

WHAT IS PROSTATE CANCER ? (CaP)

- ▶ Is a hormone dependent tumour of the prostate gland responding primarily to testosterone (androgens)
- ▶ Most common cancer in men
- ▶ 2nd leading cause of cancer death after lung cancer
- ▶ Incidence seen more in blacks than whites
- ▶ Usually occurs in males > 50 yrs (median age 70 yrs)
- ▶ Highest incidence seen in Scandinavia , Switzerland & US

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Risk factors for prostate cancer

- ▶ Ageing
- ▶ Race
- ▶ Family history
- ▶ Diet
- ▶ Hormones
- ▶ Sexual behaviour
- ▶ Environmental factors
- ▶ Infections

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Hypothalamic – Pituitary – Testicular axis

- ▶ Most prostate cancers are hormone dependent responding primarily to testosterone
- ▶ The prostate is controlled primarily by the part of the endocrine system that involves hypothalamus, pituitary & testes i.e

Hypothalamic – Pituitary – Testicular
axis

Pituitary – Test...

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Prostate cancer *what do we know ?*

- ▶ Malignant growth, commonly in the peripheral zone (70%) mainly **adenocarcinoma**
- ▶ Second highest cause of male cancer deaths world-wide after lung cancer
- ▶ Men are being diagnosed at an earlier age — **population screening by PSA assay**
- ▶ The disease can be associated with a number of distressing symptoms:
 - urinary problems e.g. obstruction
 - lower back pain,
 - bone pain
 - spinal cord compression

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Patterns of spread

- ▶ Local invasion through prostatic capsule
 - ▶ Surrounding tissues (ureters, bladder neck, seminal vesicles)
- ▶ Lymphatic / circulatory systems
 - ▶ Metastases
 - ▶ Lymph nodes – pelvis, groin, lower back)
 - ▶ Bone – pelvis & vertebrae
 - ▶ Visceral – lung & liver (rare)
- ▶ Clinical course unpredictable

Prostate cancer may therefore be defined as:

- ▶ High-grade prostatic intraepithelial neoplasia (HPIN)

likely to be a precursor of prostate cancer.

- ▶ Localised (organ-confined) non-metastatic.

This accounts for 45% (Europe) to 58% (USA) of prostate cancer patients at diagnosis.

- ▶ Locally advanced (no distant metastases).

This accounts for 10-30% of prostate cancer patients at diagnosis. The tumour is no longer organ-confined and has spread to local lymphatic glands.

- ▶ Metastatic disease (advanced prostate cancer).

At this stage the tumour has spread to distant sites (mainly bone).

- ▶ Hormone insensitive (refractory to hormonal treatment).

The tumour is no longer responsive to androgen withdrawal (ADT) despite low levels of serum T (20-30 ng/L). New terminology is castrate resistant prostate cancer (ca., CRPC).

Symptoms of prostate cancer

- ▶ Mild...moderate...severe...
- ▶ urinary symptoms (hesitancy, frequency, urgency, haematuria, incontinence, UTI)
- ▶ bone pain
- ▶ Impotence/ED
- ▶ Swelling- legs (lymph node accumulation)
- ▶ Pelvic discomfort
- ▶ lethargy, weight loss





SYMPTOMS OF PROSTATE CANCER

- ▶ Early disease
- ▶ Incontinence
- ▶ Painful or slow urination
- ▶ Urinary bleeding
- ▶ Cystitis (inflammation of bladder)

Diagnosis is based on

History (*symptomatic or asymptomatic*)
Physical Examinations
Laboratory
Imaging

see next slide

Click to add notes

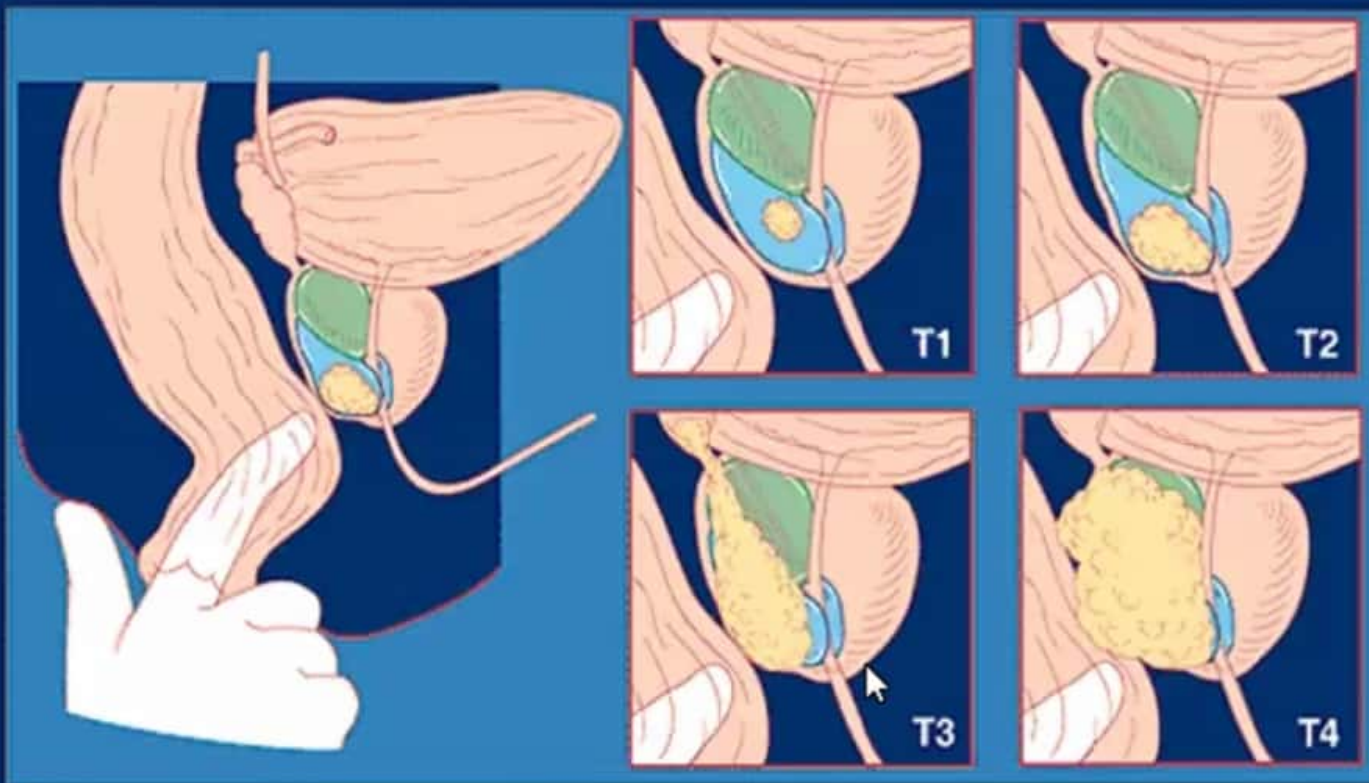
Digital rectal examination (DRE)



- ▶ Physical access of prostate via rectum
- ▶ Dr inserts a gloved, lubricated finger into rectum to feel size & shape of prostate
- ▶ Examines for lumps or hard, irregular areas of the prostate
- ▶ Quick, easy, convenient & safe
- ▶ Requires additional means as diagnosis is subjective
- ▶ PSA + biopsy as confirming tests



Digital rectal examination



to add notes

Notes

Comments



79%



Differential Diagnoses

- ▶ Acute Bacterial Prostatitis and Prostatic Abscess
- ▶ Bacterial Prostatitis
- ▶ Benign Prostatic Hyperplasia (BPH)
- ▶ Nonbacterial Prostatitis
- ▶ Tuberculosis of the Genitourinary System

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Prostate Specific Antigen (PSA)

- Protease enzyme produced almost exclusively by the prostate gland
- Its measurement provides a more reliable indicator of the presence of CaP than DRE
- Secreted in small amounts into bloodstream-role in breaking down seminal coagulants to release sperm
- Large amounts are released when prostate is enlarged, infected or in presence of PC
- PSA is measured by a simple blood test
- Useful in early detection of PC
- Also used to monitor progress of already diagnosed disease including patients on treatment

High PSA in the absence of PC:

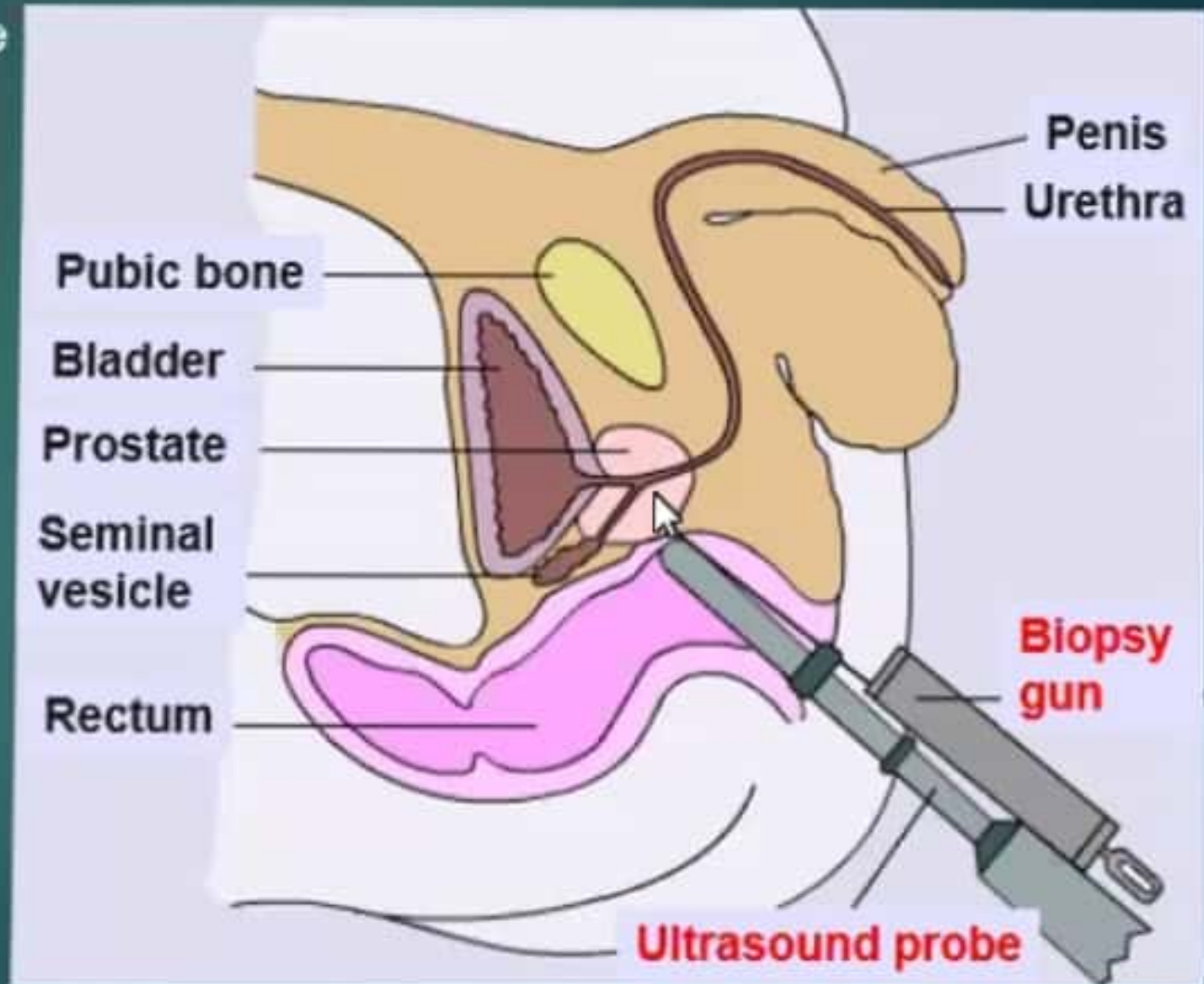
- ▶ Prostatitis
- ▶ BPH (Benign prostatic hyperplasia)
- ▶ Recent ejaculation (within 48 hrs)
- ▶ UTI

to add notes

Histological grading of prostate cancer

Samples of prostate
tissue used for
histology
TURP
TRUS

Gleason Grading



TRUS (transrectal ultrasonography-guided biopsy)

Techniques for histological grading

Tissue sampling for histological grading

TURP

(Transurethral resection of the prostate)

TRUS-guided biopsy

(Transrectal ultrasound biopsy)

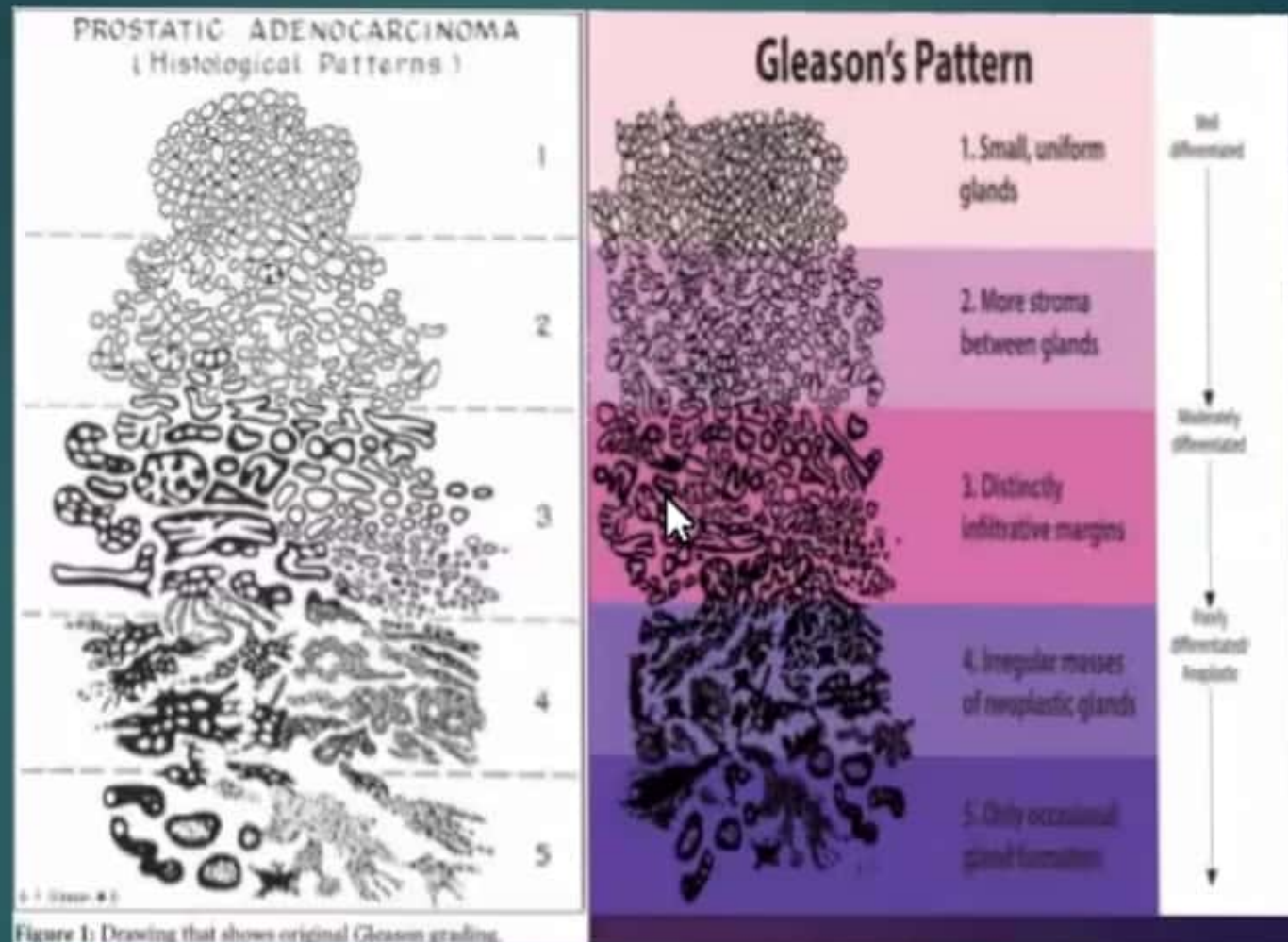
TYPES OF SPECIMEN

- ▶ Needle biopsy cores (TRUS): Indicated in patients with suspicious findings on digital rectal examinations or PSA >4.0ng
- ▶ TURP chips: indicated in BPH if symptoms are not relieved by medication.
- ▶ Radical prostatectomy: Early stage of prostate cancer

The Gleason Grading System



- ▶ If diagnostic tests confirm a malignant tumour, the Gleason grading system may be used to describe the appearance of the cancerous prostate tissue
- ▶ A Gleason score is given to grade the way the cancerous cells look compared to normal prostate cells
- ▶ Gleason scores will range from 1-10 , with higher numbers corresponding to more aggressive, faster-growing tumours



New grading system

Grade Group	Pattern definition	5 year survival rate
Grade group 1(G.S ≤6)	Only individual well-formed discrete glands	96%
Grade group 2(G.S 3 + 4 = 7)	Predominantly well-formed glands with lesser component of poorly formed/fused/ciriform glands	88%
Grade group 3(G.S 4 + 3 = 7)	Predominantly poorly formed/fused/ciriform glands with lesser component of well-formed glands	66%
Grade group 4(G.S 8)	Only poorly formed/fused/ciriform glands	48%
Grade group 5(G.S 9 - 10)	Lacks gland formation/ necrosis with or without poorly formed glands	26%

Genetic Testing

National Comprehensive Cancer Network (NCCN) guidelines ^[41] recommend that at the time of initial diagnosis of prostate cancer, clinicians should inquire about family and personal history of cancer. The NCCN recommends germline genetic testing, with or without pretest genetic counseling, for patients with prostate cancer and any of the following

- ▶ A positive family history of cancer (eg, prostate, breast)
- ▶ High-risk, very-high-risk, regional or metastatic prostate cancer, regardless of family history
- ▶ Ashkenazi Jewish ancestry
- ▶ Intraductal histology
- ▶ Germline testing, when performed, should include the following:
 - ▶ *MLH1*, *MSH2*, *MSH6*, and *PMS2* (for Lynch syndrome)
 - ▶ The homologous recombination genes *BRCA2*, *BRCA1*, *ATM*, *PALB2*, and *CHEK2*

Classification of prostate cancer

Classification



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graph TD; A[Classification] --- B[TNM Staging]; A --- C[Gleason Grading]; B --- D[Disease stage]; C --- E[Differentiation of cells]
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TNM Staging

Disease stage

Gleason Grading

Differentiation of cells

The Tumour- Nodes- Metastases (TNM) system

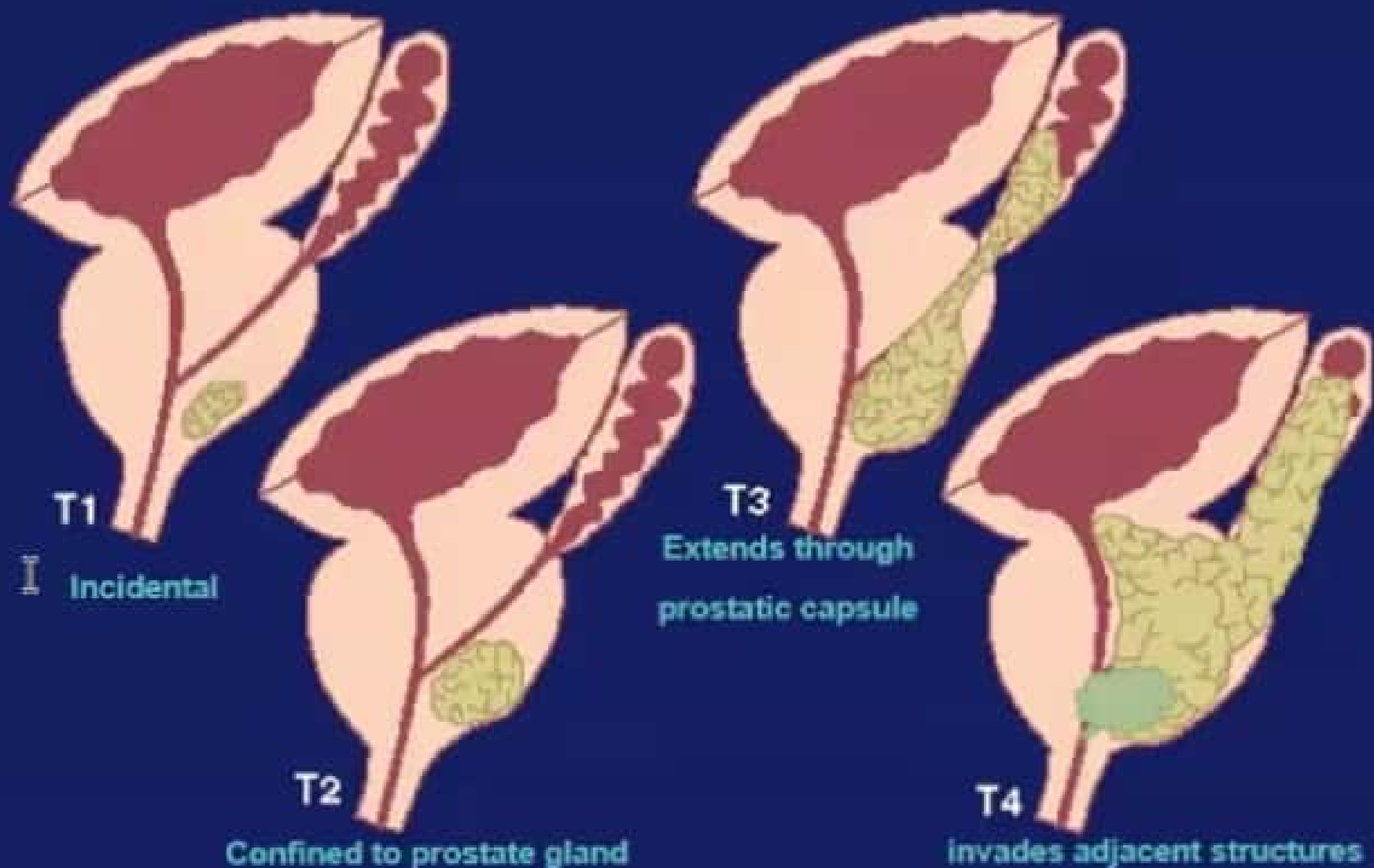
CLINICAL STAGING

Why is it important?

- ▶ Assessing extent of disease /tumour
- ▶ Determines presence or absence of metastases
- ▶ Forms the basis of management /treatment
- ▶ Guide to prognosis / survival

TNM Staging

Local staging of prostate cancer



Primary tumor (pT)

TX Primary tumor cannot be assessed

T0 No evidence of primary tumor

Clinically inapparent tumor neither palpable nor visible by imaging (T1)

T1a Tumor incidental histologic finding in $\leq$ 5% of tissue resected

T1b Tumor incidental histologic finding in $>$ 5% of tissue resected

T1c Tumor identified by needle biopsy (e.g. because of elevated PSA)

Tumor confined within prostate (T2)

T2a Tumor involves one-half of one lobe or less

T2b Tumor involves more than one-half of one lobe but not both lobes

T2c Tumor involves both lobes

Tumor extends through the prostate capsule (T3)

T3a Extracapsular extension (unilateral or bilateral)

T3b Tumor invades seminal vesicle(s)

T4 Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall

Regional lymph nodes (pN)

NX Regional lymph nodes were not assessed

N0 No regional lymph node metastasis

N1 Metastasis in regional lymph node(s)

Distant metastasis (pM)

M0 No distant metastasis

M1 Distant metastasis

M1a Non-regional lymph node(s)

M1b Bone(s)

M1c Other site(s) with or without bone disease

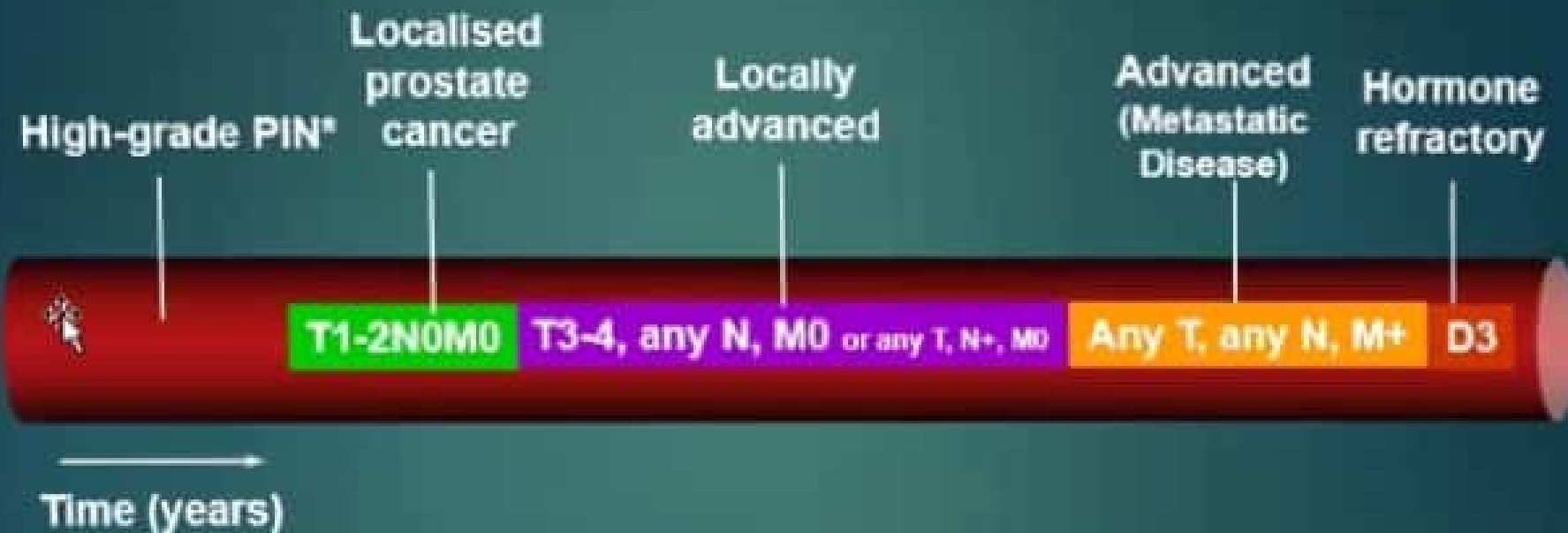
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T1b	Tumor incidental histologic finding in $> 5\%$ of tissue resected
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T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall
Regional lymph nodes (pN)	
NX	Regional lymph nodes were not assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)
Distant metastasis (pM)	
M0	No distant metastasis
M1	Distant metastasis
M1a	Non-regional lymph node(s)
M1b	Bone(s)
M1c	Other site(s) with or without bone disease

doi:10.1371/journal.pone.0155856.t001

Prostate Cancer Stage Groupings

Stage I	T1a, N0, M0, G1
Stage II	T1a, N0, M0, G2-4
	T1b, N0, M0, any G
	T1, N0, M0, any G
	T2, N0, M0, any G
Stage III	T3, N0, M0, any G
Stage IV	T4, N0, M0, any G
	Any T, N1, M0, any G
	Any T, any N, M1, any G

Prostate cancer continuum

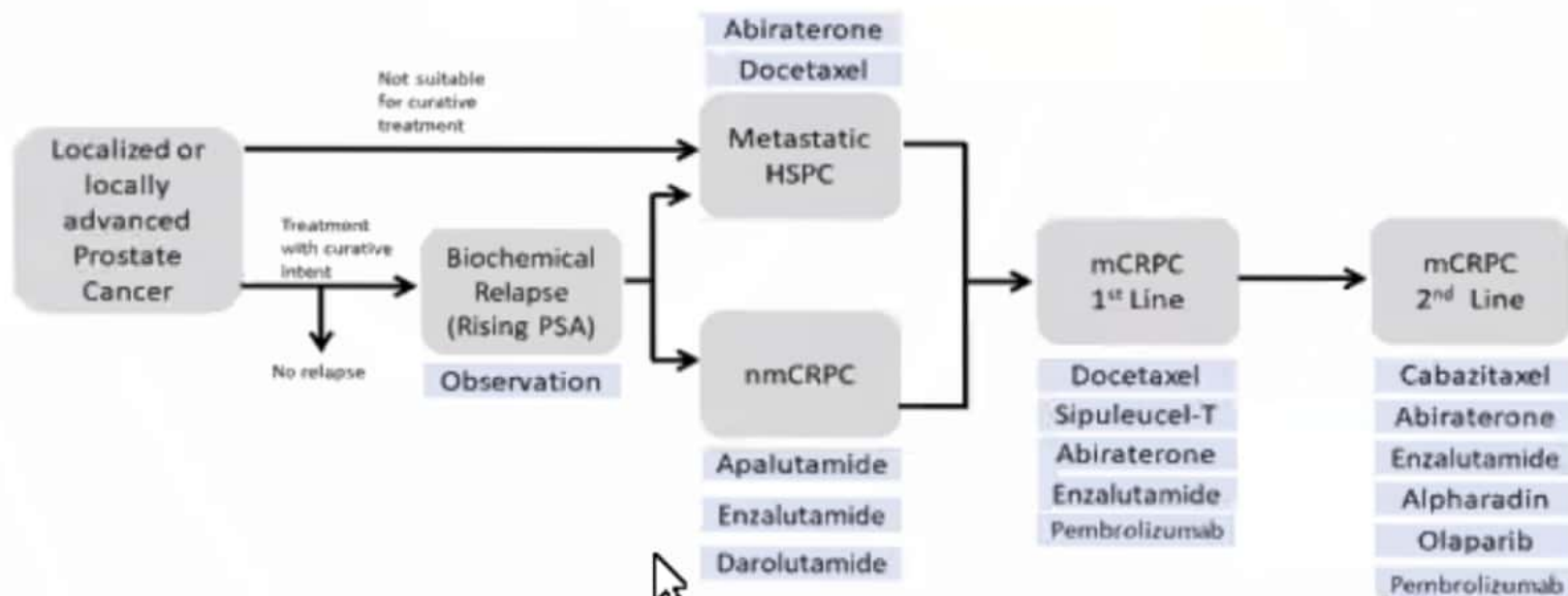


* PIN, prostatic intraepithelial neoplasia

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Zoom

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MANAGEMENT DECISIONS



- ▶ Stage of the disease [non-metastatic (localized or locally advanced), metastatic or hormone refractory).
- ▶ Age and general health of the patient
- ▶ The impact that treatment can have on quality of life, including sexual activity.
- ▶ Patient's preference for treatment.
- ▶ PSA at diagnosis



Risk Group*	Grade Group	Gleason Score
Low/Very Low	Grade Group 1	Gleason Score ≤ 6
Intermediate (Favorable/Unfavorable)	Grade Group 2	Gleason Score 7 (3 + 4)
	Grade Group 3	Gleason Score 7 (4 + 3)
High/Very High	Grade Group 4	Gleason Score 8
	Grade Group 5	Gleason Score 9-10

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Treatments of Curative Intent

- ▶ Performed for cancer that has not yet spread
(metastasized) and is still localized
- ▶ Aim to remove and eliminate all prostate cancer tissues from the body
- ▶ May include a combination of different therapies

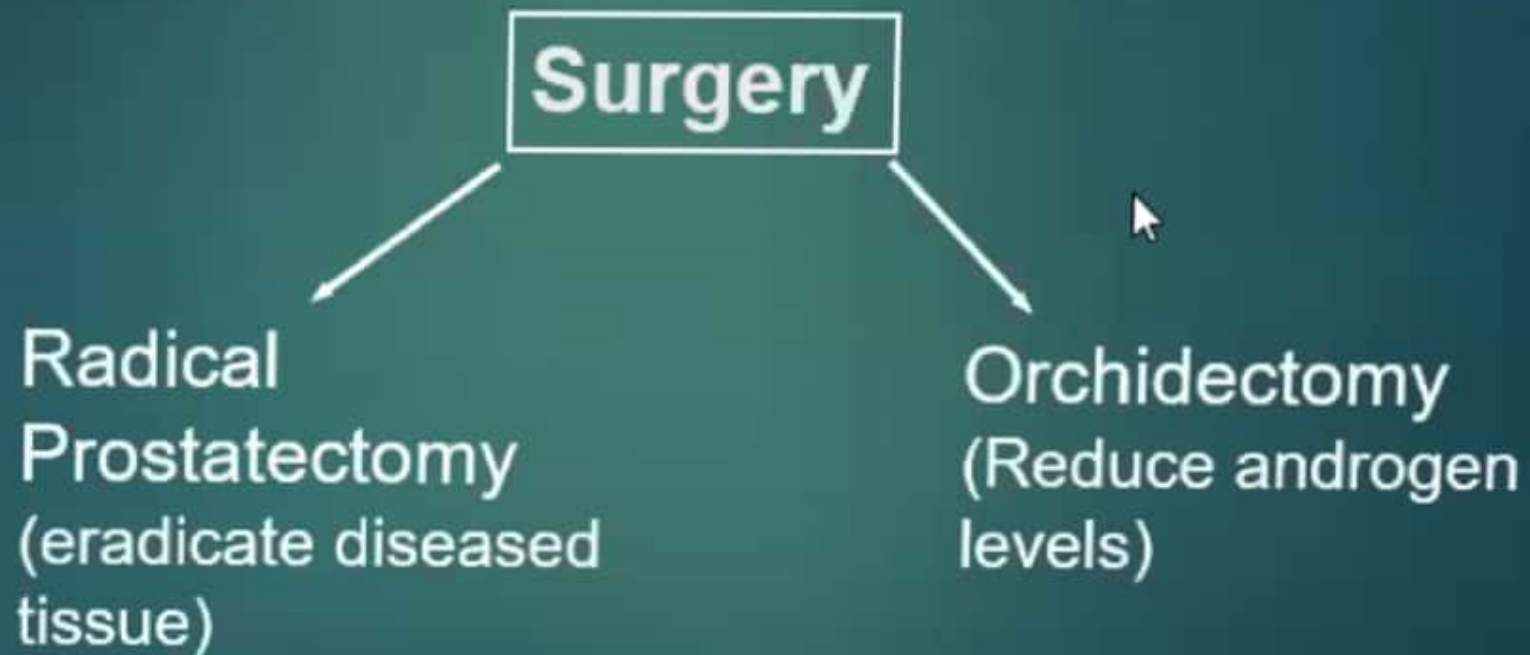
Palliative Treatment

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- Treatment that can help reduce the severity of **advanced** prostate cancer

- This treatment is also used to provide relief from symptoms of advanced disease eg bone pain

Surgery



urgery

▶ Orchidectomy (removal of testes) I

Aim: reduction of androgen levels to slow tumour growth i.e. Surgical castration

▶ Complications

- ▶ Haematoma
- ▶ Wound infections
- ▶ Loss of libido
- ▶ Erectile dysfunction
- ▶ Hot flushes
- ▶ Psychological

Radiotherapy

- Use of high energy rays to kill cancer cells
- Pts not willing to undergo surgery or in whom surgery is inappropriate
- Radiation therapy is not given all at once; usually given in small doses spread out over time
- This allows healthy cells to recover and survive, while the cancer cells eventually die

Radiotherapy

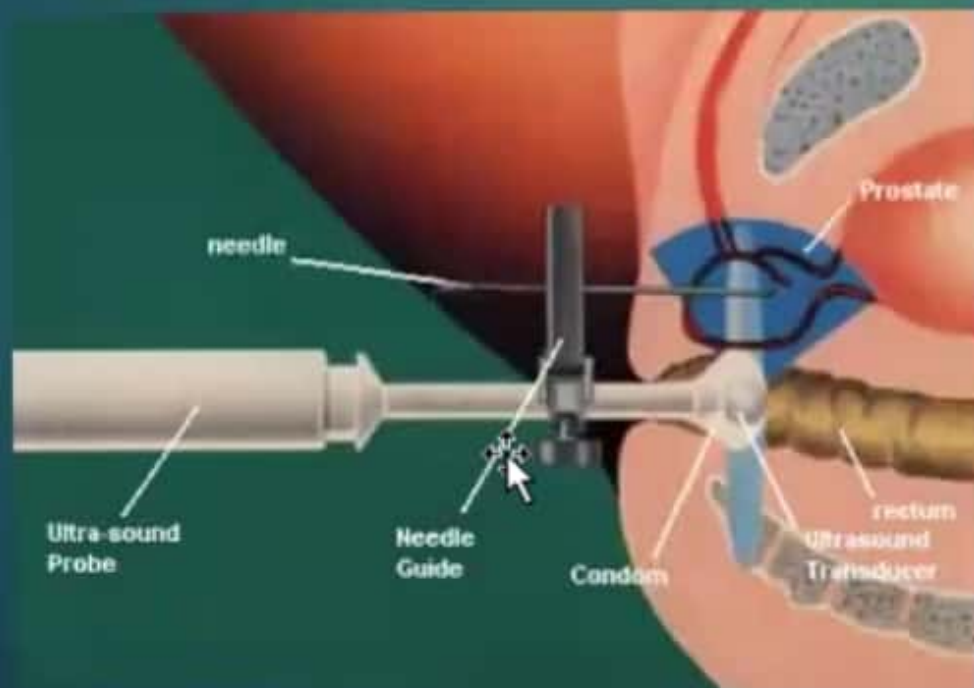


Radiotherapy

2 types :

- ▶ External beam radiation
- ▶ Internal beam radiation
(brachytherapy)

Internal beam radiotherapy (brachytherapy)



Radiotherapy

Alternative to radical prostatectomy

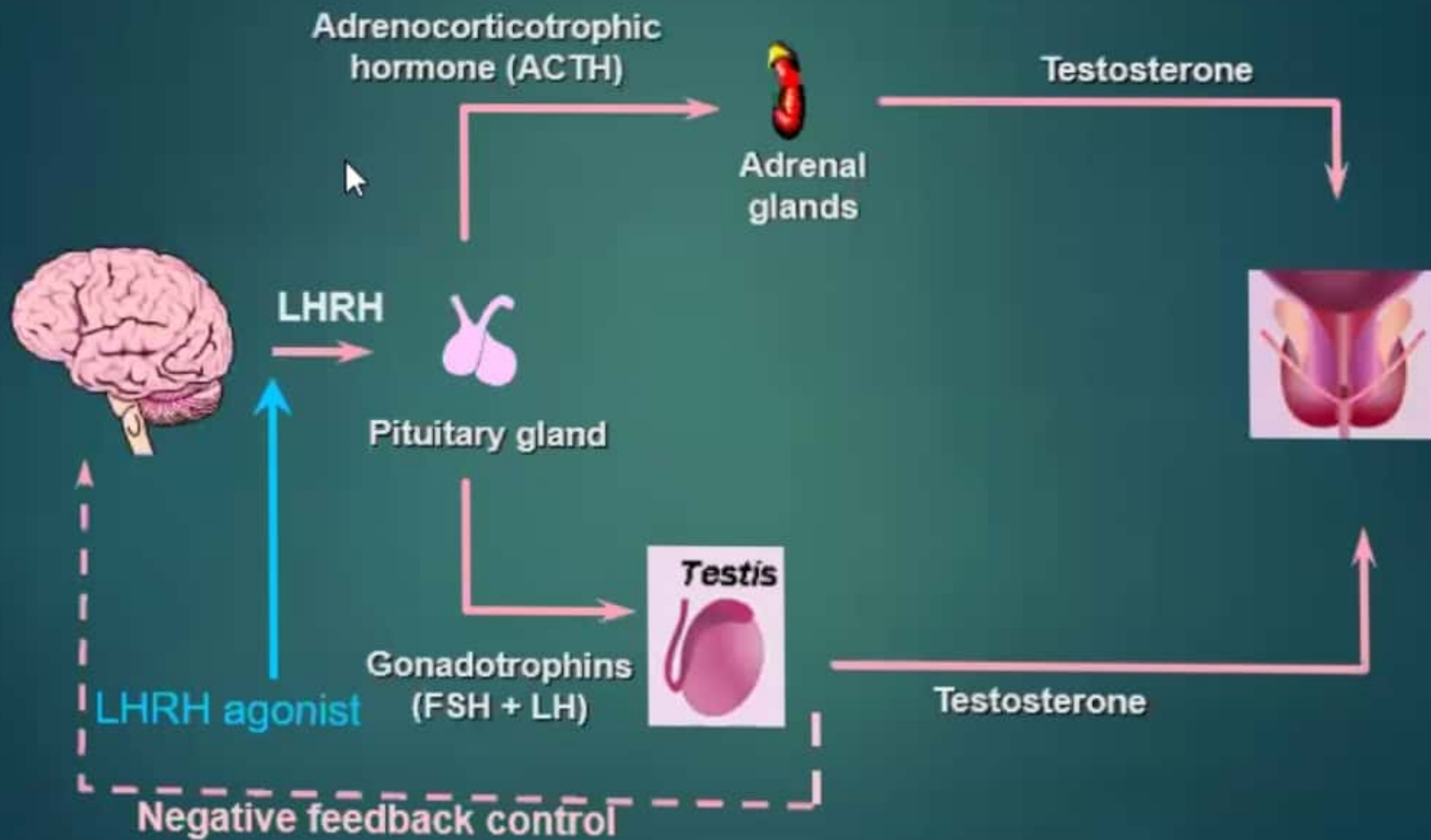
▶ EBRT (external beam radiation therapy)

- ▶ Old style EBRT I
- ▶ Conformal radiation therapy
- ▶ Survival comparable to prostatectomy
- ▶ Neo-adjuvant hormonal therapy controversial

▶ Brachytherapy (internal beam radiotherapy)

- ▶ Radioactive seeds implanted into prostate
- ▶ Higher levels of radiation than EBRT
- ▶ Fewer rectal & bladder side effects
- ▶ Comparable results to EBRT & prostatectomy

LHRH agonist mode of action



Hormonal Drug Therapy

2 main classes :

- ▶ **LHRH analogs** (luteinizing hormone-releasing hormone analogs)- prevent testosterone production by the testes eg zoladex
- ▶ **Antiandrogens** (also called non steroidal antiandrogens)—block the action of testosterone at the prostate eg casodex

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Chemotherapy

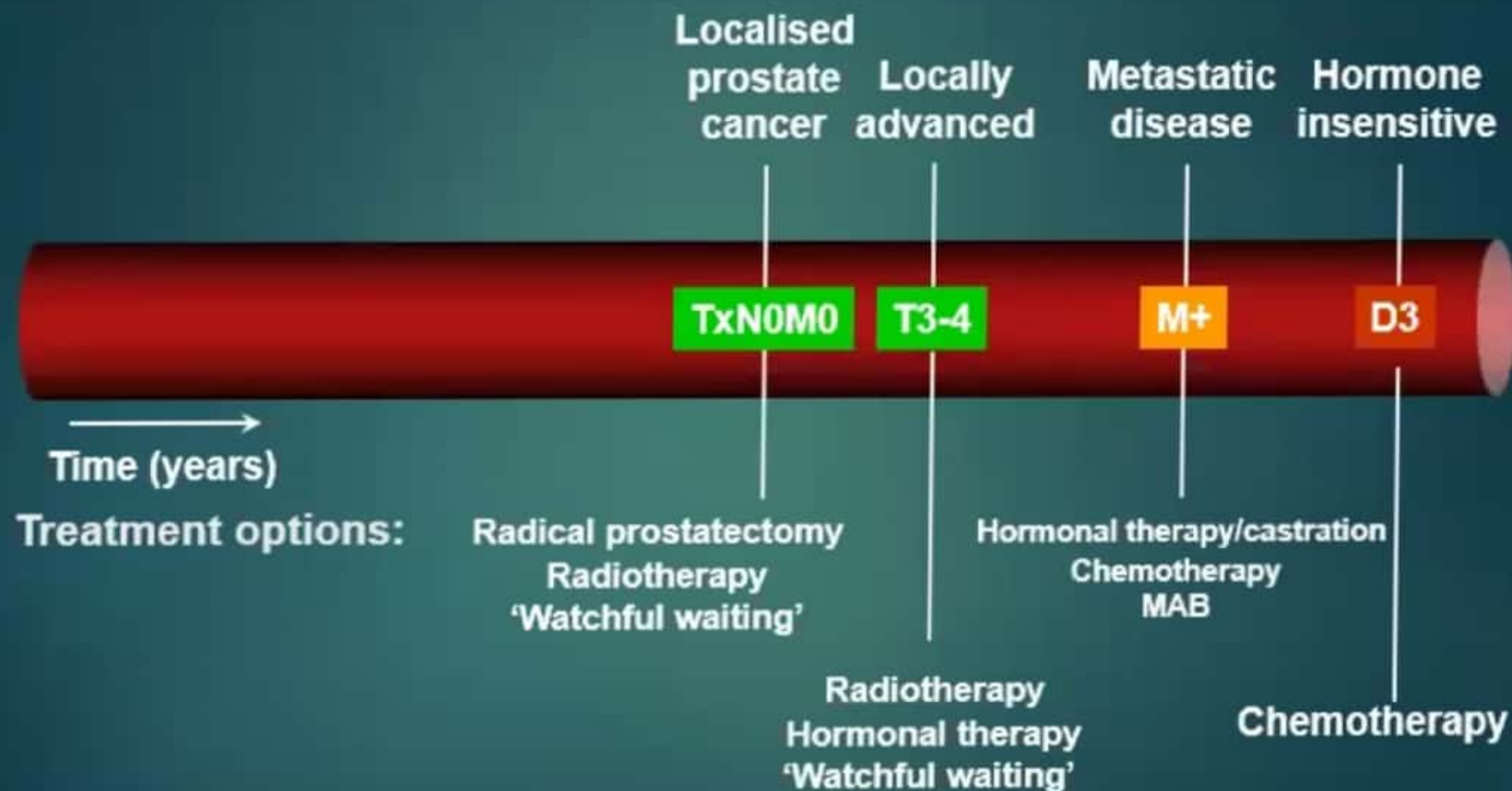
- Chemotherapy is the use of powerful and toxic drugs to attack cancer cells
- Useful in very advanced disease no longer responding to hormonal therapy
- Chemo drugs are carefully controlled in both dosage and frequency so that cancer cells are destroyed while minimizing the risk to healthy cells
- May be oral or injectable and are usually given in combination

Chemotherapy (Toxicity)

- ▶ Because chemo drugs circulate throughout the entire body, they can affect both healthy and cancerous cells leading to undesired effects:

- Hair loss
- Nausea, vomiting
- Diarrhea
- Lowered blood counts
- Reduced ability of blood to clot
- Increased risk of infection

Choice of treatment is related to stage of disease



Aim: Achieve a cure – eliminate tumour
Prevent death – minimise progression

CRPC

- ▶ Tumours may become hormone - 'independent' after median of 1.5 - 2 years
- ▶ Lack of agreement on 'best' treatment strategies and management - Docetaxel , Cabazitaxel *in Doce resistance*
 - Abiraterone, enzalutamide
 - sipuleucel-T (*autologous immunotherapy*)

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