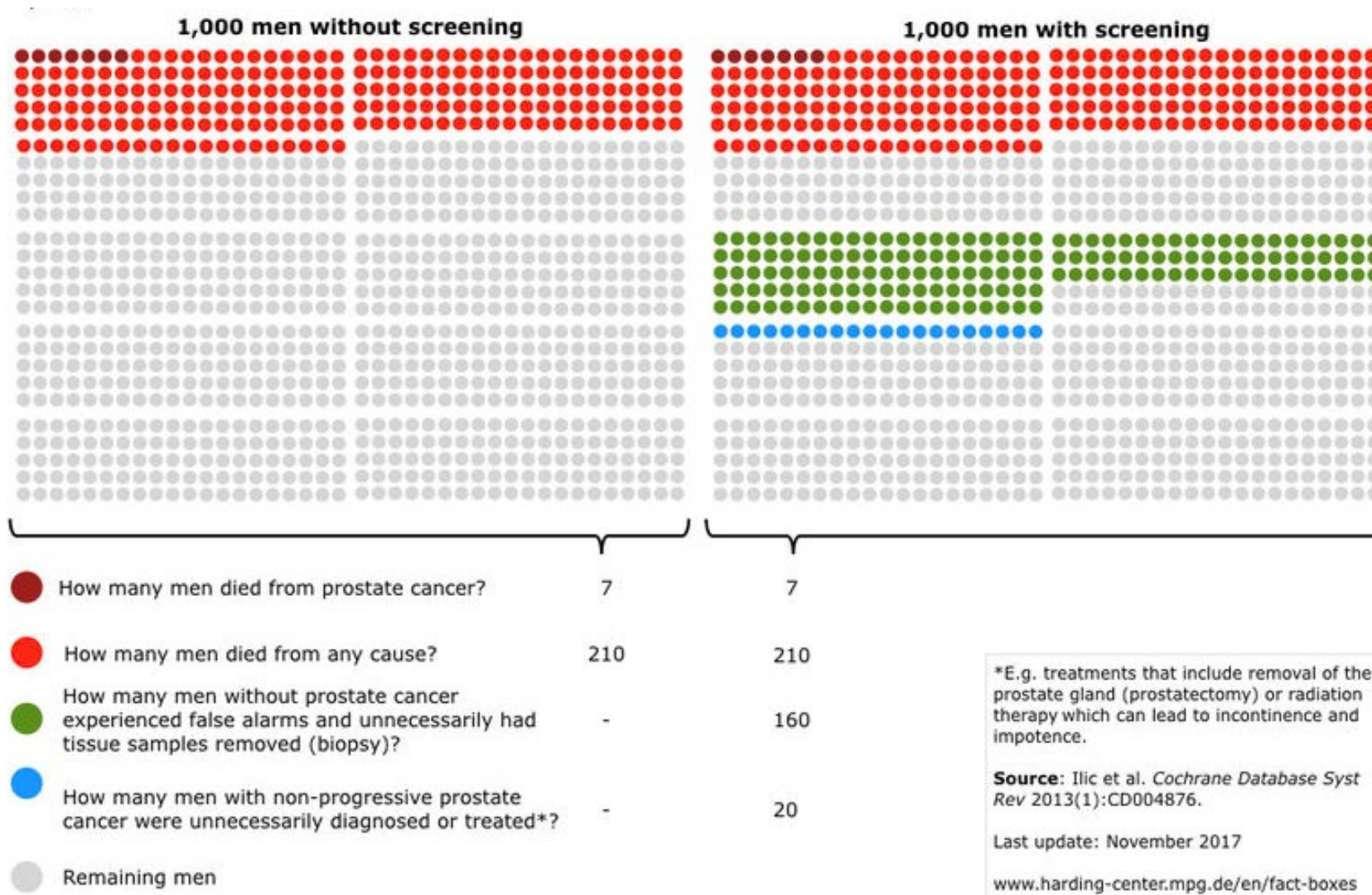
- Current prostate cancer screening is with PSA blood test.
- Systematic review of 341,342 men in trials found relative risk 1 (no difference) for mortality.
- Increases number of unnecessary biopsies and treatment.
- Screening not worthwhile.



Ilic et al 2013 Cochrane

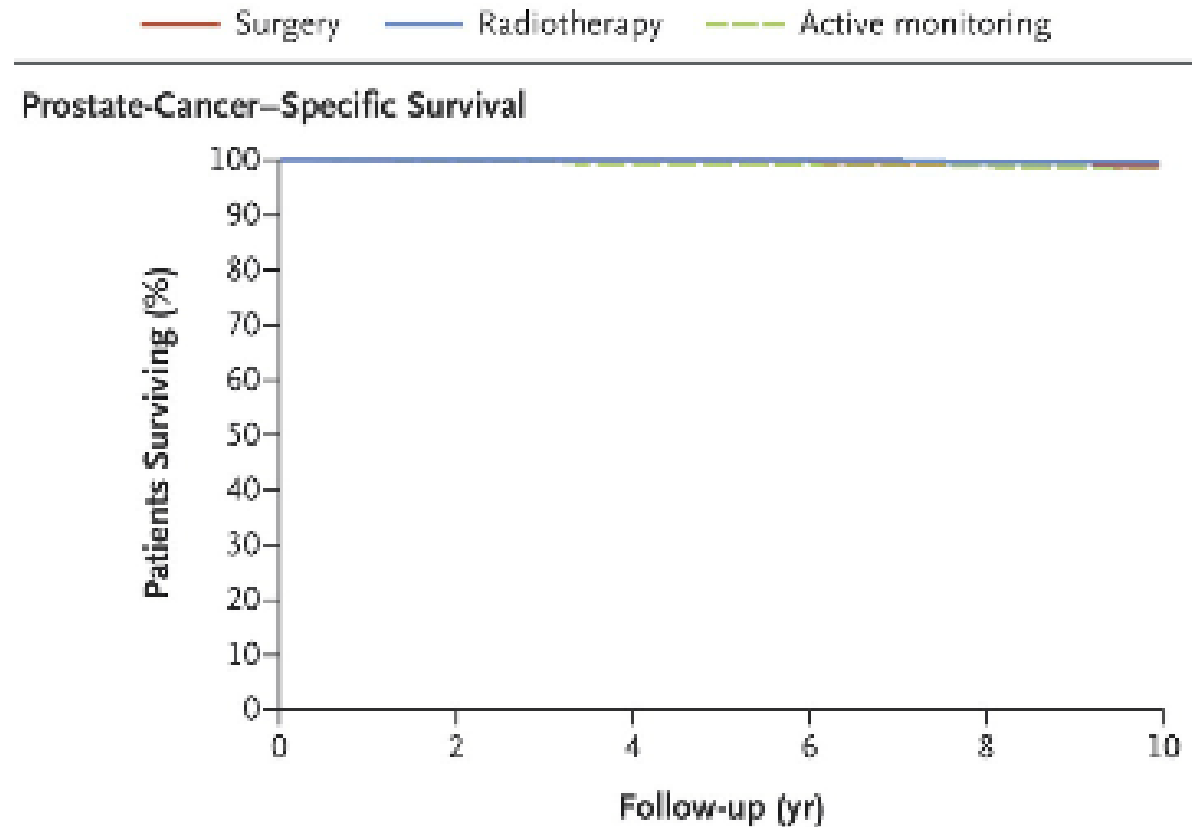
Prostate screening- a graphical representation.

Harding Centre for Risk Literacy / Cochrane.



Clear evidence watchful waiting is often the best policy in early disease. But not always.

- Prostatectomy v radiotherapy v 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.

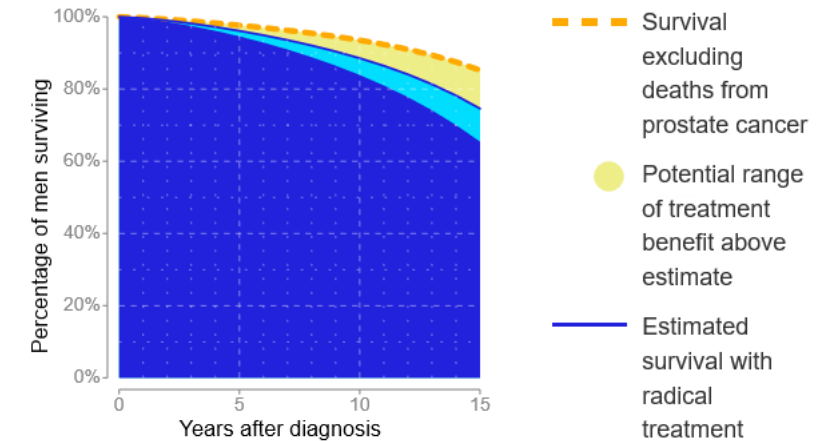


ProtecT trial, 1643 men

For those who wish to, there are tools to help understand the risks and benefits of treatment to help discussions with your doctor.

Survival curve

This graph shows the percentage of men surviving up to 15 years. These results are based on the inputs and treatment you selected



Incontinence

Defined as: 'Wore one or more pads in the last 4 weeks'

With **conservative management**, fewer than 1 in 100 men have this issue after 3 years.



With **radical prostatectomy**, about 20 in 100 men have this issue after 3 years.



With **radiotherapy**, about 3 in 100 men have this issue after 3 years.



- Potential range of treatment benefit below estimate
- Conservative management

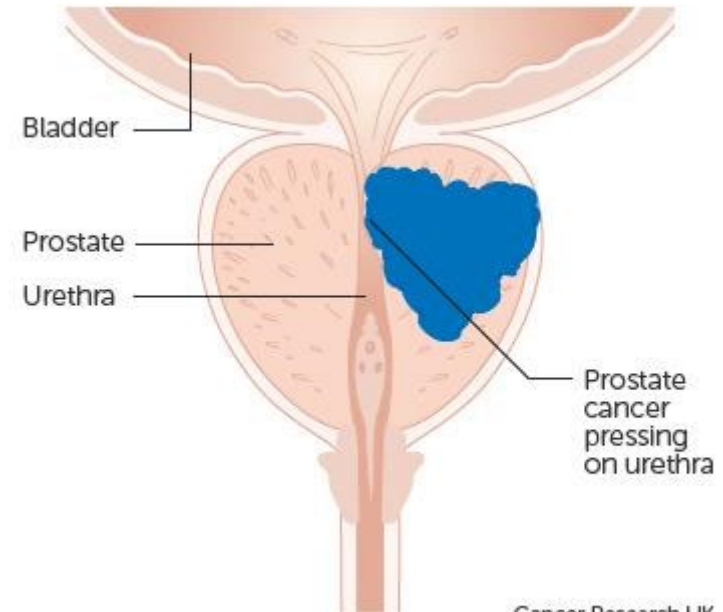
Surgery- prostatectomy.

- 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).



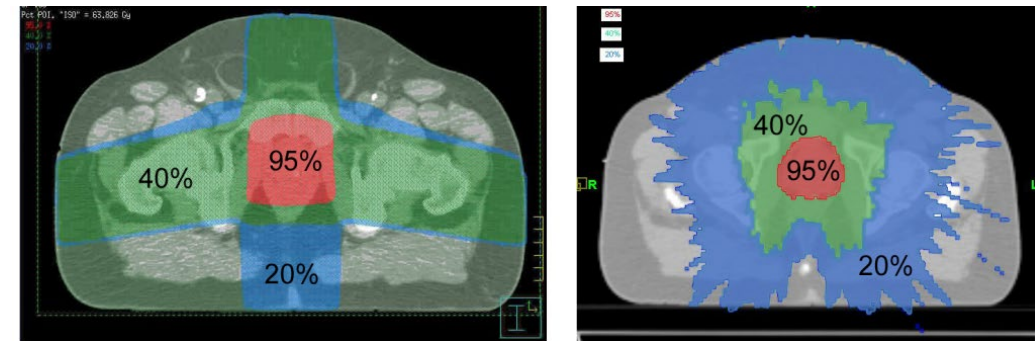
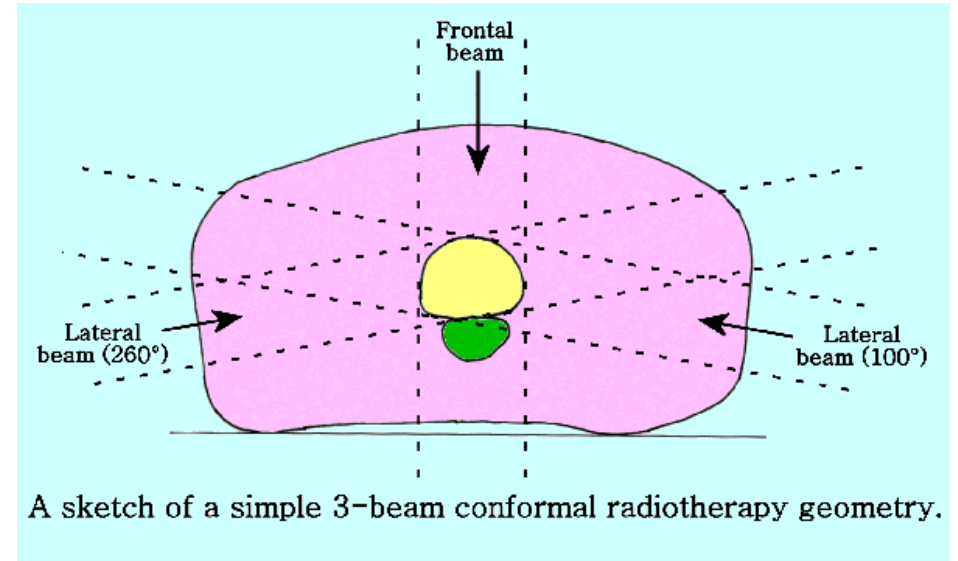
Surgery- transurethral resection.

- 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.

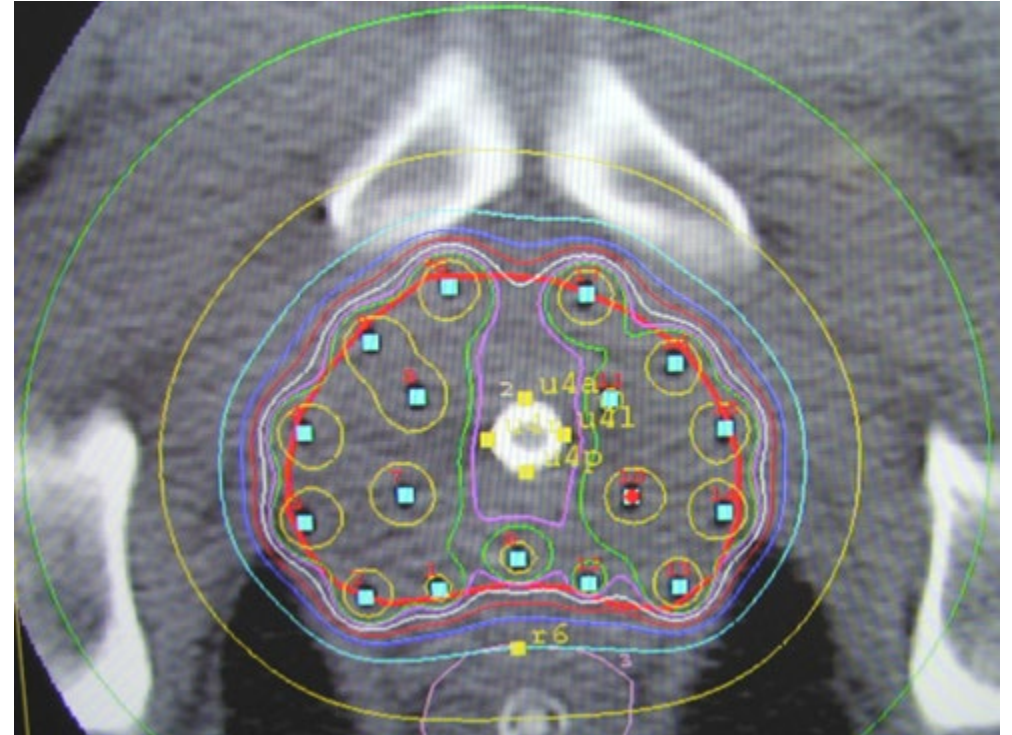
- Radiotherapy damages and kills cancer cells, healthy cells usually recover.
- May be used to treat cancer confined to the prostate; cancer that has spread; to alleviate symptoms.
- Radiotherapy over 100 years old. Modern radiotherapy much more accurate.
- Image on R compares conventional radiotherapy 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:

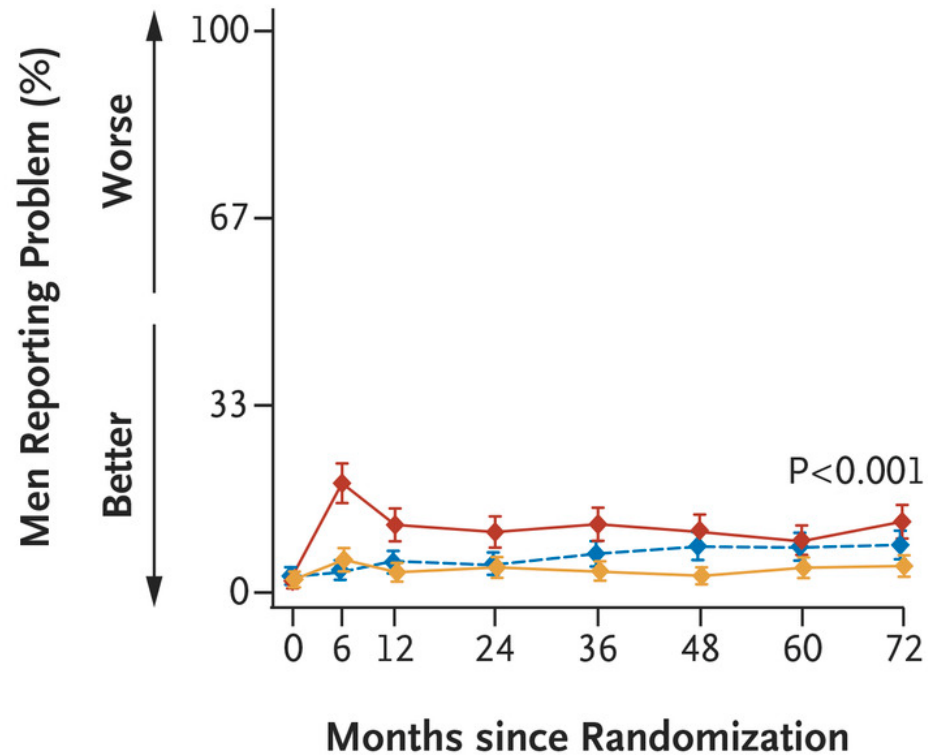
- Urinary frequency, flow reduced or incontinence.
- Diarrhoea.
- Erectile dysfunction.



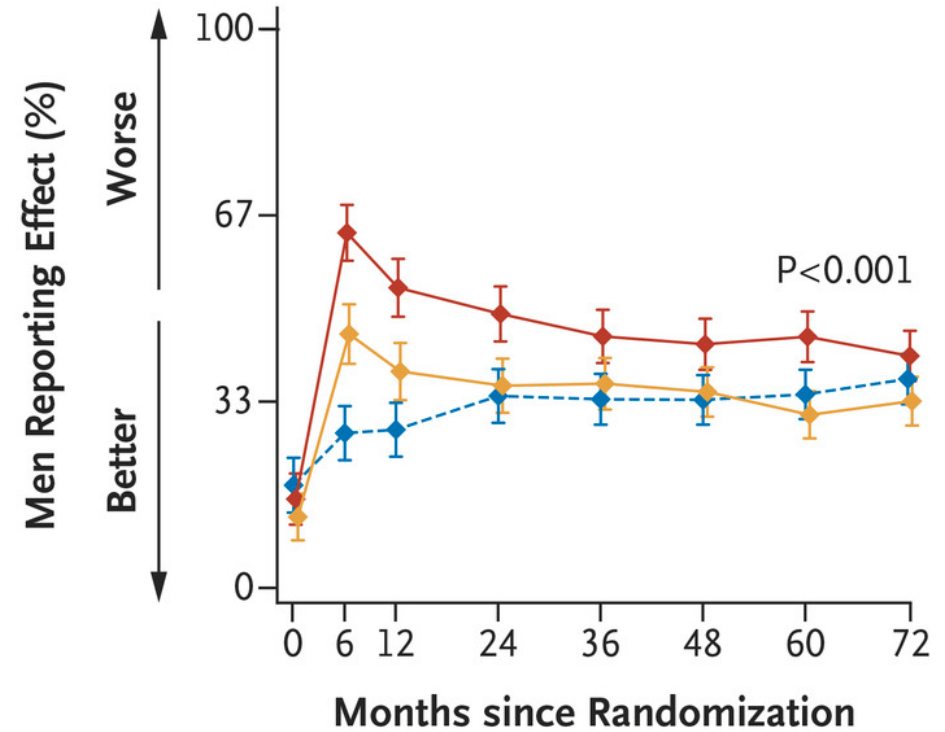
Surgery v radiotherapy v watchful wait side effects.

ProtecT trial, NEJM 2016. Self-reported, n 1643.

Urinary incontinence.

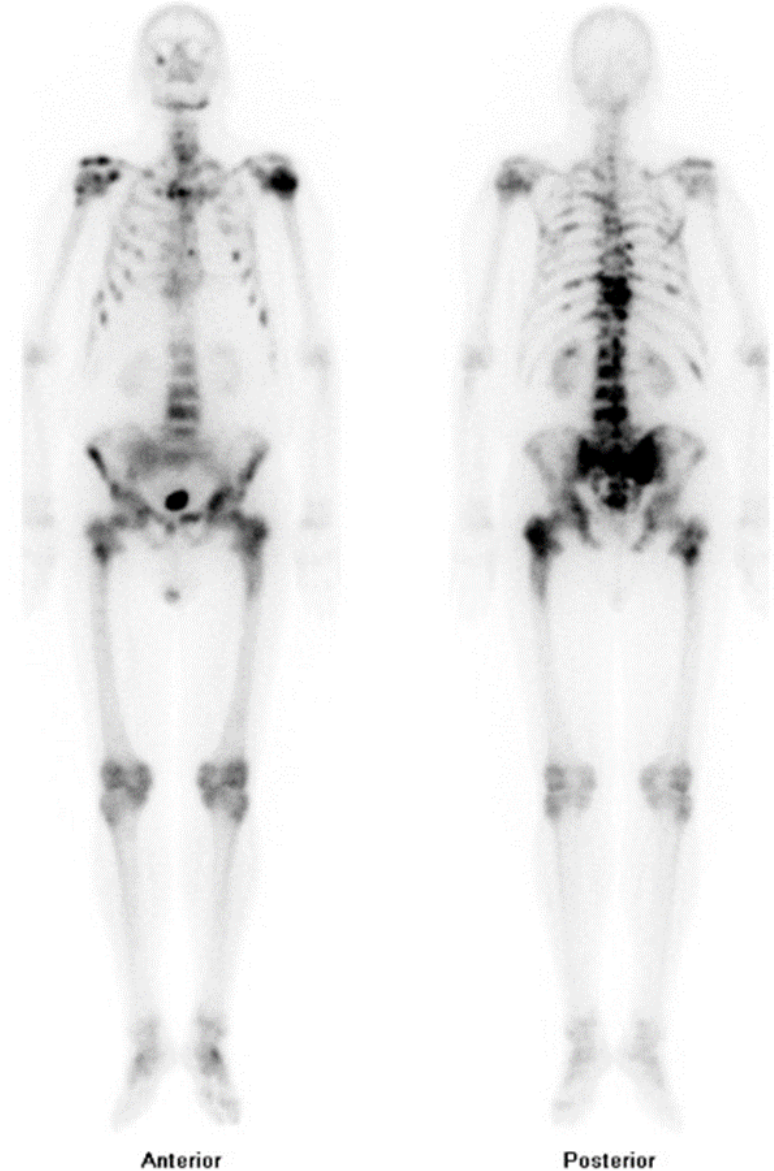


Sexual quality of life.



Radium-223 or Strontium-89

- Used for bone metastases which are not under hormone treatment control.
- Weakly radioactive α -emitting (Radium) or β -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.

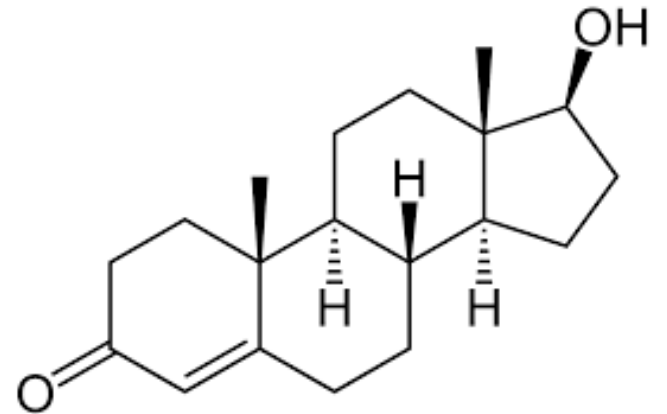


Hormone therapy for prostate cancer.

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

Broadly two indications:

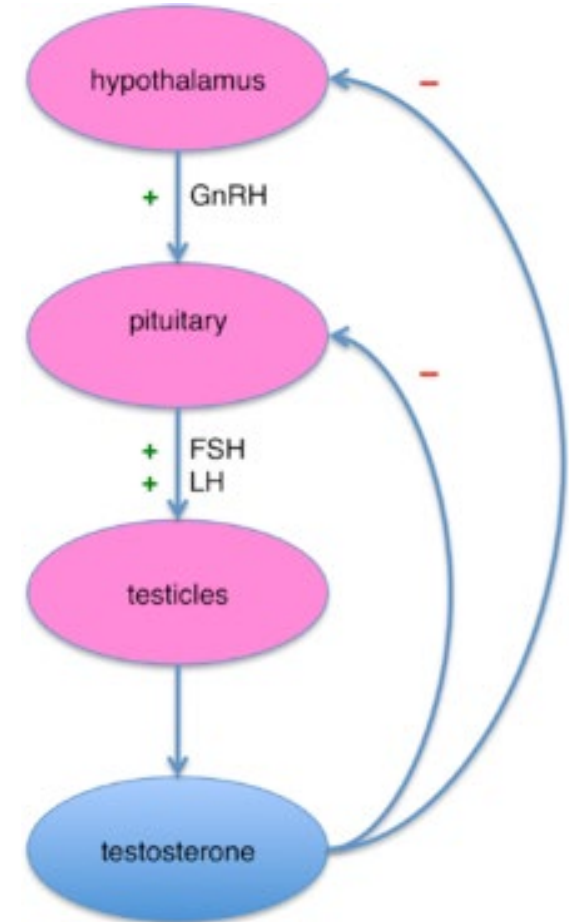
- As a temporary adjunct to other treatment like radiotherapy to shrink the tumour.
- Long term suppression of advanced cancer or cancer that has recurred.
- Long-term use becomes less effective over a number of years ('castration-resistant').



Testosterone

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).*



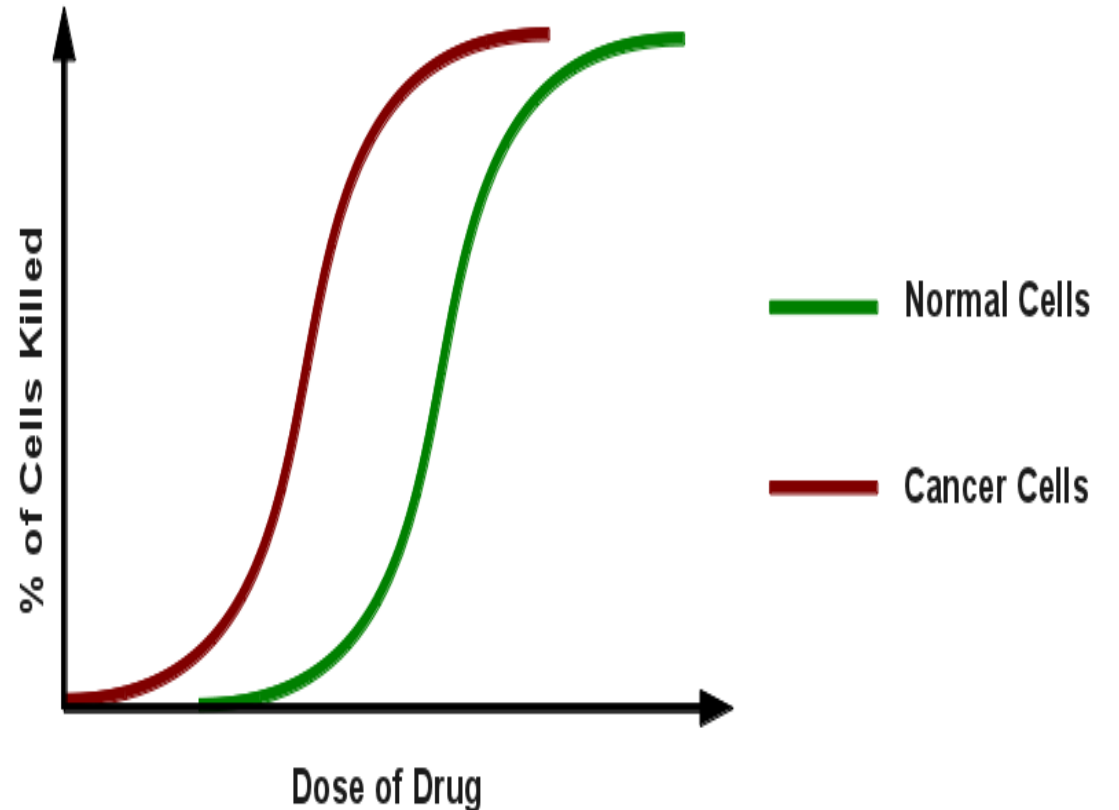
Active watching, surgery, **radiotherapy**, hormone treatment, **chemotherapy**, novel therapies.
Depends on stage of disease.

	Stage 1	Stage 2	Stage 3	Stage 4
Surgery	11%	28%	23%	3%
Radiotherapy	22%	35%	53%	28%
Chemotherapy	<1%	1%	2%	9%

% 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.

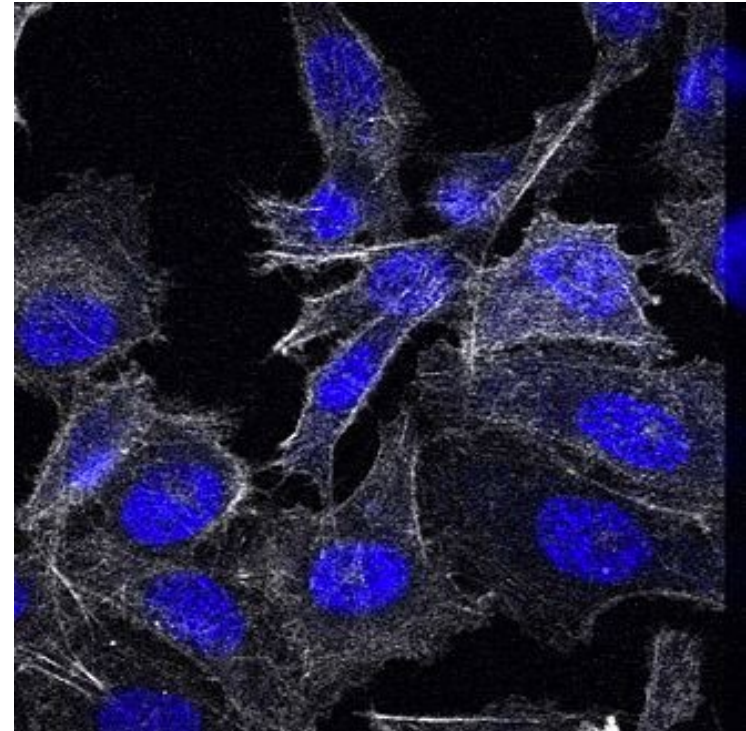
- Most common chemotherapy **docetaxel**, and sometimes **cabazitaxel**, with steroids to reduce the risk of reaction.
- Both taxanes; the class was originally derived from the bark of Pacific Yew.
- Inhibit cellular mitosis and division. Dividing cancer cells die (apoptosis).
- Side effects mainly because of effects on other rapidly dividing cells- e.g. bone marrow (infection, bleeding), hair follicles, gut. Usually temporary.



Novel therapies, mainly in trials.

Include:

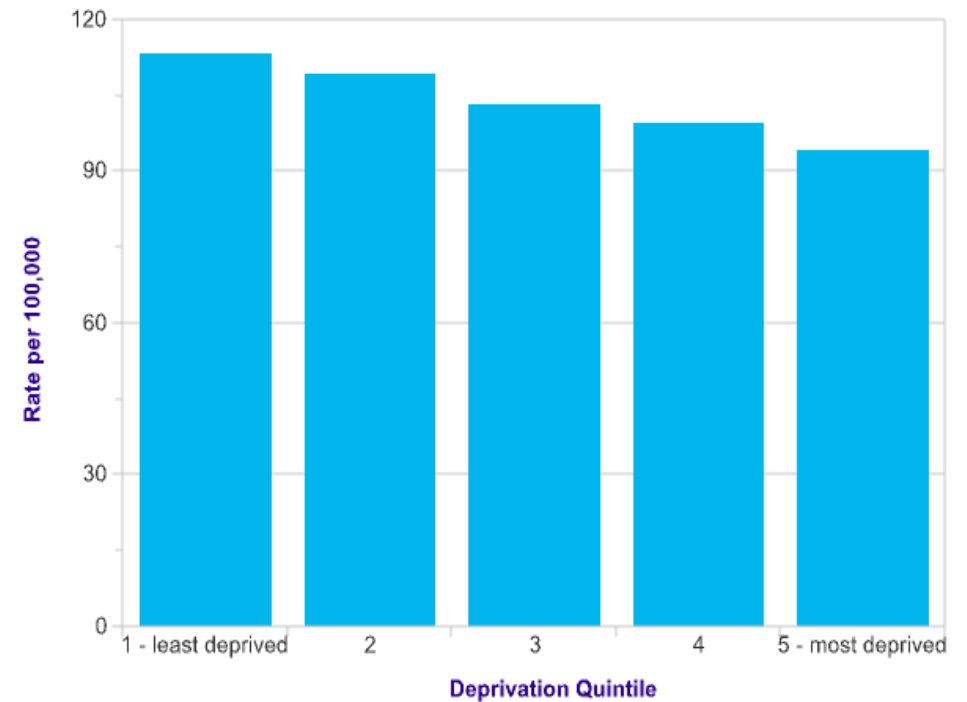
- High intensity focal ultrasound (HIFU). Kills cancer cells by heating.
- Cryotherapy. Freezing cancer cells.
- Proton beam therapy- a novel form of radiotherapy.
- Immunotherapy. Includes checkpoint inhibitors and a therapeutic vaccine.
- The single biggest advance would be being able to predict which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



PC3 prostate cancer cells. Wiki.

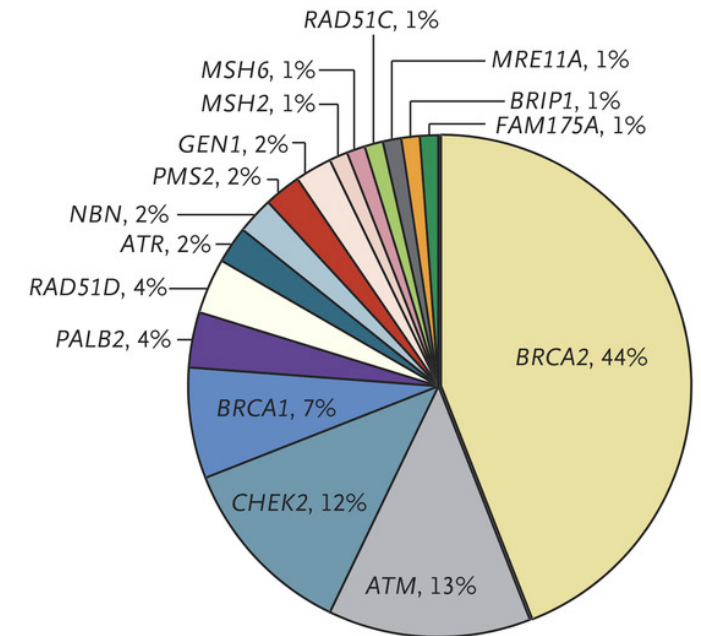
Non-modifiable risk factors for prostate cancer other than age.

- 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 4 x.
- 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.



Presumed pathogenic germline mutations in metastatic prostate cancer. Prichard et al NEJM 2016.

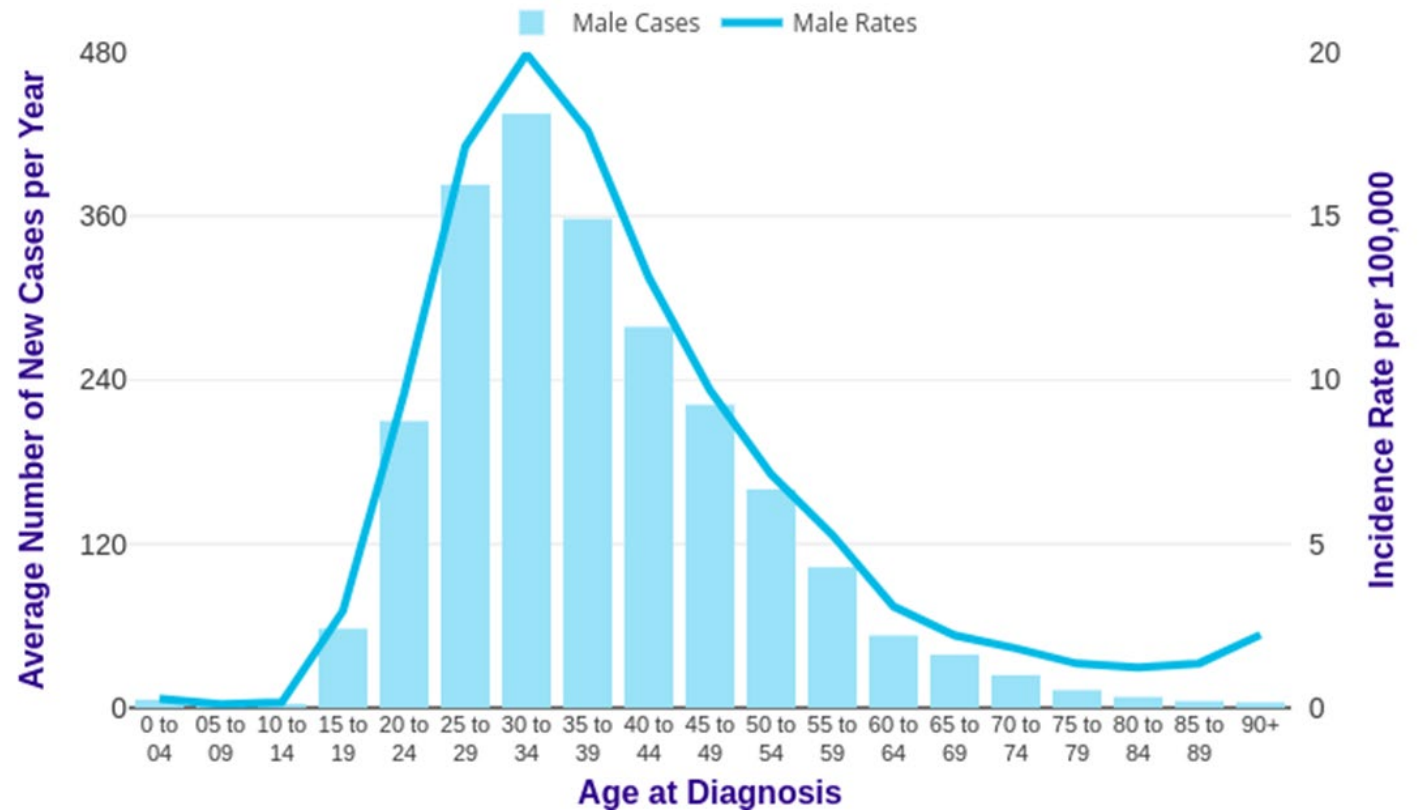
Testicular cancer.

- 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.

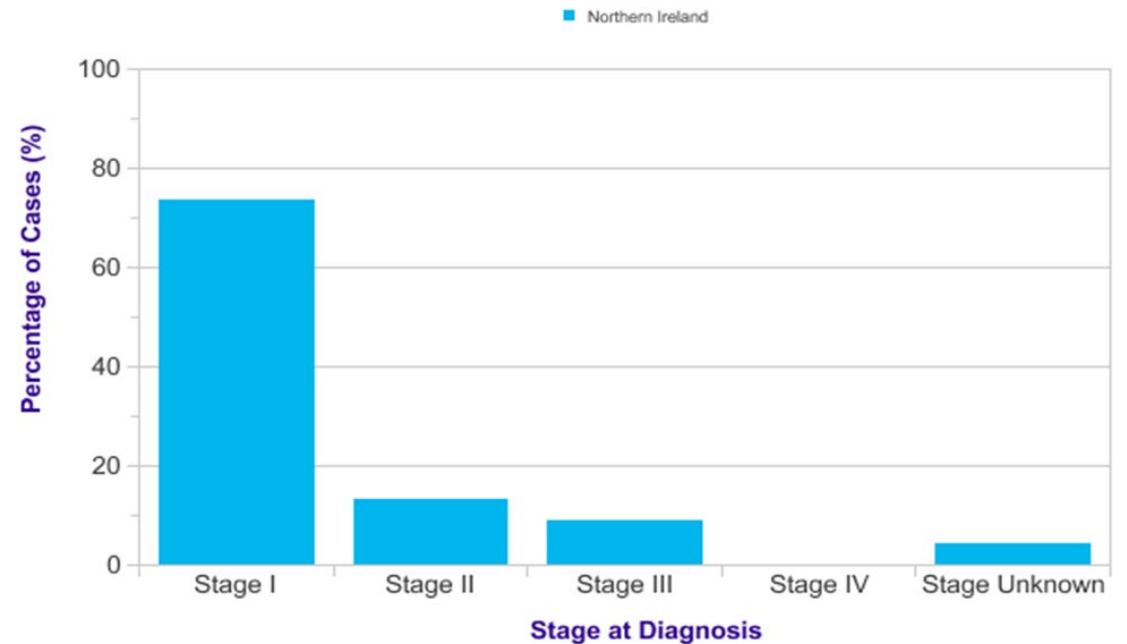
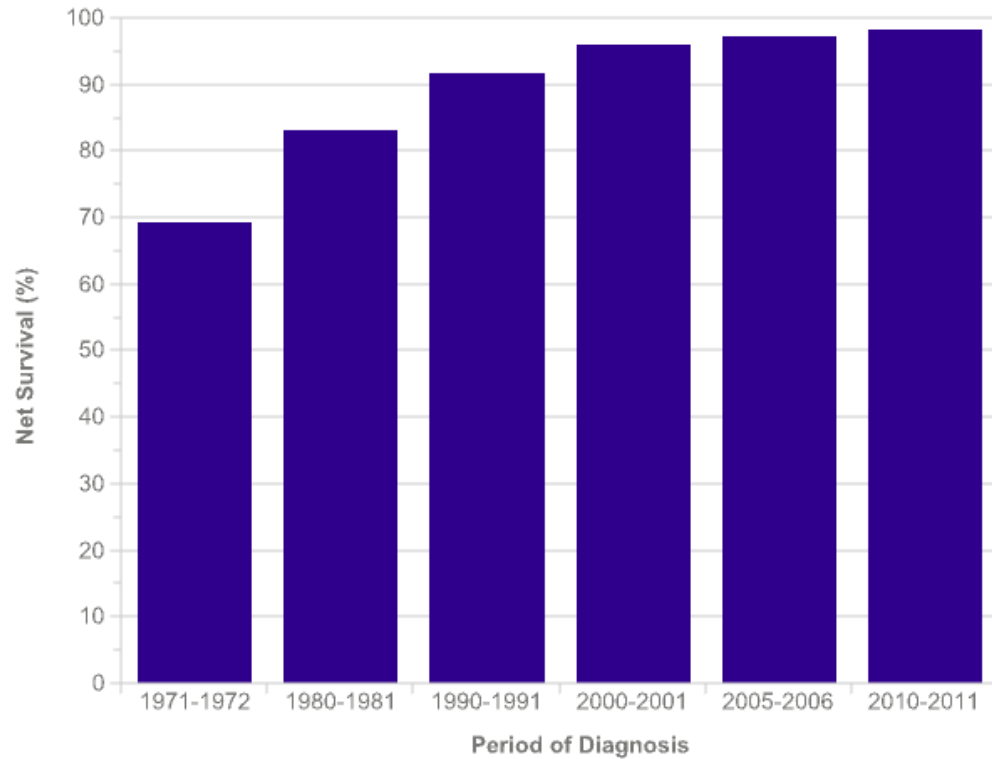
- ~1% of cancers in men.
- Peak incidence in 30s.
- Very rare after 60s.
- More common in white men, and higher SES.
- <100 deaths/year UK.



30

60

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.
- Bobby Moore, treated for testicular cancer 1964, captained England to their (last) football World Cup victory in 1966. Children 1965 and 1968. Died 1993 of an unrelated cancer.



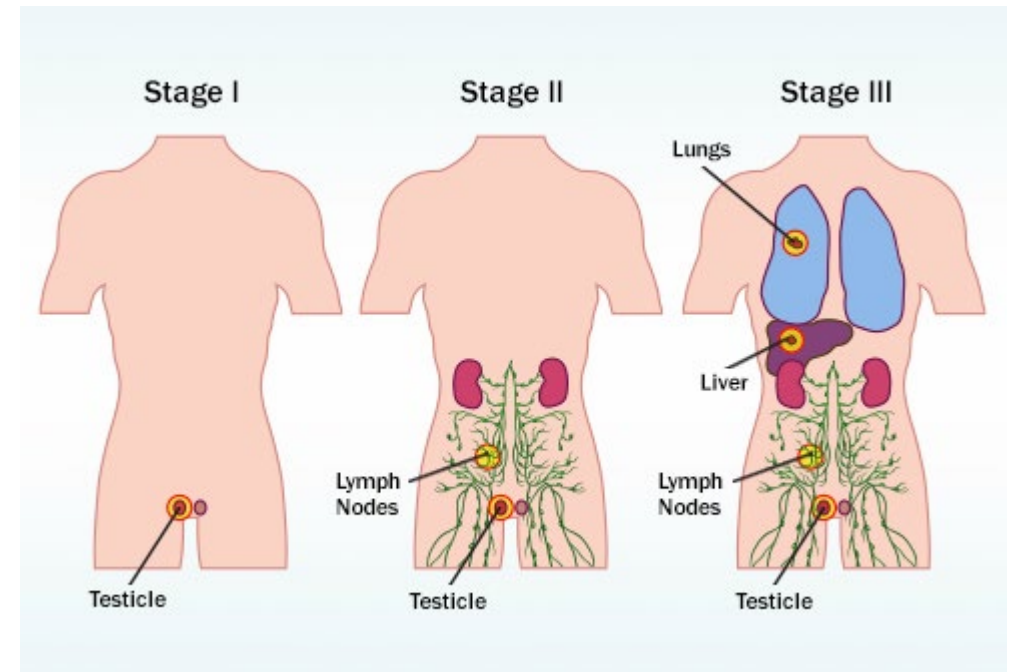
Stage and type define further treatment.

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.

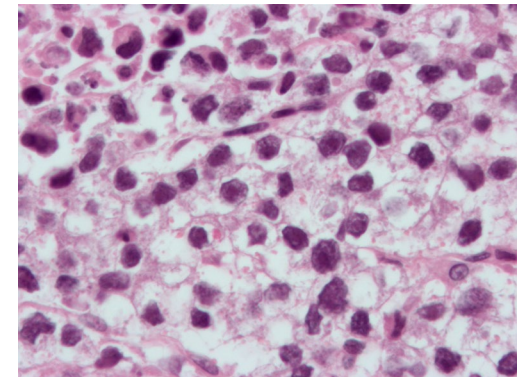
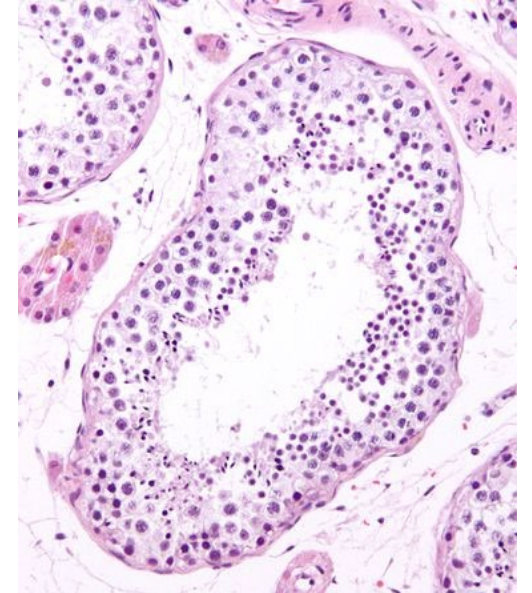
- Seminoma and nonseminoma.
- Seminoma types of testicular cancer more sensitive to radiotherapy, chemotherapy and less prone to distant metastases.



WebMD

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.

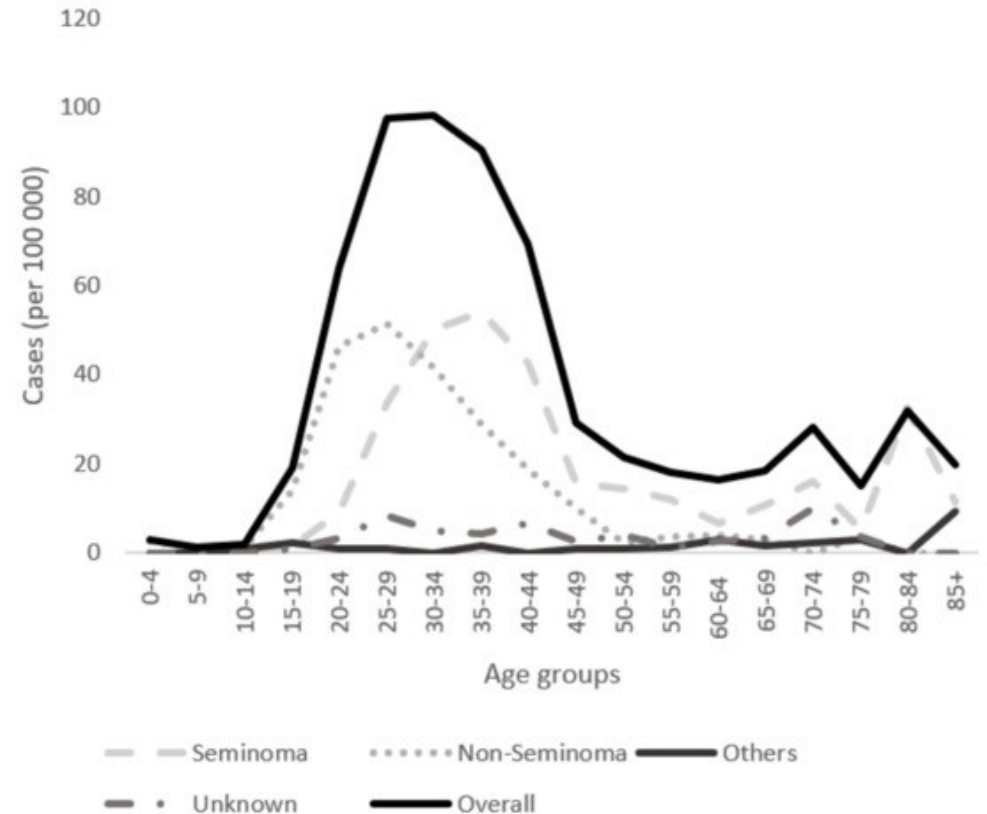


Nephron/Wiki

Non-seminoma

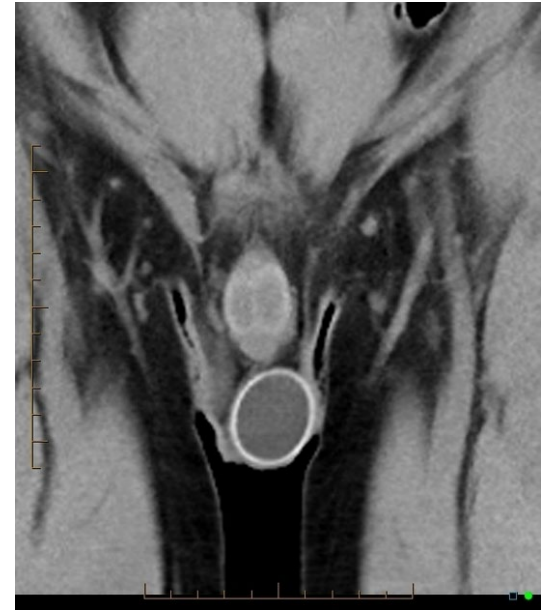
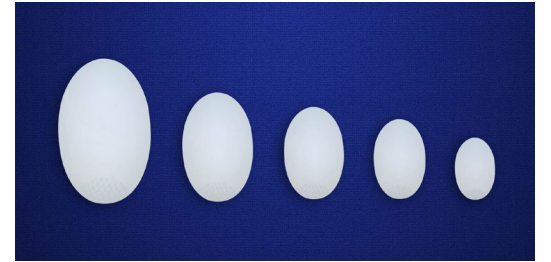
Mixed germ cell tumours. Some combination of:

- teratoma
 - embryonal carcinoma
 - choriocarcinoma
 - yolk sac tumours
-
- Treatment is slightly more complicated.



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.

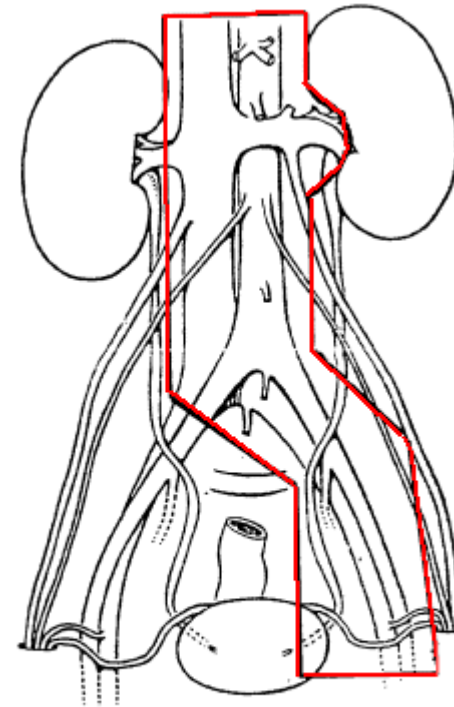


diagram of field
for left-sided tumor

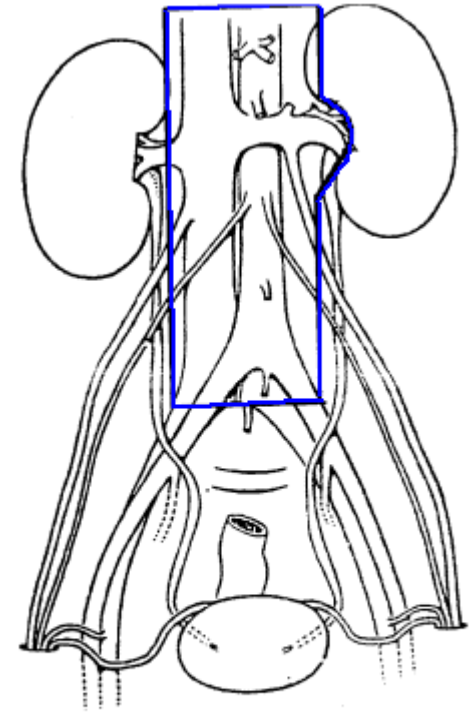


diagram para-aortic
field for low risk

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.

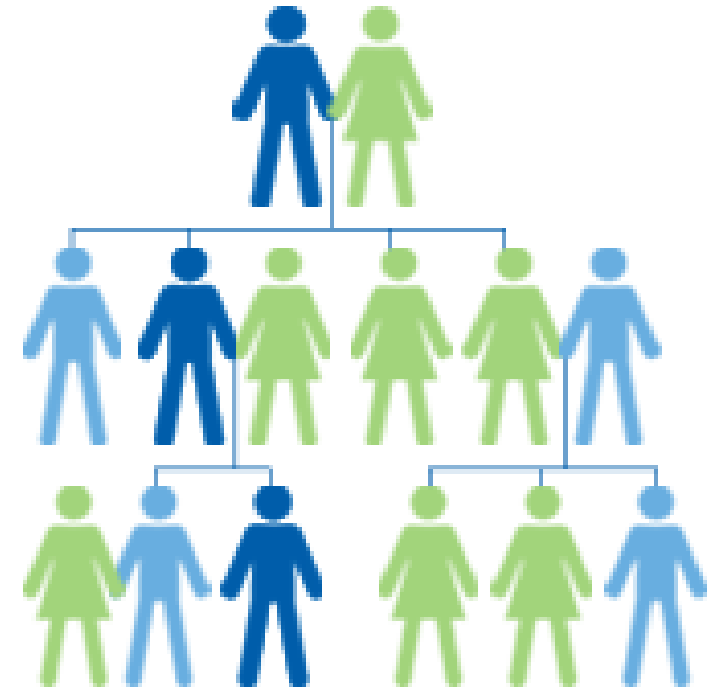
- The study illustrated at right was reported earlier this month. One cycle rather than two probably as good for cancer, fewer side effects.
- As outcomes are already good for the great majority, much of the emphasis of research is on reducing side effects further.



The image is a screenshot of a BBC News article. At the top, the BBC logo is on the left, and 'Sign in' with a bell icon is on the right. Below the logo is a red navigation bar with the word 'NEWS' in white. Underneath this bar is a secondary navigation bar with links for Home, UK, World, Business, Politics, Tech, Science, Health, and Family & Education. The article title is 'Testicular cancer: 'Kinder' chemotherapy is 'just as effective'' in bold black text. Below the title, it says 'By James Gallagher' and 'Health and science correspondent'. The date '3 January 2020' is on the left, and social media sharing icons for Facebook, Messenger, Twitter, Email, and a general 'Share' icon are on the right. At the bottom of the screenshot is a photograph of a person lying in a hospital bed, wearing a blue gown, with a medical drip in their arm.

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.



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 chimnies, 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.



Aurelio Zingoni 1881



Horace Benge
Dobell

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%).



Rembrandt self-portraits.