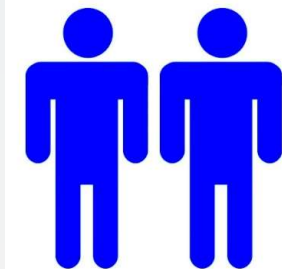




A look at the treatment pathway for Prostate Cancer

Steve Allen
3rd November 2023



Reading
Prostate
Cancer
Support
Group

PCa treatment pathway

PCa treatment pathway

Depends on the stage of disease:



+ / - lymph nodes
+ / - distant spread

Localised



Tumour well confined within prostate capsule

One-sided tumour / both sides

Stage T1 / T2 N0 M0

Brachytherapy

HIFU

Cryotherapy

Cyberknife

(Stereotactic radiotherapy)

Nanoknife

(Irreversible electroporation)

‘Treatment with curative intent’

Active Surveillance

Radical surgery – nerve sparing

Radical radiotherapy

Brachytherapy

Localised therapy

Localised Spread



Just breaching capsule

No lymph node or distant spread

Radical surgery

Robotic ? Extended / non nerve sparing

Robotic (Retzius sparing)

Robotic (Neurosafe)

Radiotherapy / Brachytherapy

Hormone therapy

? Chemotherapy

Extended Localised Spread



Probable extension to seminal vesicles
Possible pelvic lymph nodes



Hormone therapy

Monotherapy

Initial therapy before other radical Rx
(surgery or radiotherapy)

Chemotherapy (usually 2nd line Rx)

Radiotherapy – wide field of Rx

(Radical Surgery)

? Add ARTA



ARTA – Androgen receptor targeting agent

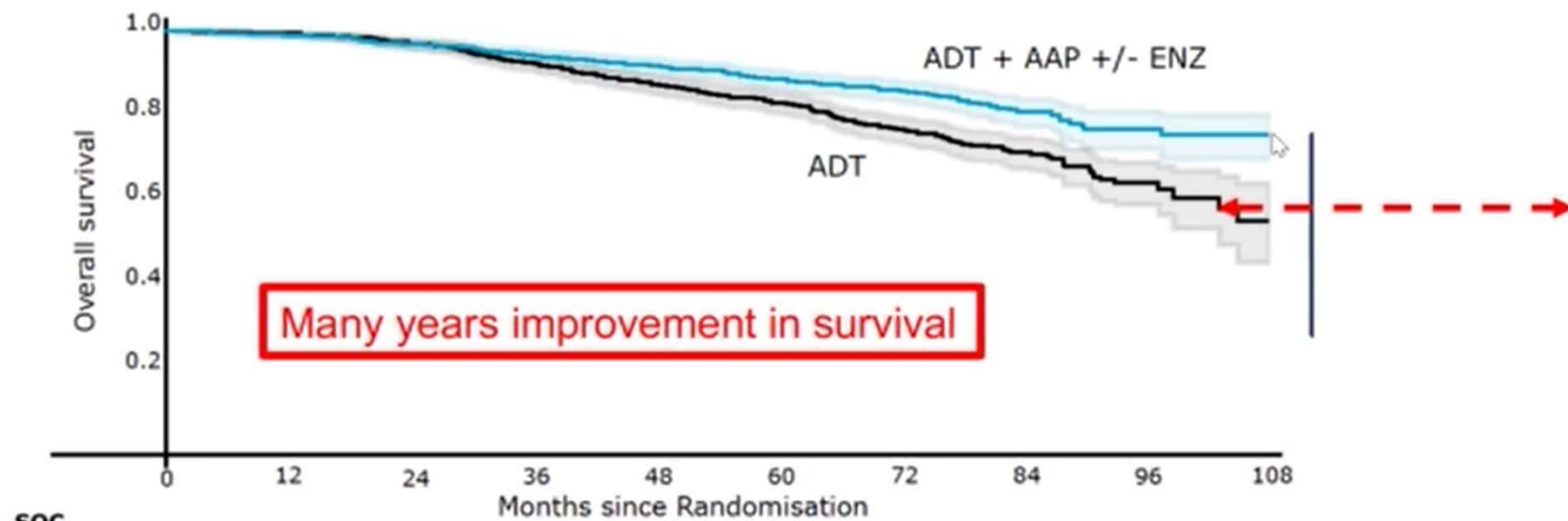


Adding Abiraterone to ADT + RadioTx significantly increases time to onset of metastasis and overall survival in men with high risk but non-metastatic disease

- i.e. potentially 'curable' if treated early

? Add Abiraterone

Abiraterone for locally advanced disease



soc

? Add ARTA



Probably any ARTA will do but
Abiraterone now v cheap!



But not NICE approved

Advanced / Distant spread



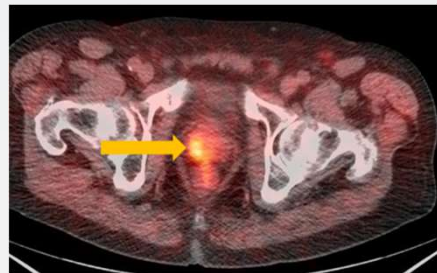
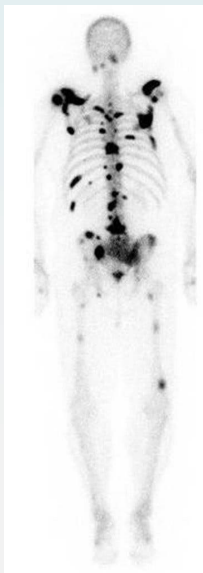
Significant spread for prostate to pelvis
and including distant metastases

Hormone therapy

+ / - Chemotherapy

+ / - 'Novel Hormonal Agents' (NHAs)

+ / - Radiotherapy



What drugs are used?

LHRH analogues:

Goserelin **Zoladex**[®]

Leuprorelin acetate **Prostap**[®] or Lutrate[®]

Triptorelin Decapeptyl[®] or Gonapeptyl Depot[®]

Buserelin acetate Suprefact[®]

*All produce an initial rise in testosterone / PSA
and the negative effects of this on PCa prevented by
co-prescribing of Bicalutamde*

What drugs are used?

LHRH antagonists:

Degarelix Firmagon[®]

This does not produce an initial surge of testosterone.
It is often used where there are bone metastases near the spine at danger of producing spinal cord compression and immediate treatment is vital

So, what's new?

LHRH antagonists

Relugolix Orgavyx[®]

Given as oral dose daily

So, what's new?

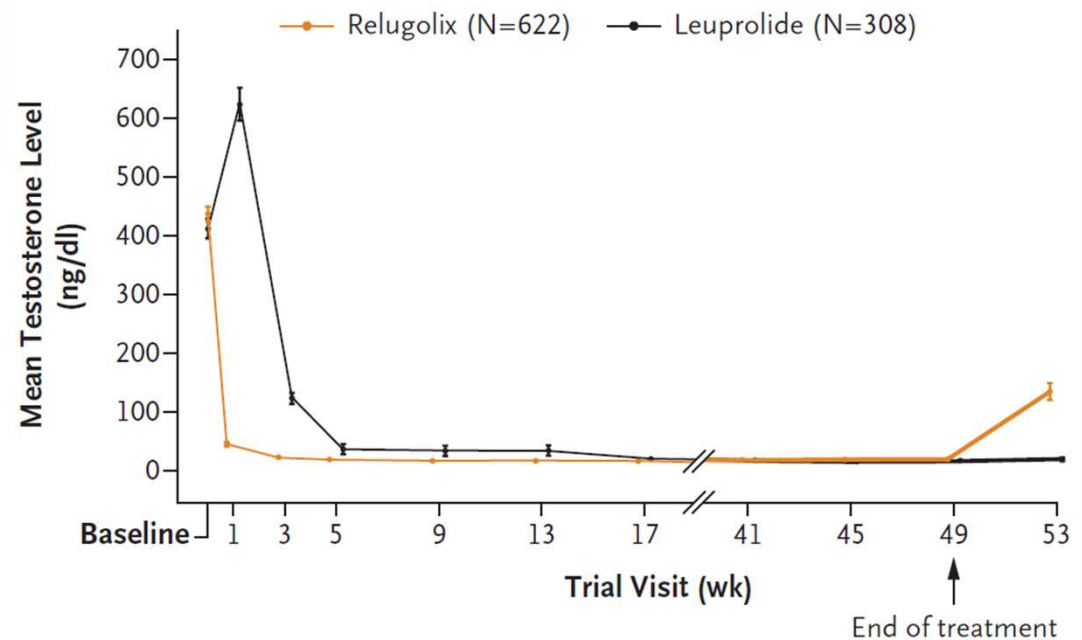
Relugolix Orgavix®

Compared to injectable LHRH agonist
(HERO trial)

Equal or superior reduction in
testosterone

Faster onset of testosterone
reduction

B Mean Testosterone Level among All Patients



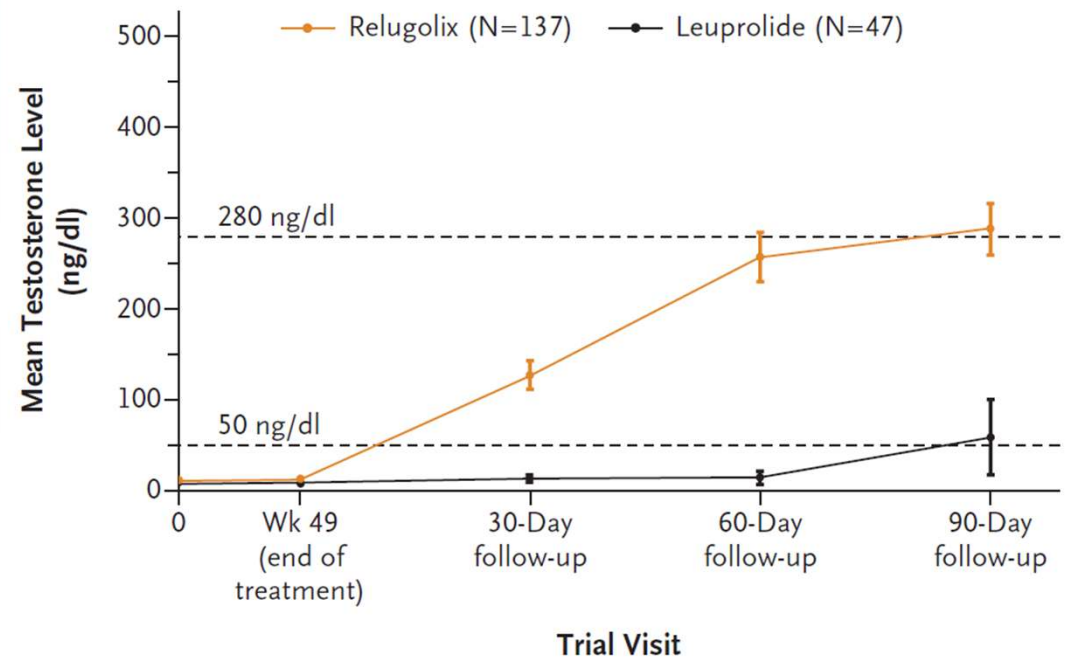
So, what's new?

Relugolix Orgavix®

Compared to injectable LHRH agonist
(HERO trial)

Faster recovery of
testosterone after stopping
treatment

C Mean Testosterone Level in Subgroup Followed for Testosterone Recovery

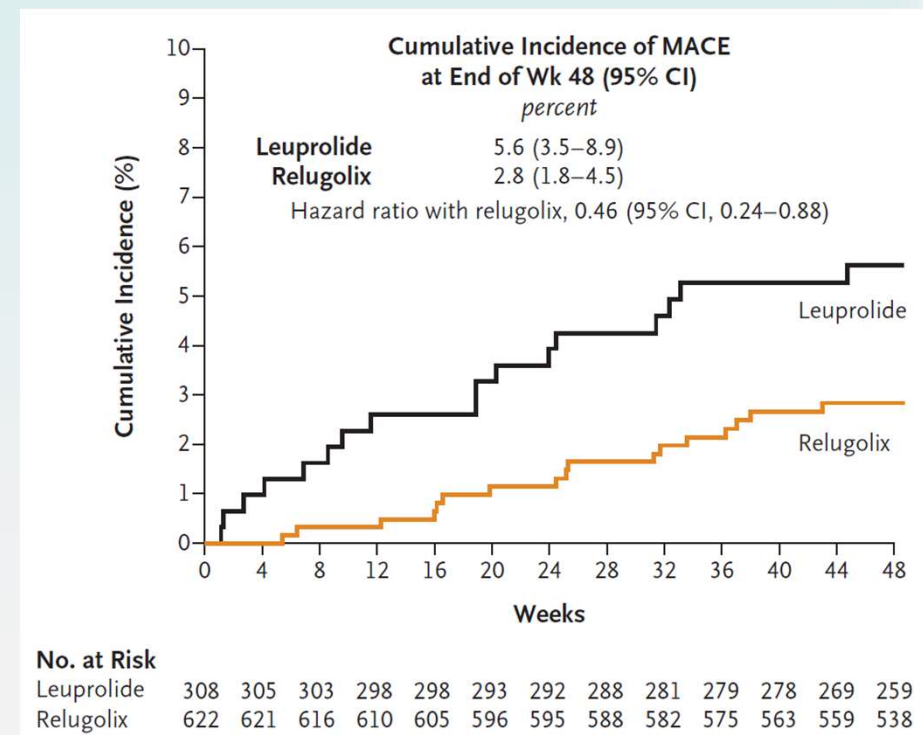


So, what's new?

Relugolix Orgavix®

Compared to injectable LHRH agonist
(HERO trial)

Overall incidence of S/E
equal or lower



What is 'hormone resistance?'

What is 'hormone resistance?'

Hormone resistant

Hormone insensitive

Castrate resistant

When growth of PCa no longer controlled by conventional hormone treatment

Will occur in almost all men on ADT

Very variable time scale

- Do some men have a different cancer sub-type?

What is 'hormone resistance?'

Testosterone rises PSA begins to rise

Cancer grows and metastasis may occur

At least 2/3 mets need to be identified on 'conventional'
scanning

CT or MRI

Why does hormone resistance occur?

It's all about how testosterone is made and how testosterone acts on the cancer cells

Where is testosterone made?

Testicles –mainly

Adrenal glands (to a small extent)

With continued hormone therapy,
some cancer cells mutate and are
***able to produce their own
testosterone***

A major factor in 'hormone resistance'

*What can be done
about this?*

What are 'NHAs'?
*How can they help with hormone
resistance?*

What are 'NHAs?'

Novel **H**ormonal **A**gents

Reduce growth of prostate cancer cells by:

- Decreasing production of testosterone

OR

- Blocking the action of testosterone on cancer cells

Not 'hormones' as such but have the same clinical effect

What are 'NHAs?'

Novel **H**ormonal **A**gents

Common drugs:

Enzalutamide

Abiraterone

(Bicalutamide)

What are 'NHAs?'

Novel **H**ormonal **A**gents

Common drugs:

Enzalutamide

Abiraterone

(Bicalutamide)

Newer Drugs:

Darolutamide

Apalutamide

How can NHAs help?

Abiraterone

Reduces testosterone levels

Acts on enzyme system producing testosterone in ALL areas (not just testicles)

Androgen bio-synthesis inhibitors

Used *in addition* to normal ADT

Cancer growth reduced

How can NHAs help?

Abiraterone

Side effects can occur

Regular blood testing needed

Need to be taken on empty stomach

Prednisone additionally required

'-utamides'

1st generation drugs:

Bicalutamide

2nd generation drugs:

Enzalutamide

Apalutamide

Darolutamide

'-utamides'

How do they work?

Testosterone gets into PCa cell via the *androgen receptor*

'-utamides' sit on this receptor site and prevent testosterone from entering cell

Testosterone levels not greatly reduced but PSA falls because cancer cells no longer grow

'-utamides'

1st generation drugs:

Bicalutamide Casodex[®]

(Flutamide)

Used primarily at start of Zoladex treatment to block initial surge of testosterone

May also be used later

Comparatively cheap

BUT is only a *partial* blocker

'-utamides'

2nd generation drugs:

Enzalutamide *Xtandi*[®]

Apalutamide *Erleada*[®]

Fully block the androgen receptor

Used in *advanced* disease

- Must have 2 or more confirmed mets on conventional MRI / CT

NOT Cheap!!

'-utamides'

2nd generation drugs:

Darolutamide Nubeqa[®]

Fully block the androgen receptor

Used in *advancing* disease

- Presence of metastases NOT required
 - 'non-metastatic hormone resistant PCa'
- Crosses into brain less than others. Side effect profile reduced

Treatment options for Hormone resistance

Chemotherapy:

Often offered first

Cheap

Effective

Needs in hospital treatment (6 -10 cycles)

Significant side effects for many patients

‘Chemotherapy –unsuitable’ patients

- Physiological / medical
- Age & frailty
- Patient choice

Treatment options for Hormone resistance

Abiraterone or Enzalutamide:

Can be as effective as chemotherapy

Continuous use until they cease to work

- NOT just a limited course of treatment

Comparatively expensive

- NHS discounted price confidential

Not without side effects

Regular blood tests needed

Evidence of metastases needed for NHS use

Treatment options for Hormone resistance

Radiotherapy:

Areas needing treatment need clear identification

- Salvage Radiotherapy' after radical surgery
 - pelvic Treatment to 'prostate bed' +/- pelvic lymph nodes
- May be useful where very localised mets present
 - SABR or Cyberknife®

Cannot be used in areas already treated with RadioTx

Systemic Rx may be more appropriate for some patients to ensure all mets are being treated.

Specific cases

ndhsmPCa - newly diagnosed, hormone sensitive, metastatic **PCa**

Specific cases

ndhsmPCa - newly diagnosed, hormone sensitive, metastatic **PCa**

Around 15 – 17% new patients seen

- A significant number are asymptomatic
- Many are comparatively young

Distant as well as local spread

Previously:

ADT immediately – e.g. Zoladex

No further Rx until ADT wears off

Specific cases

ndhsmPCa - newly diagnosed, hormone sensitive, metastatic **PCa**

STAMPEDE trial showed early use of chemotherapy in combination with ADT gave superior outcomes and longer lifespan

ADT + Chemotherapy now best standard of care

But *under-used* currently

Specific cases

ndhsmPCa - newly diagnosed, hormone sensitive, metastatic **PCa**

Abiraterone or **Enzalutamide** give similar results to chemotherapy + ADT

COVID has influenced use away from chemotherapy to NHAs.

NICE & SMC have now approved use in place of chemotherapy (Drug used depends on where you live!)

Specific cases

nmhrPCa – non-metastatic, hormone resistant **PCa**

Specific cases

nmhrPCa – non-metastatic, hormone resistant **PCa**

Sometimes known as ‘biochemical recurrence’ of cancer

Patient has already had treatments (surgery +/- radiotherapy) which no longer controlled cancer

Added ADT / hormone therapy given with effect but this now wearing off

Specific cases

nmhrPCa – non-metastatic, hormone resistant **PCa**

By definition, no mets seen on conventional MRI /
Ct scans

NHAs (Abi or Enza) not approved or funded for use
by NHS

Specific cases

nmhrPCa – non-metastatic, hormone resistant **PCa**

Bicalutamide – often used. ‘Off-licence’ but cheap

Chemotherapy – cheap, can be effective but ‘off licence’

Many patients not suitable for chemotherapy clinically

Steroids – Dexamethasone used by some. Clinically may help some pts. ‘Off licence’ No research evidence

Specific cases

nmhrPCa – non-metastatic hormone resistant PCa

Bicalutamide – cheap but

Chemotherapy – effective but 'off licence' not suitable for chemotherapy clinically

Steroids – Dexamethasone used by some. Clinically may help some pts. 'Off licence' No research evidence

Many patients forced to wait until mets are seen - may be too late

Specific cases

nmhrPCa – non-metastatic, hormone resistant **PCa**

Darolutamide and Apalutamide now approved by both NICE and SMC for use in this clinical scenario

Very expensive

As effective as chemotherapy

Fewer side effects

PSA > 2ng.ml PSA doubling rate in less than 10 months
--

Many clinicians still using Bicalutamide first

- ? Purely on cost grounds

Specific cases

nmhrPCa – non-metastatic, hormone resistant **PCa**

More sensitive scanning:

PET

PSMA-PET-CT

Both can detect mets at very low levels of PSA and when mets very small (5mm+)

But NHS will not approve use of Abi or Enza on non-conventional scans

Specific cases

More sensitive scanning:

PET-CT

PSMA-PET-CT

Significant advantages if small remote mets can be found – systemic Rx can be avoided Localised Rx with focussed RadioTx can be used.

Lower ‘tumour load’ gives better outcomes from treatment

Progressive disease

I've had chemotherapy, RadioTx, NHAs.....

What else is there?

Progressive disease

I've had chemotherapy, RadioTx, NHAs.....

What else is there?

Further chemotherapy:

2 courses of Docetaxel are allowed

(licenced for 10 session in total)

Or Cabazitaxel if Docetaxel already used

Clinical fitness of patient may not be sufficient to tolerate further chemotherapy

Are the remaining cancer cells chemotherapy-sensitive – why were they not destroyed by previous chemotherapy?

Progressive disease

I've had chemotherapy, RadioTx, NHAs.....

What else is there?

Further NHAs?

NO - NHS will only fund **1** course of drugs

Despite drugs having different mode of action

No research evidence to support switching drugs

Some emerging anecdotal evidence only

Progressive disease

I've had chemotherapy, RadioTx, NHAs.....
What else is there?

Radium 223

Specifically taken up by bone mets only

- Similar to Technetium used for bone scans but highly radioactive

Progressive disease

I've had chemotherapy, RadioTx, NHAs.....
What else is there?

Radium 223

Can be effective

- May need up to 6 courses at 1 month intervals
- Potential for side effects, particularly for bone marrow
- £25,000 for full course of 6 doses of drug
- Approved by NHS / NICE
- Care needed with radioactive waste products

Progressive disease

I've had chemotherapy, RadioTx, NHAs.....
What else is there?

Lutetium 177

Taken up by both bone and soft tissue

Approved by MHRA but has failed appraisals by
NICE and SMC

Progressive disease

I've had chemotherapy, RadioTx, NHAs.....
What else is there?

Lutetium 177

- Course of 4 infusions
- Around £70,000 for a full course
 - Much cheaper in Europe
- Used in other rare neuroendocrine tumours
- Radio-active waste

Progressive disease

I've had chemotherapy, RadioTx, NHAs.....
What else is there?

Olaparib

Specifically for use in advanced PCa in patients with BRCA 1 / 2 genetic abnormality

- Now approved by NICE & SMC
- Needs appropriate genetic testing
- Approval in England requires previous taxane (chemotherapy) and NAH treatment – but not in Scotland

Progressive disease

I've had chemotherapy, RadioTx, NHAs.....
What else is there?

Talazoparib

Another PARP inhibitor

Ongoing trials for use of

ADT+Enzalutamide+Talazoparib

Hormone resistant metastatic PCa

The future.....

Formalised genetic screening

Targeted gene therapies

- Other genetic abnormalities assoc with PCa
- P-TEN Involved in control of all cell growth
 - Prevents uncontrolled cell division
 - Up to 50% men with advanced PCa are missing this gene
 - ? Increases resistance to RadioTx
 - May help predict aggressiveness in early PCa
- **IPATASERTIB**

The future.....

‘Personalised’ medicine

Immunotherapy

CAR-T (Chimeric antigen receptor – T Cell)

Re-programmes patients own immune system

- T-cells altered genetically
- Recognise specific cancer cells as being ‘foreign’
- Re-introduced into patient
- Specific cells now destroyed by patient’s own immune system
- Not yet available for PCa

The future.....

Developments in imaging techniques

- Ultrasound / MRI fusion targeted biopsies
- PSMA scanning
- SPECT scanning
 - Single Photon Emission Computerised Technology
- Photon counting and multi-spectral X-ray analysis

What is the cheapest treatment for advanced prostate cancer?

What is the cheapest treatment for advanced prostate cancer?

Don't let it get to an advanced stage

Diagnose the cancer early whilst it is still localised

? Increased use of localised therapies

The future.....

Further improvements in localised treatments

- Less invasive
- Reduced side effects
- Day-case treatment

Brachytherapy

HIFU

Cryotherapy

Cyberknife

(Stereotactic radiotherapy)

Nanoknife

(Irreversible
electroporation)

Local Therapy

What types are there?

All focal therapies aim to destroy cancer cells locally without damaging surrounding tissues

Localised Radiotherapy (Brachytherapy)

Heat

Cold

Electricity

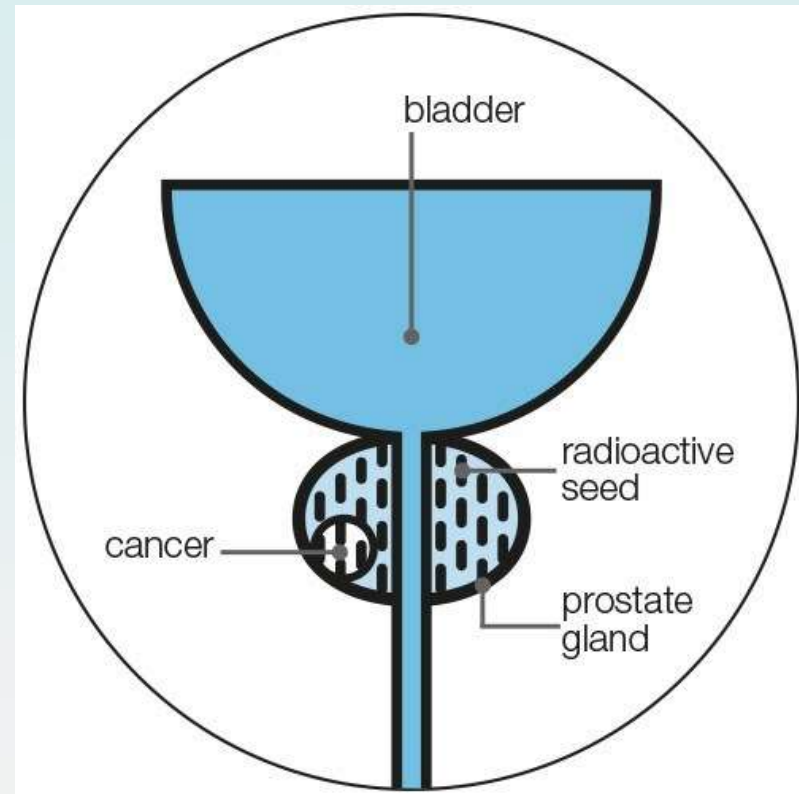
Toxic chemicals

Local Therapy

Brachytherapy

Low-dose

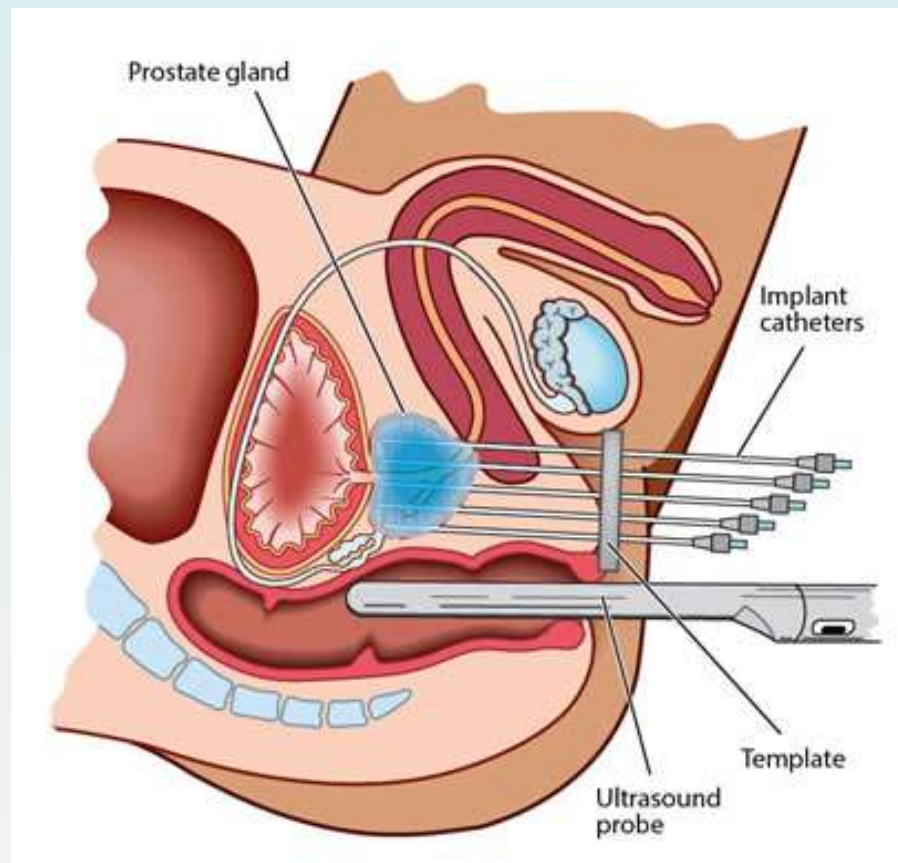
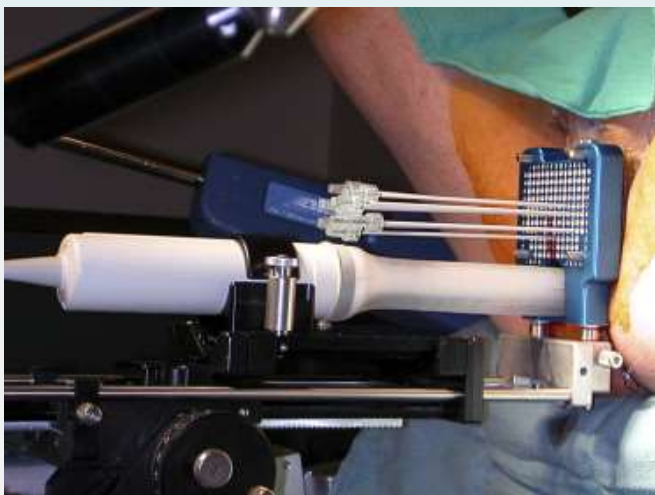
Permanently implanted
seeds



Local Therapy

Brachytherapy

High dose

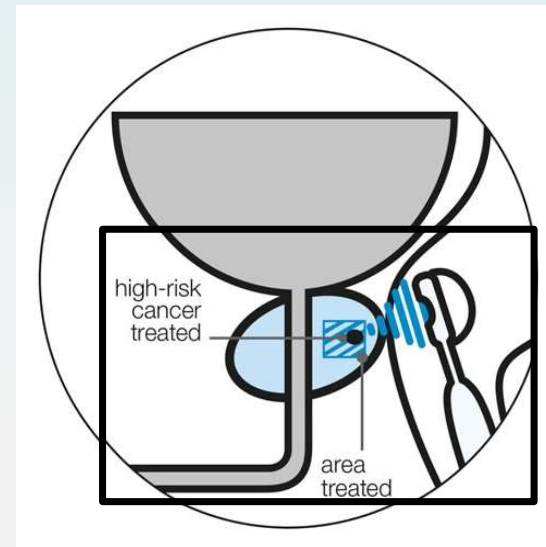


Local Therapy

Heat:

HIFU – High Intensity Focussed Ultrasound

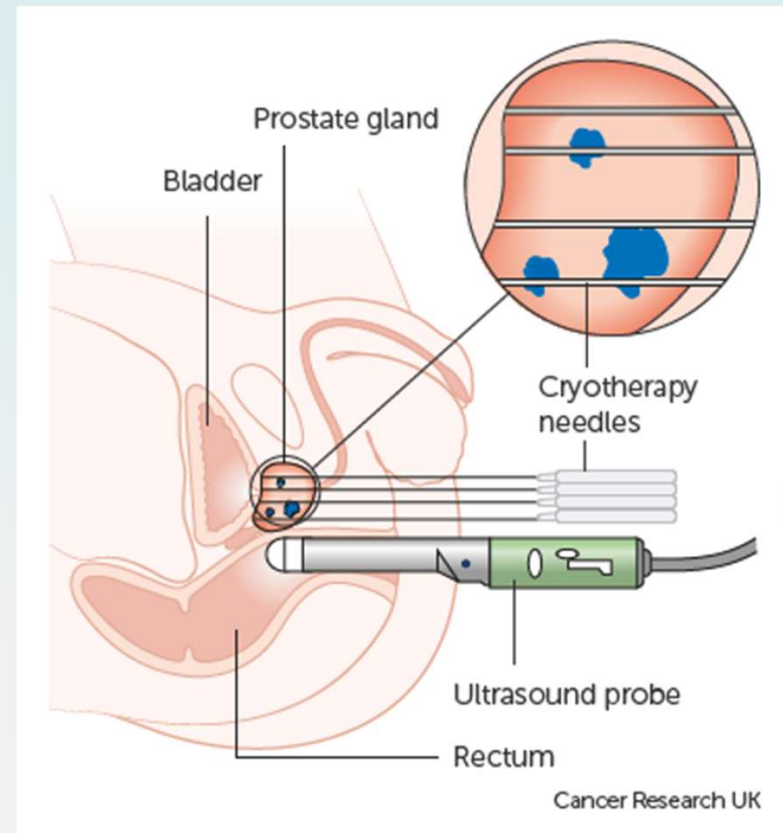
- Shakes up the molecules in the cell so much they get very hot and die!



Local Therapy

Cold:

Cryotherapy – use of multiple cryo needles to target local areas of PCa in prostate



Local Therapy

Making external beam radiotherapy less
'harmful'

More focussed beam shaping
Stereotactic beam radiation

'Cyberknife'®



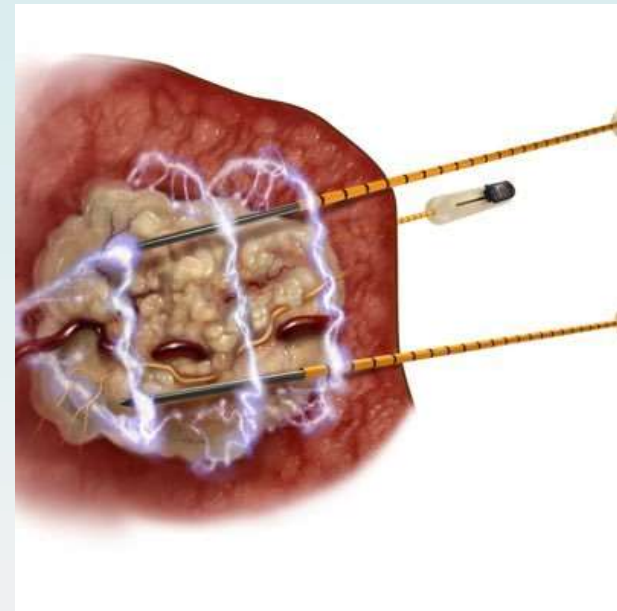
Local Therapy

Electricity:

Irreversible
electroporation

Nanoknife®

Use of electric
currents to damage
PCa cell membranes
(and thus kill them)



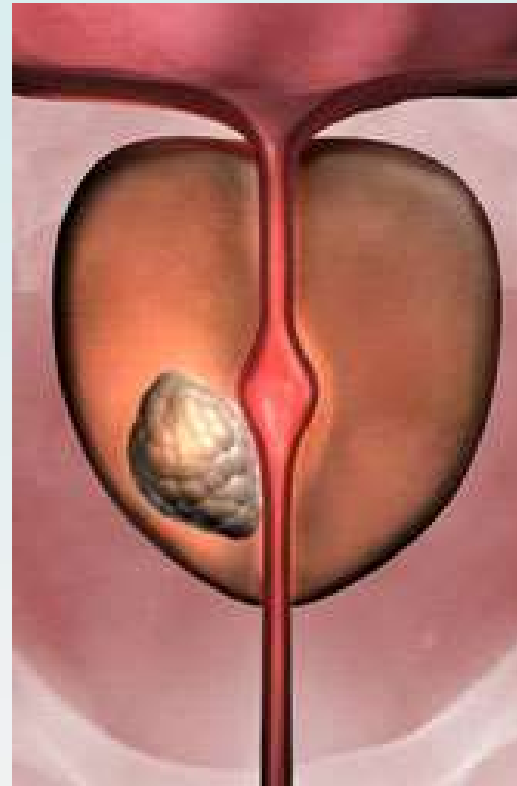
Limited approval by
NICE – research etc

Local Therapy

Local Toxic Chemicals

Vascular-targeted
photo-dynamic therapy

Injection of an inert
chemical that becomes
toxic when specific
wavelength of light used



Local Therapy

Local Toxic Chemicals

Padeliporfin

- Releases high levels of toxic oxygen radicals when activated
- Rapid death of cancer cells
- Only for one-sided low risk PCa
- Doubles time taken to progression



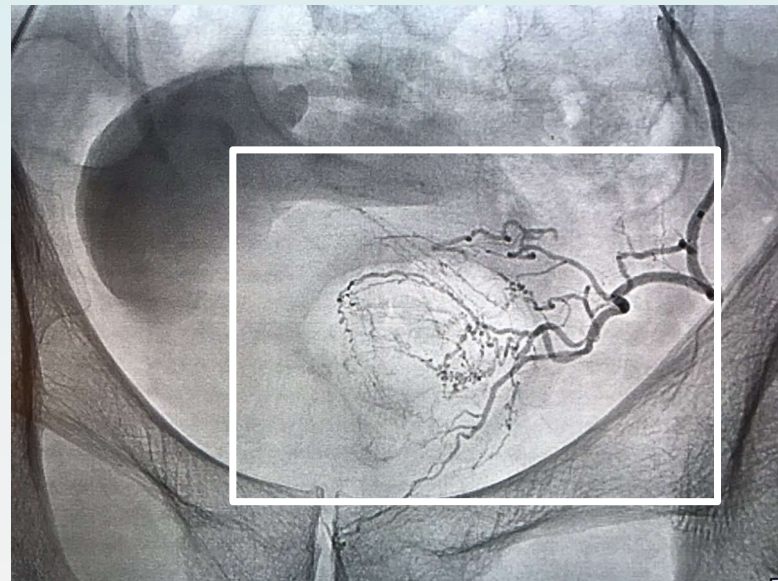
*Not currently approved by
FDA or NICE for PCa*

Local Therapy

Local Toxic Chemicals

Local infusion of
chemotherapy drugs

Accurate localisation of
blood supply





Is there anything
new to reduce the
progression of
cancer that's
already?

Can we reduce the
incidence of
advanced disease



Double / twin therapy

Use 2 drugs together
ADT + chemotherapy
ADT + NHA/ARTA

Current standard of care

Triplet therapy

Use 3 drugs together



Triplet therapy

ADT

+

Chemotherapy

Enzalutamide

Abiraterone

Darolutamide

Apalutamide

Triplet therapy

ADT

+

Chemotherapy

Enzalutamide

Abiraterone

Darolutamide

Hormone sensitive metastatic PCa

Apalutamide

Other things that can help?

Exercise



5K YOUR WAY
MOVE AGAINST CANCER



Other things that can help?

Exercise

Diet



Other things that can help?

Exercise

Diet

Added food supplements?





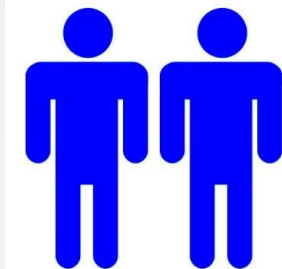
BUT WAIT..

THERE'S MORE..



A look at the treatment pathway for Prostate Cancer

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Reading
Prostate
Cancer
Support
Group