① Family history
② Germaline genetic defects → BOXB13 on (CHS 17q)
                            → BRAC 1+2
③ Inflammation + infection
④ Androgen
⑤ Estrogen
⑥ smoking
⑦ obesity

Prostate Cancer

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Epidemiology

2nd after lung

* prostate ca. more common than bladder ca. → 4th
* RCC in urological tumors → less common but most fatal

- The m. c. noncutaneous malignancy in U.S. men since 1984, accounting for 27% of all such cancers
- 1/7 (15.3%) men will be diagnosed with prost ca &
- 1/38 (2.6%) men will die from prost ca
- African-Americans experience 59% higher incidence rates
- Prost ca is the 2nd leading cause of cancer death
- Mortality in an average rate of 4.1% per year
- African-American death rates are 2.4 times higher

higher incidence / higher mortality

RISK FACTORS

- Both genetics and environment are important in the origin and evolution of prostate cancer

Familial
genetic

- I) **Family History:** Father (↑2.17), Brother (↑3.37), First-degree family member affected with age <65 yr at diagnosis (↑3.34), >2 first-degree relatives affected (↑**5.08**), Second-degree relative affected (↑1.68)

1st degree relative | screening at younger age every 2 years

- II) **Germline Genetic defects:** Too many prost ca susceptibility genes and loci, (> 70) only 2 have clinical significance.

RISK FACTORS

- II-a: A recurrent mutation in the coding region of the HOXB13 gene (CMS 17q): This mutation increases overall risk of disease 5x, and > 8x under age 55 yr or with a family history
- II-b: BRCA1 and BRCA2: BRCA1 increases risk by 1.8- to 3.5-fold & BRCA2 4.6- to 8.6-fold in men under 65 y.o.
- BRCA-associated cancers, especially BRCA2, are also more likely to present with higher grade, locally advanced, and metastatic disease and have worse cancer-specific and metastasis-free survival after prostatectomy

→ Any inflammation in the body may change the cells type and this → is a risk of metaplasia then Ca development.

RISK FACTORS

- III) **Inflammation and Infection:** Chronic inflammation leading to cellular hyperproliferation to replace damaged tissue contributes to the development of infection-associated cancers
- Inflammatory infiltrates and the histologic lesion called proliferative inflammatory atrophy (PIA) are frequent in clinical prostate specimens
- PIA is often found adjacent to high-grade prostatic intraepithelial neoplasia (HGPIN) or early cancer
- Inflammation may be triggered by diet, infection, estrogens, or other environmental agents

RISK FACTORS

- **IV) Androgens:** are important in the maintenance of established cancers.
- Long-term absence of androgen protect against the development of cancer
- **V) Estrogens:** also important in prost ca development, and may have varying effects depending upon local tissue activity of ER-α and ER-β.
- Intraprostatic estrogen production may also be important in prostate cancer development

RISK FACTORS

- **VI) Others:**
- Smoking increases the risk of disease recurrence and death resulting from prostate cancer
- Obesity is associated with lower serum PSA, increases the risk of getting high-grade prost ca, and is associated with higher treatment failure rates and disease-specific mortality

Early Detection of Prostate Cancer

nowadays: less the 55 → screening in high risk pt's only

1) • <40 y.o: do not do PSA screening

2) • 40 to 54 y.o: Do not do PSA as a routine (Just for high risk)

- High Risk: 1. African American 2. family history of metastatic or lethal adenocarcinomas (e.g., prostate, male and female breast cancer, ovarian, pancreatic)
- But the harms of screening in this population were at least equal to the benefits

→ sepsis → septic shock ①
progression of ca. ②

Early Detection of Prostate Cancer

- 55-69 y.o: Do PSA screening
- relative risk reduction of prost ca-specific death of 25-30%
- Screening should be done every 2 years
- Or every 4 years if initial PSA is less that 1 ng/ml.
- ≥ 70 y.o: have a higher prevalence of prost ca and a higher incidence of fatal tumors, but also increased mortality.
- □ Do not do routine screening (only if the patient elected)

depending on the baseline PSA.

because no benefits from knowing that there ↑PSA

higher risk for ca. but there is no survival benefits so we don't do screening

No improvement

Diagnosis & staging

- 1) PSA: → gives us a hint about the ca. if it's localized to the organ or mets.
- PSA levels are associated directly with pathologic stage and tumor extent.
- pathologically **organ-confined disease** is found in 80% of men with a PSA less than 4.0 ng/mL, 66% of those with PSA levels between 4.0 and 10.0 ng/mL, and fewer than 50% of men with PSA levels greater than 10.0 ng/mL.
- Also, 20% of men with PSA levels greater than 20 ng/mL and 75% of those with PSA levels greater than 50 ng/mL are found to have **pelvic lymph node involvement**.

→ reflect if the disease already advanced

Diagnosis & staging

- 2) Digital Rectal Examination: (subjective)
- DRE is used to determine whether a lesion is palpable and is associated with local disease extent (clinical T stage).
- An abnormal DRE was associated with an increased risk for detecting high-grade (Gleason 8 to 10) prostate cancer.
- Has poor sensitivity and lack of reproducibility, DRE can both overestimate and underestimate the extent of disease.
- DRE can be used in combination with other parameters to help predict tumor extent.

* DRE + PSA → ↑ predictive values before doing biopsy

*biopsy → definitive

Diagnosis & staging

- PSA testing improves the positive predictive value (PPV) of DRE for cancer.
- Overall, when DRE and PSA tests are used in prostate cancer screening, detection rates are higher with PSA testing than with DRE and highest with the tests together.
- 3) Prostate Needle Biopsy:
- Histologic grade is the most important information obtained from prostate needle biopsy, and the Gleason grading system is the most commonly used
  - 12 samples; 6 from each side (Lt and Rt); examine it under microscope
  - MC site of ca. → peripheral (assum. of most commonly 2 readings)

*staging by imaging *grading by histology

Diagnosis & staging

- 3) Prostate Needle Biopsy: At low-power magnification, the sum of a grade (1 to 5) assigned to the predominant pattern (occupying the largest area of the specimen) and the second most common pattern yield a score ranging from 2 to 10.

most well differentiated (3+3)

- 5-grade group system: Grade Group 1 (Gleason score ≤6) (2-10)

Grade Group 2 (Gleason score 3+4=7) better than 4+3 (favourable intermediate risk)

worse

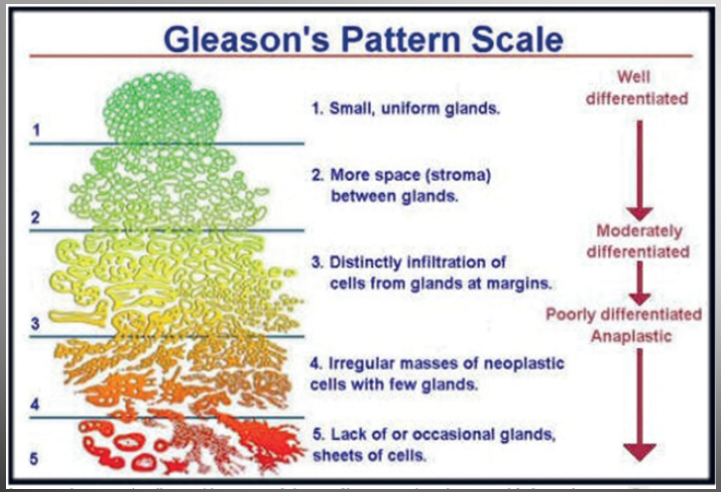
Grade Group 3 (Gleason score 4+3=7)

Grade Group 4 (Gleason score 4+4=8)

Grade Group 5 (Gleason scores 9 and 10) most undifferentiated

glands closer to the normal → better prognosis

Diagnosis & staging



less glandular but more infiltrative

Diagnosis & staging

3) Prostate Needle Biopsy:

- Typically transrectal sextant biopsy (TRUS Bx) involves samples from the parasagittal plane on the right and left sides of the base, midzone, and apex, with each site arbitrarily assigned by the operator.
- Involve extracting 10–12 cores per biopsy, often from the standard sextant and other areas of the peripheral, transition, or anterior zones.

Diagnosis & staging: TNM

≤T2 → localized / locally advanced / mets.

T3 + T4 without regional LNs

T4 with LNs + invasion to other organs

- TX: Primary tumor cannot be assessed
- T0: No evidence of primary tumor
- T1: Nonpalpable tumor—not evident by imaging

T1 a/b → after TUR or abnormal PSA

- T1a: Tumor found in tissue removed at TUR; ≤5% is cancerous and histologic grade <7.
- T1b: Tumor found in tissue removed at TUR; >5% is cancerous or histologic grade >7
- T1c: Tumor identified by prostate needle biopsy as a result of elevation in PSA

Diagnosis & staging: TNM

- T2: Palpable tumor confined to the prostate
- T2a: Tumor involves one lobe or less
- T2b: Tumor involves more than one lobe
- T3: Palpable tumor beyond prostate
- T3a: Unilateral extracapsular extension
- T3b: Bilateral extracapsular extension
- T3c: Tumor invades seminal vesicle(s)
- T4: Tumor is fixed or invades adjacent structures

management for localized ca.
if locally advanced → referred to medical oncology

Diagnosis & staging: TNM

- N0: No lymph node metastases
- N1: Metastases in single regional lymph node, ≤2 cm in dimension
- N2: Metastases in single (>2 but ≤5 cm)/multiple with none >5 cm
- N3: Metastases in regional lymph node >5 cm in dimension
- M0: No evidence of distant metastases
- M1: Distant metastases
- M1a: Involvement of nonregional lymph nodes
- M1b: Involvement of bones (osteoblastic)

Clinically Localized Prost Ca: W/U

- Do not perform abdomino-pelvic CT or routine bone scans in the staging of asymptomatic very low- or low-risk localized prost ca patients
- In intermediate-risk & High-risk localized prostate cancer patients: Do cross sectional imaging abdomino-pelvic (CT or MRI) and bone scan.

Clinically Localized Prost Ca: Risk Stratification

- Risk stratification of prostate cancer severity or aggressiveness should include PSA, clinical stage (DRE), Grade Group, and amount of cancer on biopsy (i.e. number of cores involved, maximum involvement of any single core) PSA density, and imaging.
- Risk Groups: Low-, Intermediate-. & High-Risk group

Clinically Localized Prost Ca:

Risk Stratification for Localized Prostate Cancer		
1. Low Risk Group	Very low risk	PSA <10 ng/ml AND Grade Group 1 AND clinical stage T1-T2a AND <34% of biopsy cores positive AND no core with >50% involved, AND PSA density <0.15 ng/ml/cc
	Low Risk	PSA <10 ng/ml AND Grade Group 1 AND clinical stage T1-T2a
2. Intermediate	Favorable	Grade Group 1 (with PSA 10-<20) OR Grade Group 2 (with PSA<10)
	Unfavorable	Grade Group 2 (with either PSA 10-<20 or Clinical stage T2b-c) OR Grade Group 3 (with PSA < 20)

Clinically Localized Prost Ca:

Risk Stratification for Localized Prostate Cancer	
3. High Risk group	PSA ≥ 20 ng/ml OR Grade Group 4-5 OR Clinical stage ≥T3

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

Clinically Localized Prost Ca

- Selecting management strategy for localized prost ca (patient, tumor, and treatment-related factors):
- (-) Shared decision making, (-) cancer severity (risk category),
- (-) Patient values and preferences, (-) life expectancy,
- (-) Previous general functional & genitourinary symptoms,
- (-) Expected post-treatment functional status, and
- (-) Potential for salvage treatment

① watch full waiting → life expectancy < 10 years
(observation ⊕ intervention only for complication).

② Active surveillince : for low risk
- PSA & DRE and multi-parametric MRI
3 months ↓ annual ↓
- biopsy : Gleason score
(only if any progression or every 2 years).

→ life expectancy > 10 years

intermediate risk ⊕ high risk

③ Radical prostatectomy
(True incontinance, ED directly after surgery)

④ External beam radiation
(True incontinance, ED, bowel & bladder SE due to fibrosis, leukemia, lymphoma)
gradually over 2 years or more.

⑤ Androgen - deprivation therapy : for high risk

4 lines of HT according to life expectancy: ① more than 10 → low: active surveillance with PSA (3 months) + DRE (1 year) + if progressed → biopsy

inter: radical prostatectomy + radiation

high: radical prostatectomy + radiation + androgen replac. therapy

② less than 10 → not do anything (observation)/ just HT the complications

Clinically Localized Prost Ca: Mx selection

- Smoking & obesity are correlated with prost ca death.
- In Surgically treated patients, smoking, older age, and obesity increase the risk of perioperative complications, including bleeding, infections, and DVT.
- Each of the initial localized prostate cancer management strategies has a typical pattern of side effects, frequently different from those of other treatments
- Active surveillance (AS): (+ve): no immediate effect on urinary, bowel, or sexual function

*we measure life expectancy for the patient, if its < 10 years → watchful waiting (if not complications and symptomes)

Clinically Localized Prost Ca: Mx selection

- Active surveillance (AS): (-ve):
  - as retention / obstruction → TURP
- (-) declines in urinary, bowel, and sexual function over time,
- (-) anxiety over deferring definitive management
- (-) Previous obstructive urinary symptoms are known to be worse in AS patients in comparison to surgery.
- 50-73% of men who elect active surveillance as an initial management strategy have discontinued it by year 10

Clinically Localized Prost Ca: Mx selection

slower - - -

*If its >10 years
① AS
② Radical Prostatectomy
③ Radiation therapy.

- Radiation Therapy: (+ve):
  - definitive ††
- Sexual & continence problems: longer time to develop
- Radiation Therapy: (-ve):
  - * Anti-androgen therapy is not definitive ††
- (-) Bowel problems are more common
- (-) More urinary irritation (LUTS)
- (-) Very small but increased risk for secondary cancer, specifically bladder cancer & rectal cancer.

Clinically Localized Prost Ca: Mx selection

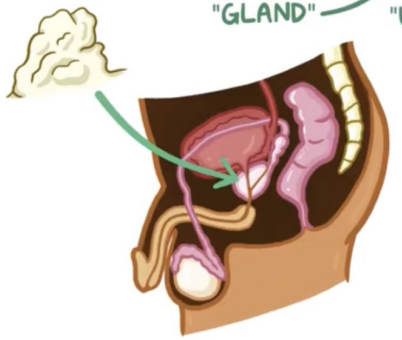
faster / immediate true incontinence after surgery

- Radical Prostatectomy (RP): (-ve): → Removal of prostate gland with its capsule + seminal vesicles + urethra
- (-) Immediate side effects: bleeding, infection, and pain
- (-) Later: ED, urinary incontinence, urethral stricture.
- (-) perioperative death from prost ca surgery: <0.1%
- (=) ED and urinary bother beyond 2-5 years may be similar between surgery and radiation (1-3%)

PROSTATE CANCER

PROSTATE ADENOCARCINOMA

"GLAND" — "UNCONTROLLED GROWTH OF CELLS"



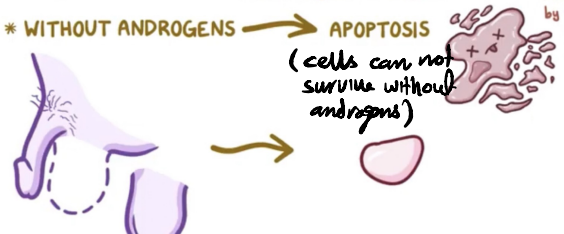
* ONLY AFFECTS MALES
* USUALLY MALIGNANT
  - CAN METASTASIZE (invade & destroy tissues)

BASAL CELLS & LUMINAL CELLS RELY on ANDROGENS

MALE SEX HORMONES

- TESTOSTERONE — PRODUCED by TESTICLES
- ANDROSTENEDIONE & DEHYDROEPIANDROSTERONE — PRODUCED by ADRENAL GLANDS
- DIHYDROTESTOSTERONE — MADE FROM TESTOSTERONE by the PROSTATE

* WITHOUT ANDROGENS → APOPTOSIS (cells can not survive without androgens)



Castrated testicles → the prostate significantly shrink in size (due to the death of luminal cells)

PROSTATE ADENOCARCINOMA

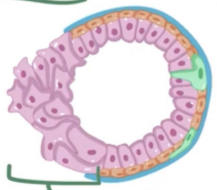
GENETIC MUTATION in a LUMINAL CELL or BASAL CELL
- CELL DIVIDES UNCONTROLLABLY

[RISK FACTORS]:

1. * OLD AGE
2. * OBESITY
3. * HIGH FAT/LOW FIBER DIET

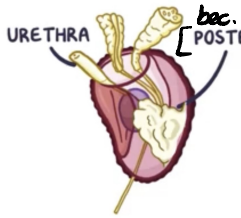
Types:

1. **PROSTATE ADENOCARCINOMA**
   - * MUTATIONS in 2 GENES: BREAST CANCER GENE 1 (BRCA1) & BREAST CANCER GENE 2 (BRCA2)
     - ALSO CAUSE BREAST CANCER
   - * MOST COMMON TYPE of PROSTATE CANCER
     - OTHER TYPES EXIST:
2. * TRANSITIONAL CELL CARCINOMA (transitional zone)
3. * SMALL CELL PROSTATE CANCER (neuroendocrine cells)



TUMOR
- CELLS MUTATE & KEEP MULTIPLYING WITHOUT ANDROGENS
- RELATIVELY SLOW GROWTH RATE

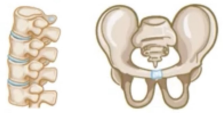
EARLY ON → NO SYMPTOMS



bec. the majority of cases arise in [POSTERIOR PERIPHERAL ZONE] → which is far away from the urethra

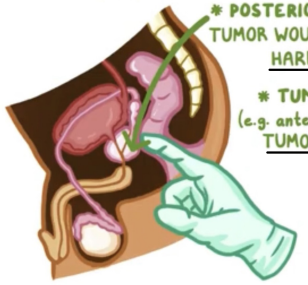
* IF CANCER DOES COMPRESS URETHRA or BLADDER:
  - * difficulty urinating
  - * bleeding
  - * pain with urination & ejaculation

* IF METASTATIC, SPREADS to BONES (e.g. vertebrae or pelvis)
  - → hip or lower back pain



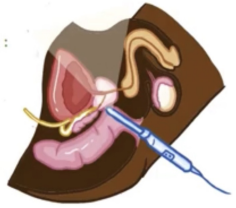
DIAGNOSIS

1) DIGITAL RECTAL EXAM



* POSTERIOR PROSTATE: TUMOR WOULD FEEL like a HARD LUMP
* TUMOR ELSEWHERE (e.g. anterior peripheral zone): TUMOR OUT OF REACH

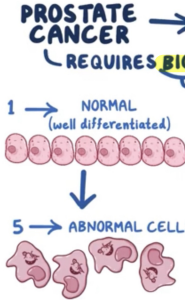
2) TRANSRECTAL ULTRASOUND or MRI



3) ELEVATION in PROSTATE SPECIFIC ANTIGEN

4) PROSTATE CANCER → REQUIRES BIOPSY

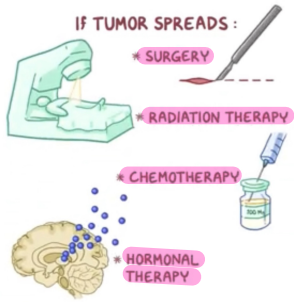
GLEASON GRADING SYSTEM
- 2 MOST COMMON CELL PATTERNS
- SCORE (1-5)
- NUMBERS ADDED = TOTAL GLEASON SCORE (2-10)



TREATMENT

* TUMOR CONFINED to the PROSTATE & HASN'T METASTASIZED
  - → ACTIVE SURVEILLANCE [ROUTINE TUMOR MARKER MEASUREMENT & IMAGING]
    - ENSURE CANCER REMAINS CONFINED to PROSTATE

IF TUMOR SPREADS:



* SURGERY
* RADIATION THERAPY
* CHEMOTHERAPY
* HORMONAL THERAPY

Thank you