PROSTATE CANCER
EPIDEMIOLOGY, DIAGNOSIS, AND PRINCIPLES OF MANAGEMENT

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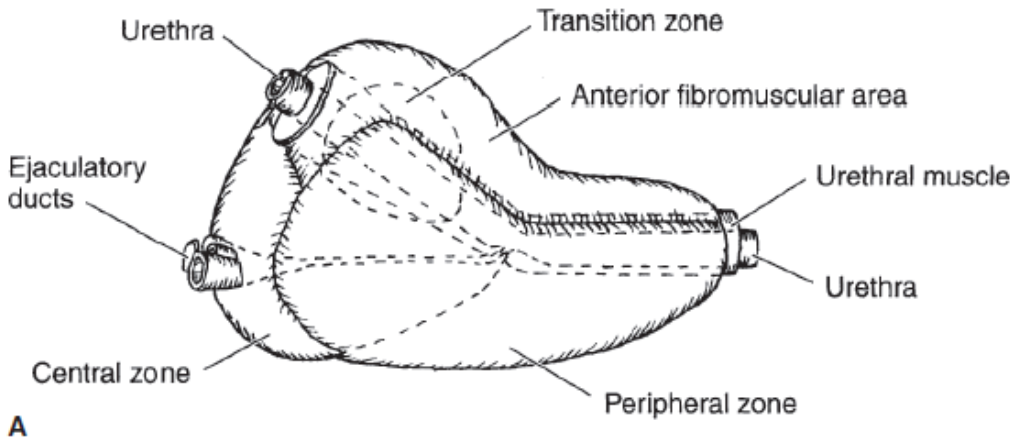
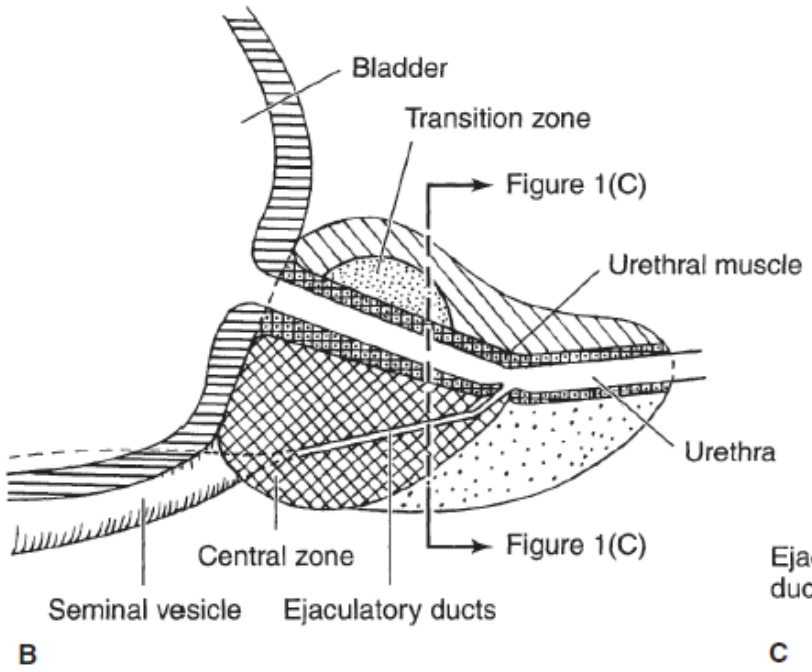
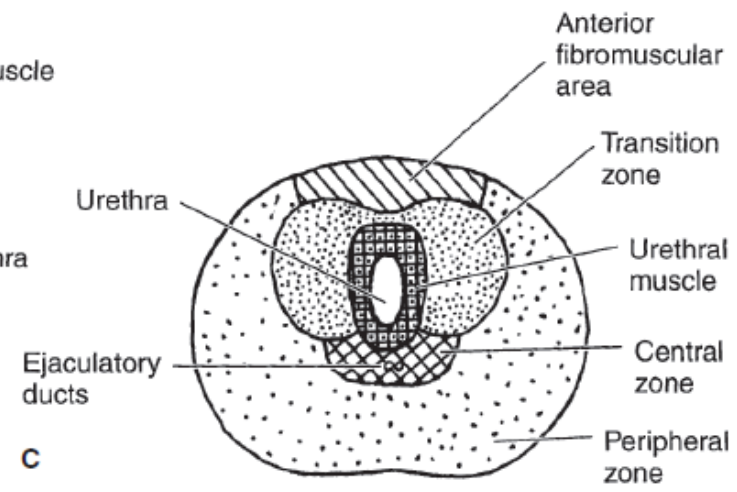
Anatomy of Prostate Gland

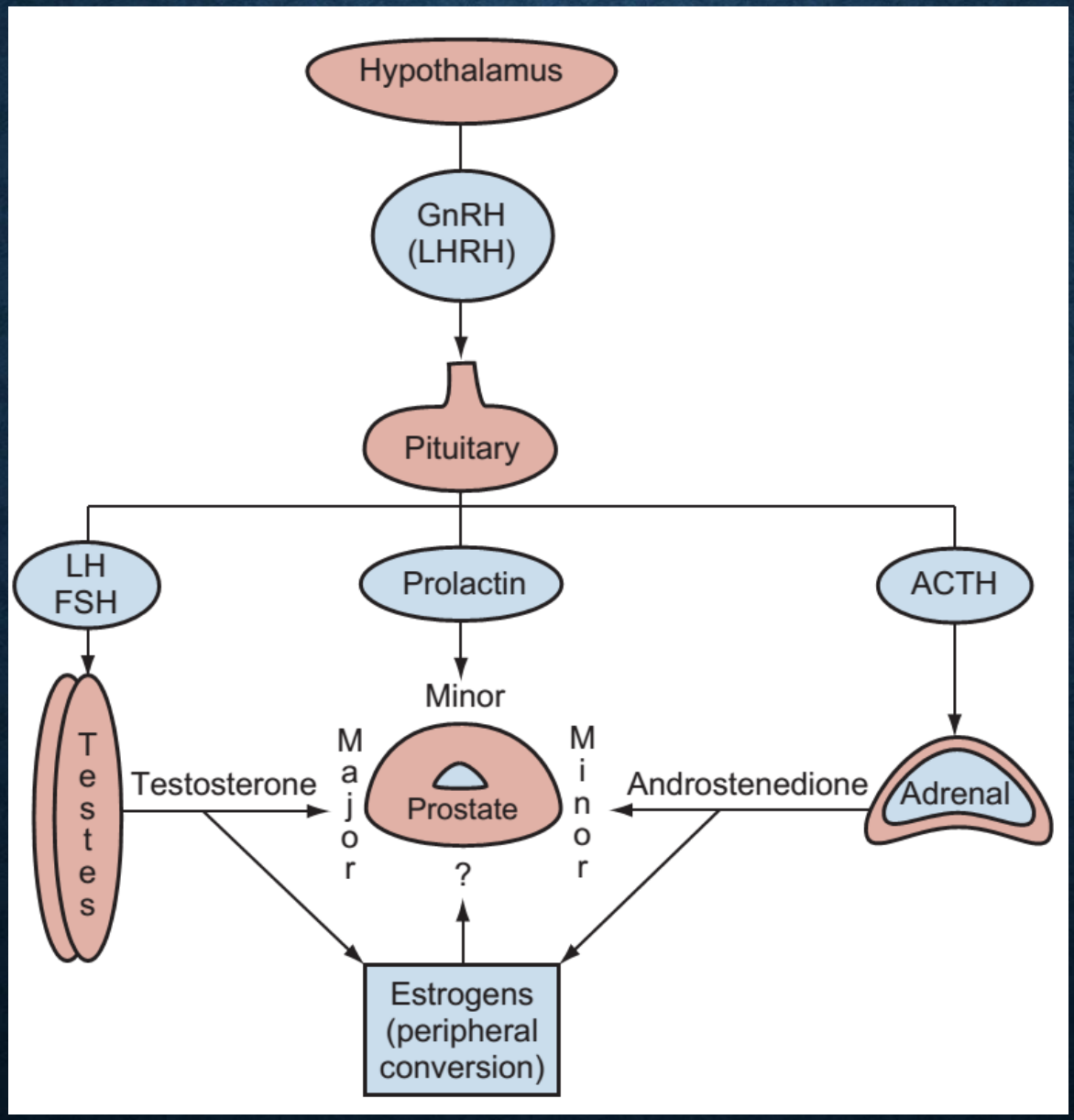






- **Normal prostate:** peripheral (P) zone 90% ; transitional (T) zone 5~10%
- **BPH:** hyperplasia of **"T zone"**
- **Prostate cancer: 70% from P zone, 20~25% from T zone**
  - DRE: "P zone"
- Key in prostatic growth: **androgen**
  - Dihydrotestosterone (DHT): main
  - Testosterone

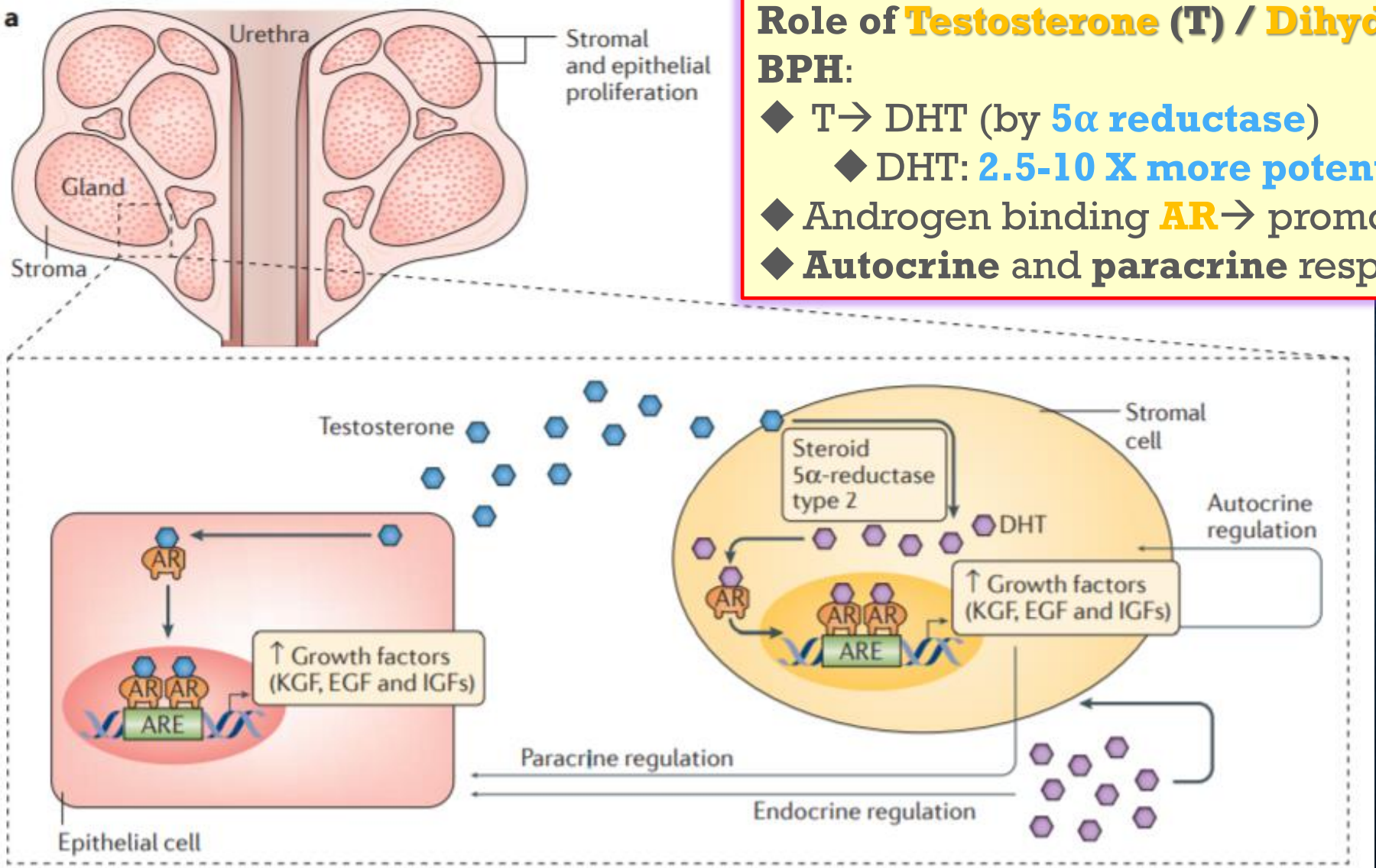
ENDOCRINOLOGY OF PROSTATE



Molecular Control of Prostate Growth

Role of Testosterone (T) / Dihydrotestetrone (DHT) in BPH:

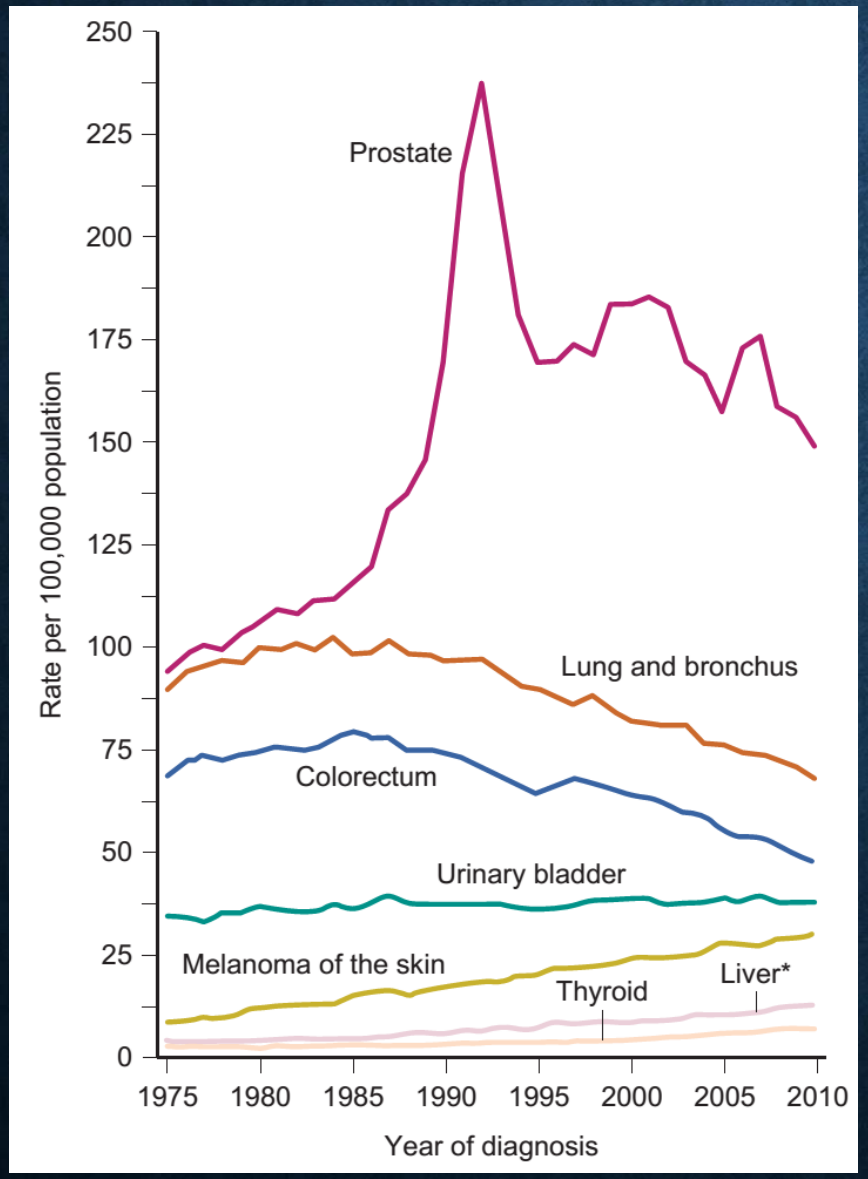
- T→ DHT (by **5α reductase**)
  - DHT: **2.5-10 X more potent** than T
- Androgen binding **AR**→ promote **proliferation**
- **Autocrine** and **paracrine** response within prostate



AR, androgen receptor
KGF, keratinocyte growth factor
EGF, epidermal growth factor
IGF, insulin-like growth factors

Nat Rev Dis Primers. 2016 May 5;2:16031

INCIDENCE OF PROSTATE CANCER



- Incidence peak in 1992 due to **PSA screening**; declined until 1995
- Generally, **increased incidence rate**

Incidence of Prostate Cancer

TABLE 107-1 Prostate Cancer Incidence and Mortality by Race/Ethnicity, United States, 2006-2010

	INCIDENCE*	MORTALITY*
White	138.6	21.3
African-American	220	50.9
Hispanic/Latino	124.2	19.2
Asian-American and Pacific Islander	75	10.1
American Indian and Alaska Native	104.1	20.7

*Per 100,000, age adjusted to the 2000 U.S. standard population.
Data from Siegel R, Ma J, Zou Z, et al. Cancer statistics, 2014. CA Cancer J Clin 2014;64:9–29.

- **Taiwan 2019**:
  - 7115 new cases
  - 發生率 35.83/ 10萬人年 (5th)
  - 死亡率 7.01/ 10萬人年 (7th)
  - ➔ 皆逐年增加

- World wide: incidence and mortality vary between countries and regions

MORTALITY RATE OF PROSTATE CANCER

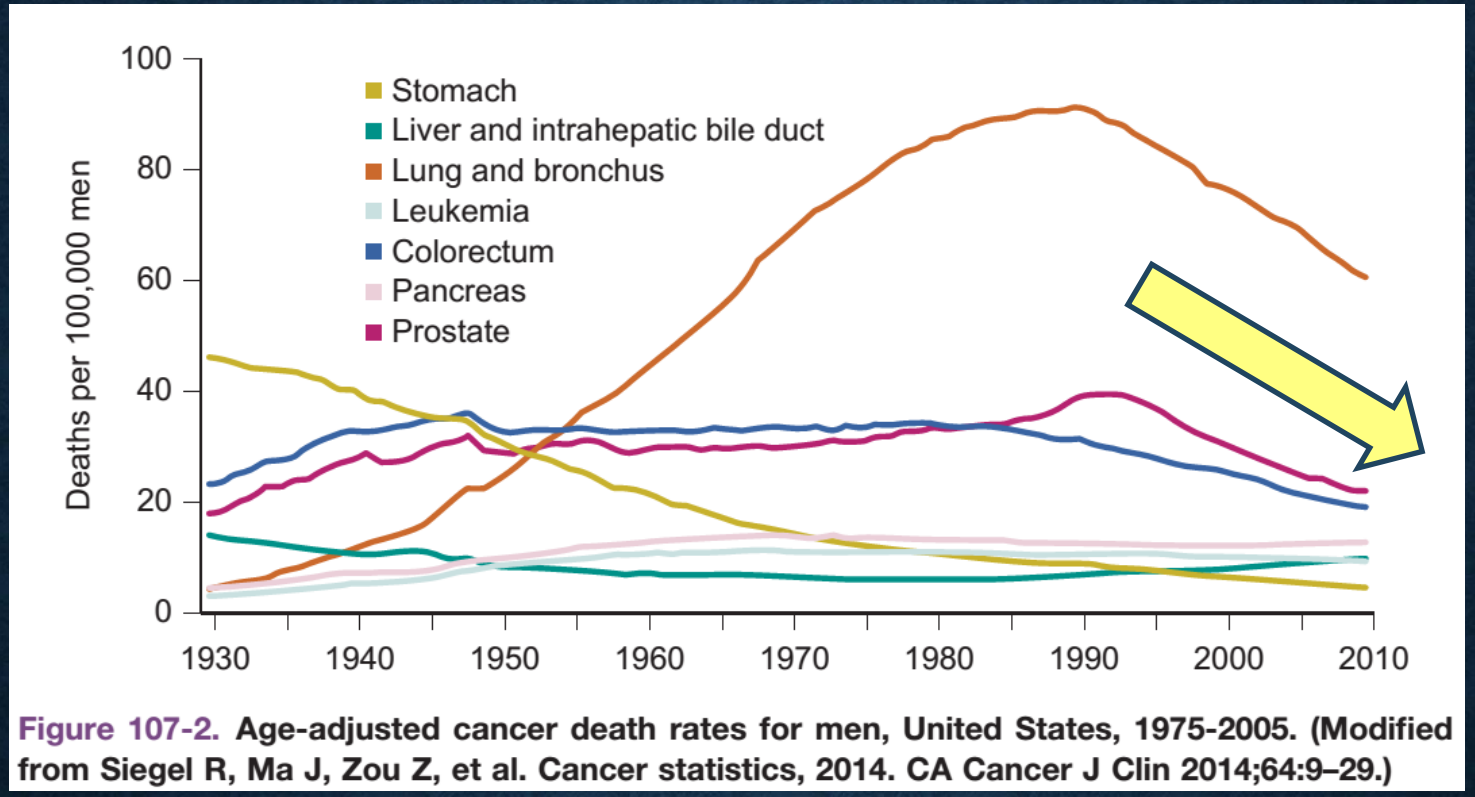


Figure 107-2. Age-adjusted cancer death rates for men, United States, 1975-2005. (Modified from Siegel R, Ma J, Zou Z, et al. Cancer statistics, 2014. CA Cancer J Clin 2014;64:9–29.)

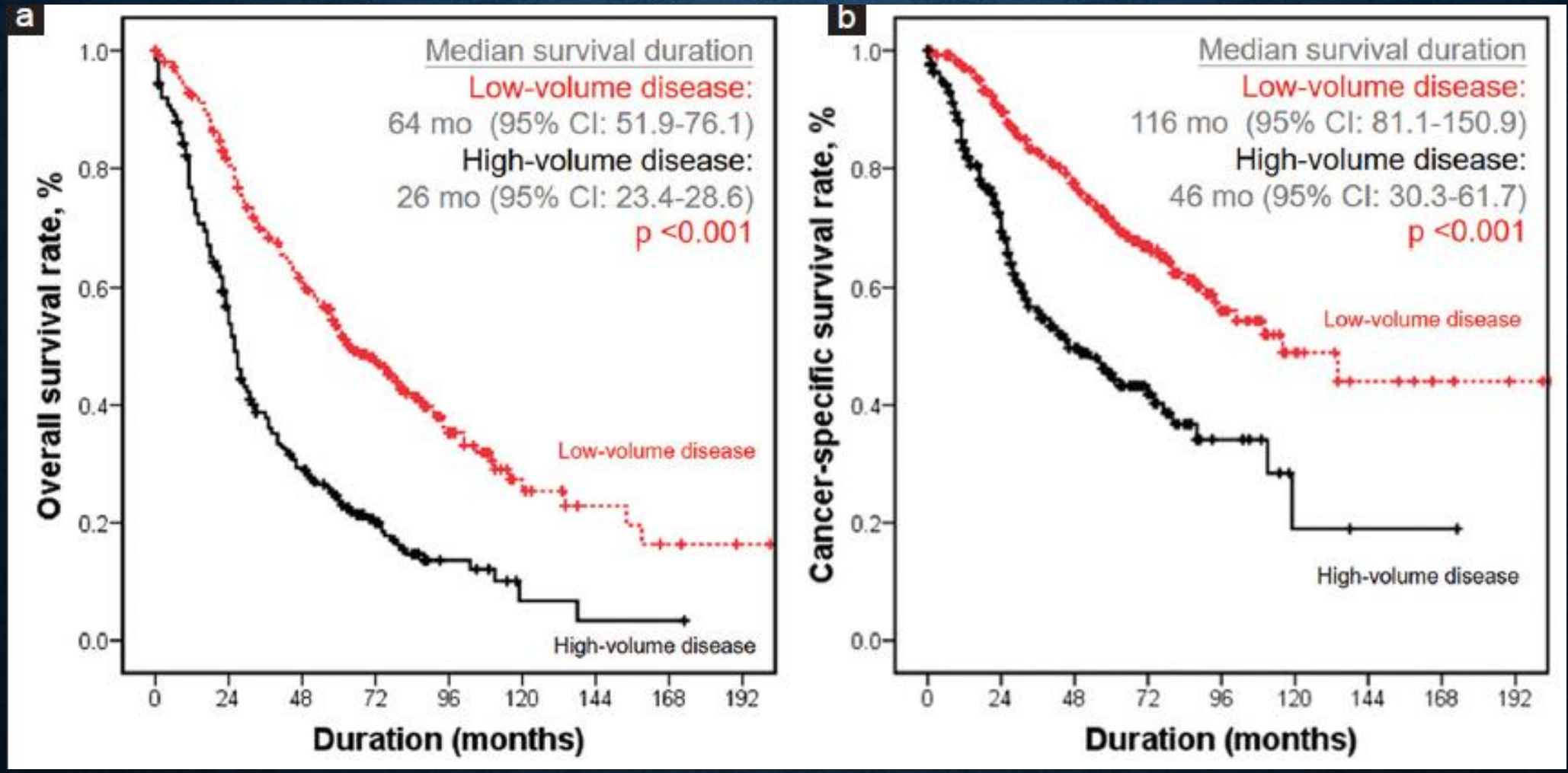
- **Decreasing** trends in prostate cancer mortality were mainly observed in **high-income countries**
- **PSA screening**: ↓age, ↓ stage at diagnosis; beneficial effect on mortality rate

台灣男性攝護腺癌期別 (2019)

特性	合計		男性	
	N	%	N	%
總個案數	6406	100.00	6406	100.00
TNM 診斷組合(整併期別 [5])				
Stage I				
cT1a-cN0M0	378	6.05	378	6.05
cT2aN0M0	76	1.22	76	1.22
pT2N0M0	134	2.14	134	2.14
Stage IIA				
cT1a-cN0M0	106	1.70	106	1.70
cT2aN0M0	44	0.70	44	0.70
pT2N0M0	1	0.02	1	0.02
cT2bN0M0	14	0.22	14	0.22
cT2cN0M0	136	2.18	136	2.18
Stage IIB				
T1-2N0M0	679	10.86	679	10.86
Stage IIC				
T1-2N0M0 Grade3	360	5.76	360	5.76
T1-2N0M0 Grade4	157	2.51	157	2.51
Stage IIIA				
T1-2N0M0	524	8.38	524	8.38
Stage IIIB				
T3-4N0M0	969	15.50	969	15.50
Stage IIIC				
TanyN0M0	641	10.26	641	10.26
Stage IVA				
TanyN1M0	448	7.17	448	7.17
Stage IVB				
TanyNanyM1	1583	25.33	1583	25.33

- 22.84%接受根除性攝護腺切除手術

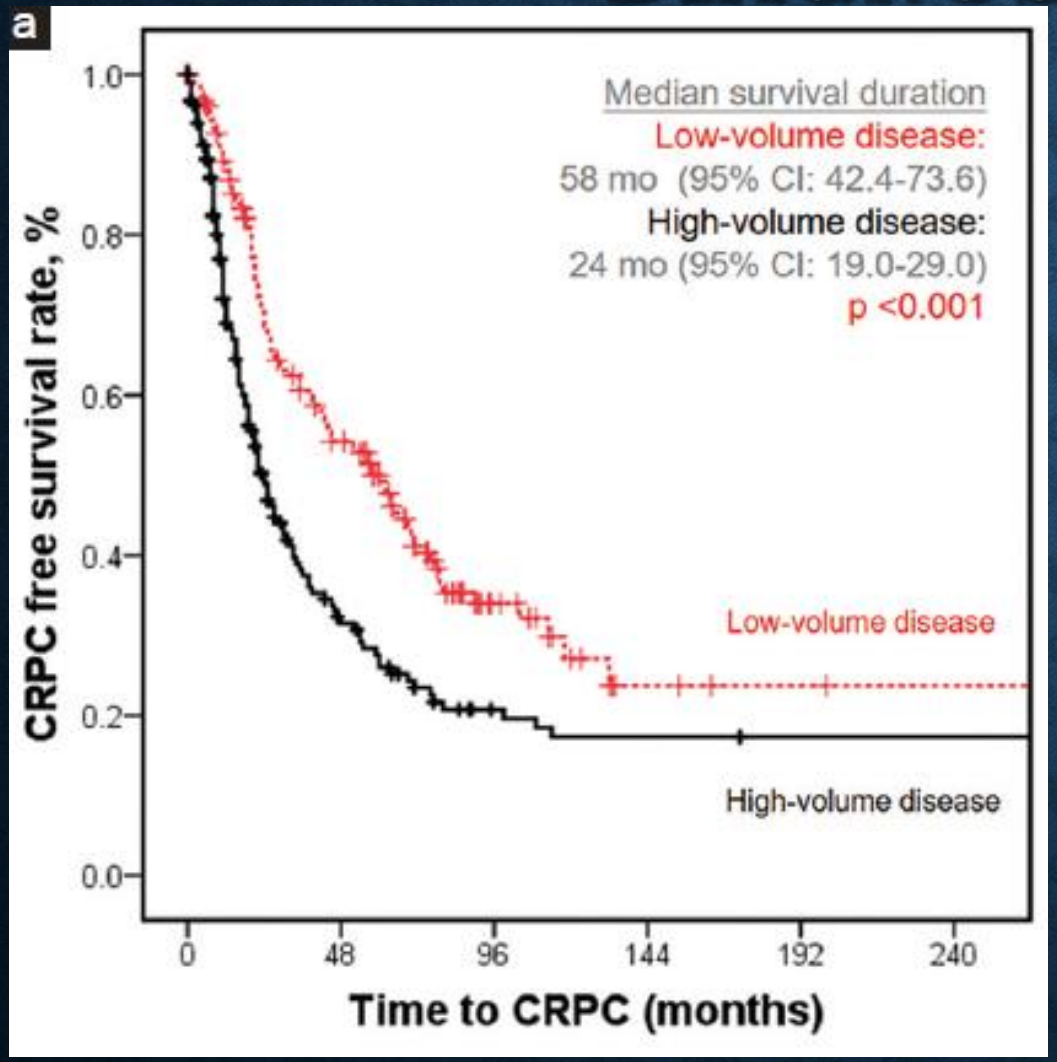
TAIWAN'S COHORT STUDY OF NEWLY DIAGNOSED MPC



* 1998-2012
* High volume disease: visceral meta,
and/or ≥4 bone lesions with ≥1 lesion beyond the vertebral bodies and pelvis

Urol Sci 2018;29:136

TAIWAN'S COHORT STUDY OF NEWLY DIAGNOSED MPC



267 patients (267/503= **53.1%**) progressed to mCRPC status.

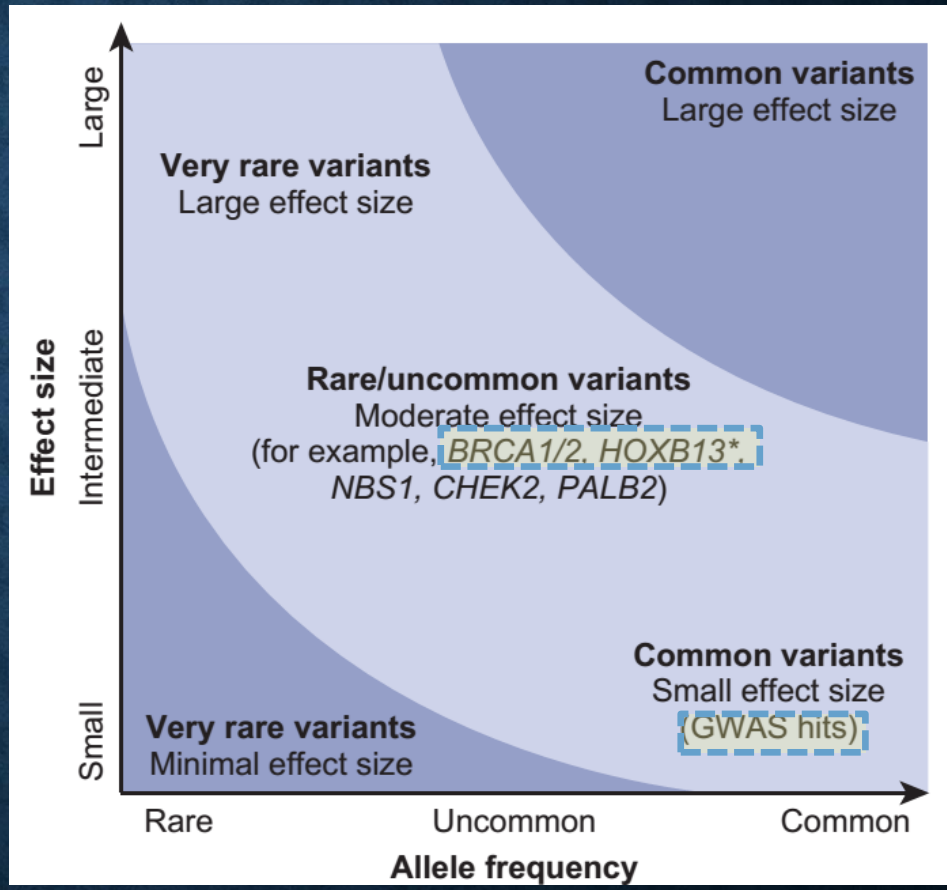
* 1998-2012
* High volume disease: visceral meta,
and/or ≥4 bone lesions with ≥1 lesion beyond the vertebral bodies and pelvis

Urol Sci 2018;29:136

RISK FACTORS OF PROSTATE CANCER: GENETICS

TABLE 107-2 Family History and Risk of Prostate Cancer

FAMILY HISTORY	RELATIVE RISK	95% CONFIDENCE INTERVAL
None	1	
Father affected	2.17	1.90-2.49
Brother affected	3.37	2.97-3.83
First-degree family member affected, age <65 yr at diagnosis	3.34	2.64-4.23
>2 first-degree relatives affected	5.08	3.31-7.79
Second-degree relative affected	1.68	1.07-2.64



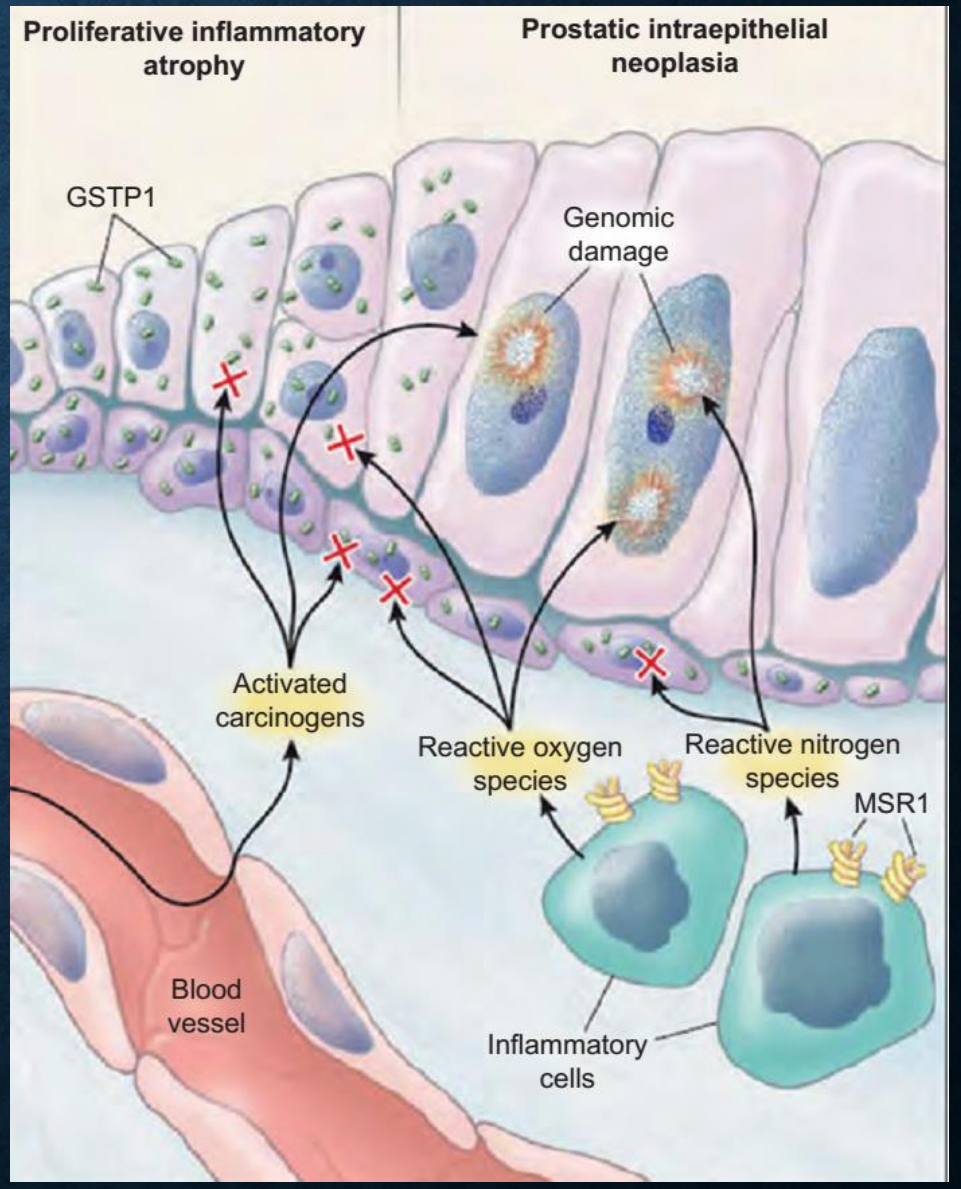
- Both **genetics** and **environment** are important in the origin and evolution of PC.

RISK FACTORS OF PROSTATE CANCER

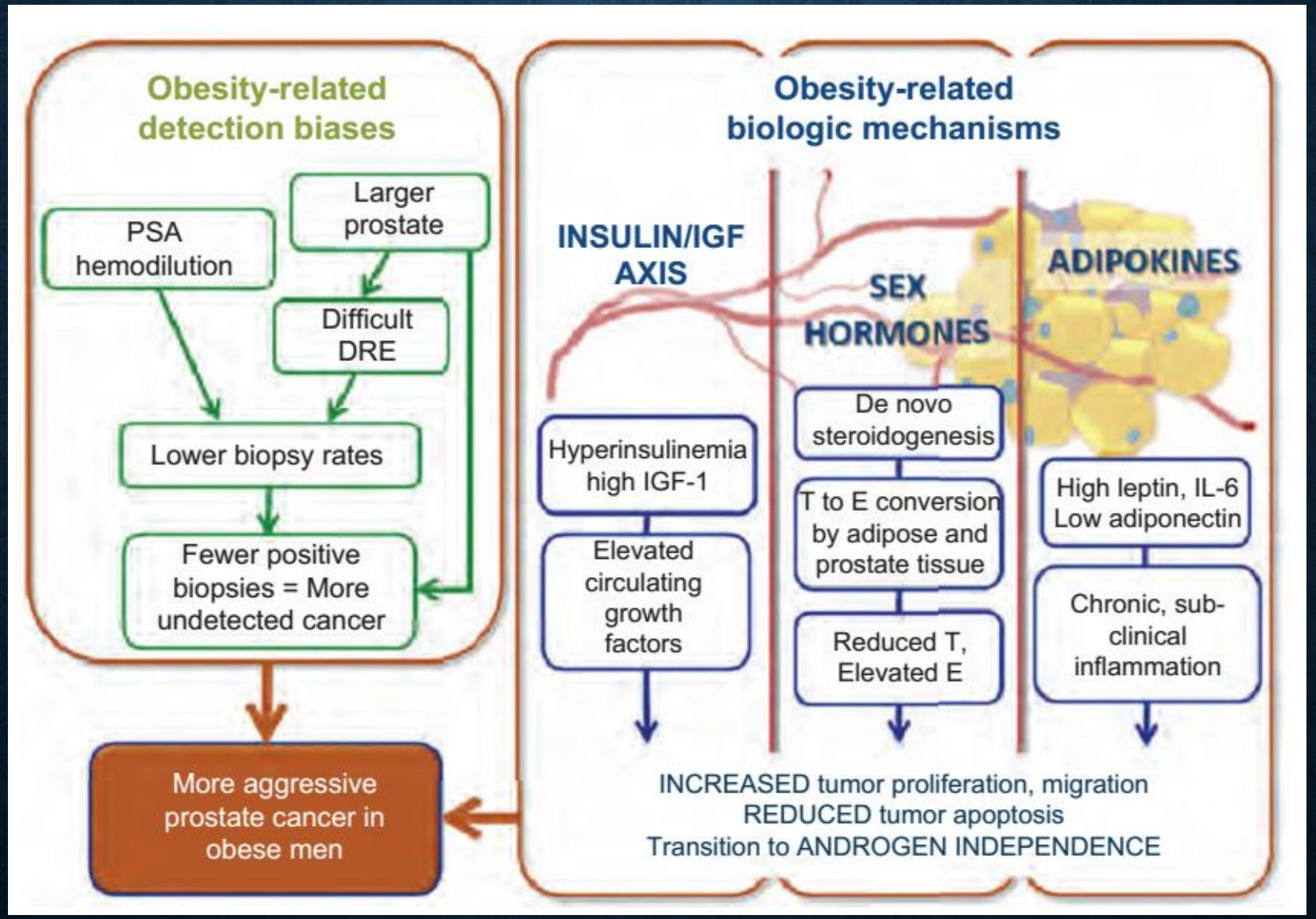
- **Chronic inflammation** leading to cellular hyperproliferation to replace damaged tissue contributes to the development of PC.

- **Smoking**: ↑ risk of disease recurrence and death resulting from PC

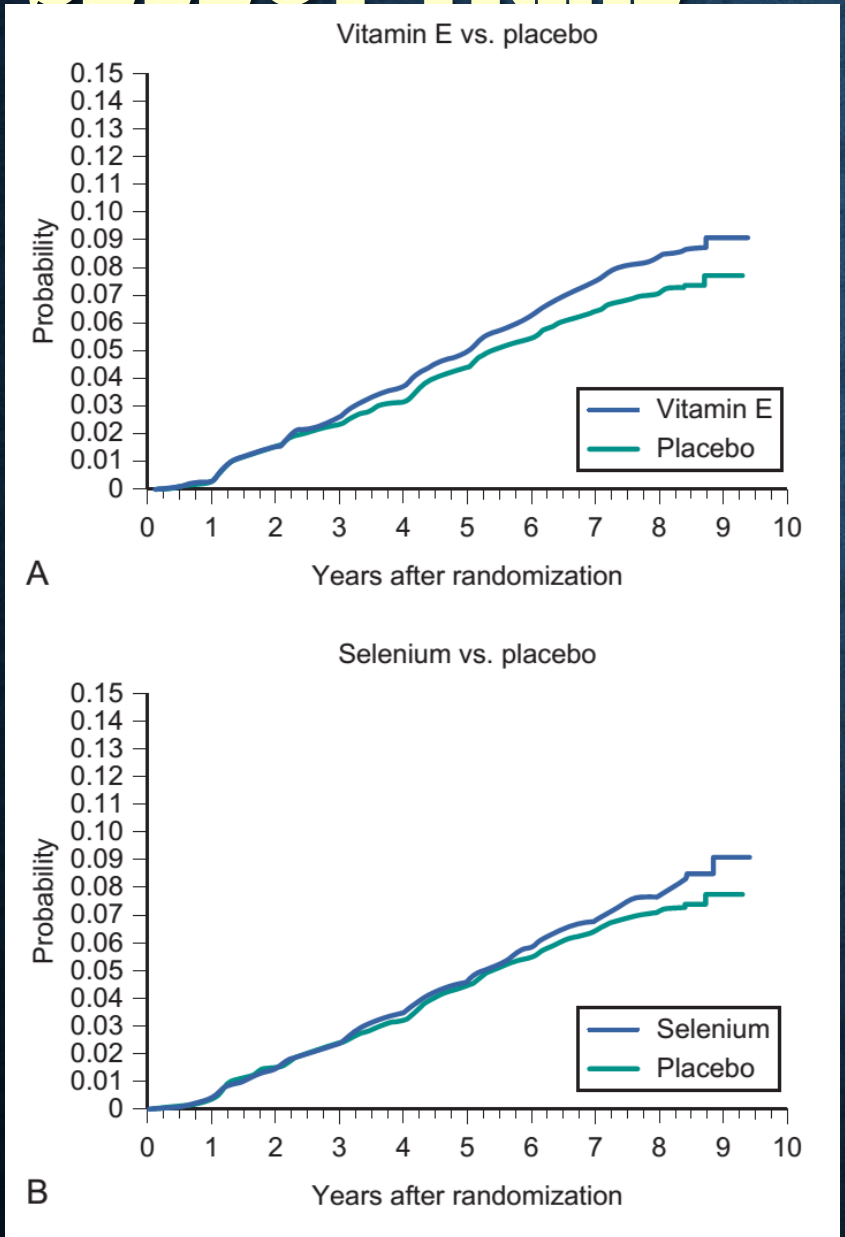
- **Diet:** Western diet
- **Obesity:** ↓ serum PSA, ↑ high-grade PC, ↑ treatment failure rates and ↑ disease-specific mortality.



COMPLEX INTERPLAY OF OBESITY AND PROSTATE CANCER



RISK FACTORS OF PROSTATE CANCER: SELECT TRIAL



The Selenium and Vitamin E Cancer Prevention Trial (SELECT)

- **Vit. E/ Selenium:**

NO prevention role in PC

- **Vit.E:**

increased risk of PC !

(HR 1.17)

CHEMOPREVENTION OF PROSTATE CANCER

- **PCPT (Prostate cancer prevention trial)**
  - 18882 men: ≥55y/o, normal DRE, PSA ≤ 3 ng/mL
  - random **Finasteride** VS Placebo x 7 years

  Results:
  - **25% reduction of PC** (Finasteride 18.4%, Placebo 24.4%)

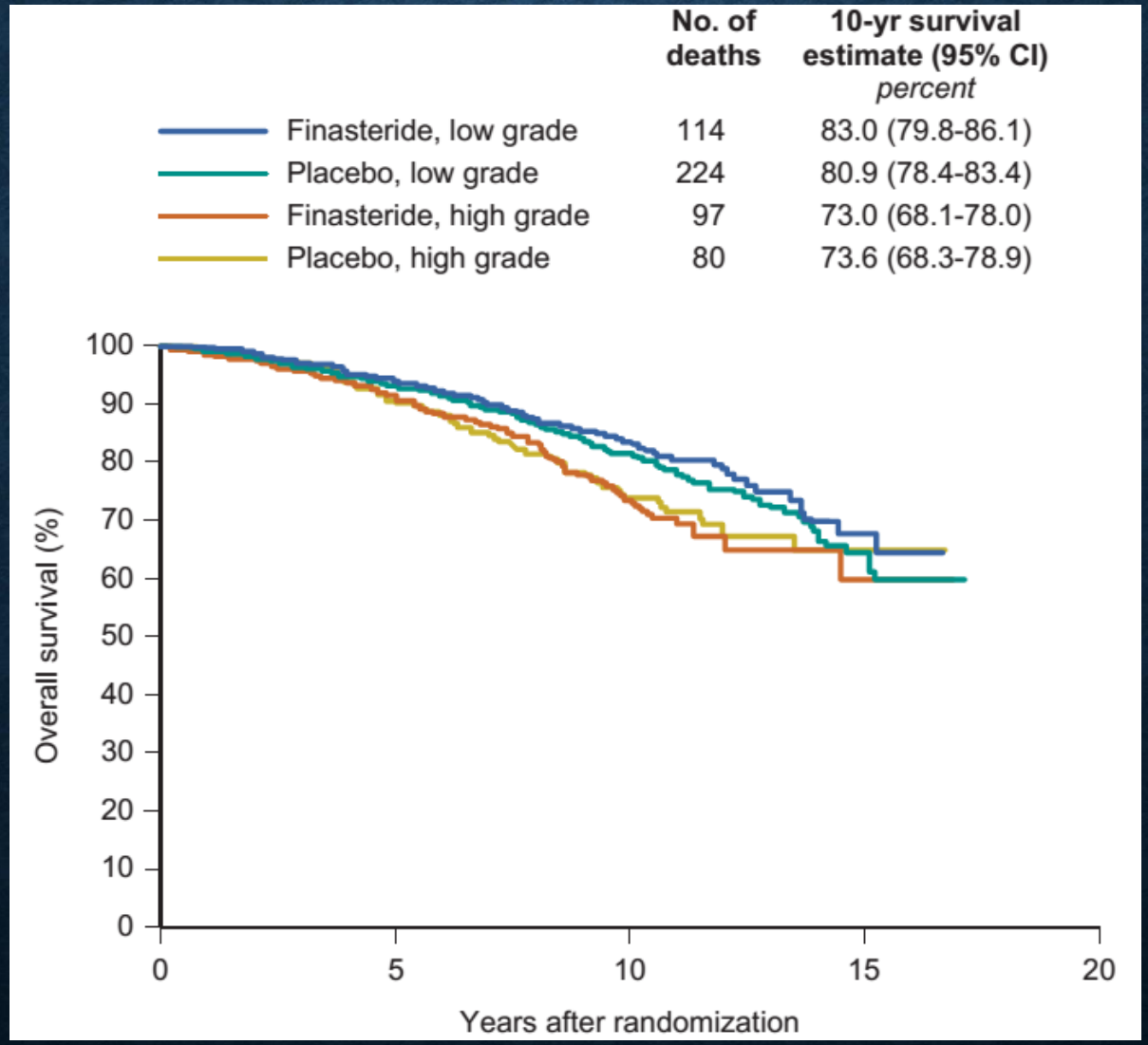
  → benefit across all groups as defined by age, ethnicity, family history, and PSA level at study entry (HR: 0.66 -0.81)
  - However,

  a significant **increase** in the prevalence of biopsy **Gleason score 8-10 cancers !** (Finasteride 12%, Placebo 5%)

- Similar results revealed in **REDUCE trial**

  (**Dutasteride**, PSA 3-10 ng/mL)

EFFECTS OF 5-ARI:
REDUCE THE RISK OF PC, BUT NOT AFFECT LONG-TERM SURVIVAL



TUMOR MARKER OF PROSTATE CANCER: PSA (MOST COMMON)

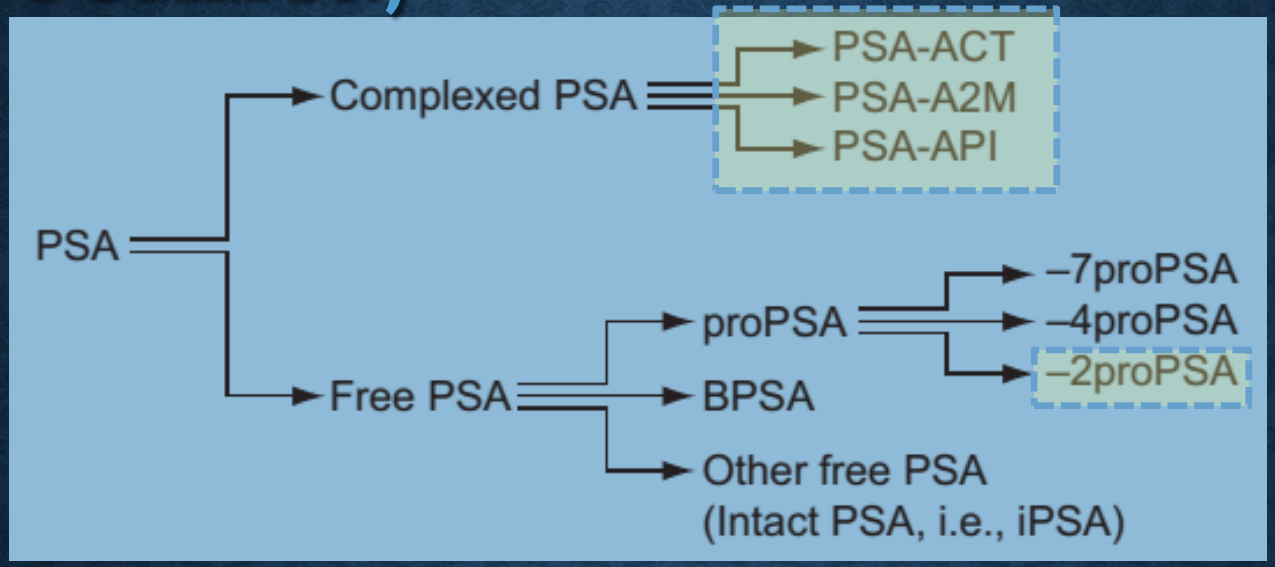


TABLE 108-1 Molecular Derivatives of Prostate-Specific Antigen

PSA TYPE	% IN SERUM
Complexed PSA	60-95
PSA-ACT	60-90
PSA-API	1-5
PSA-A2M	10-20
Free PSA	5-40

ACT, α_1-antichymotrypsin; API, α_1-protease inhibitor; A2M, α_2-macroglobulin; PSA, prostate-specific antigen.

DECREASED FPSA % IN PROSTATE CANCER

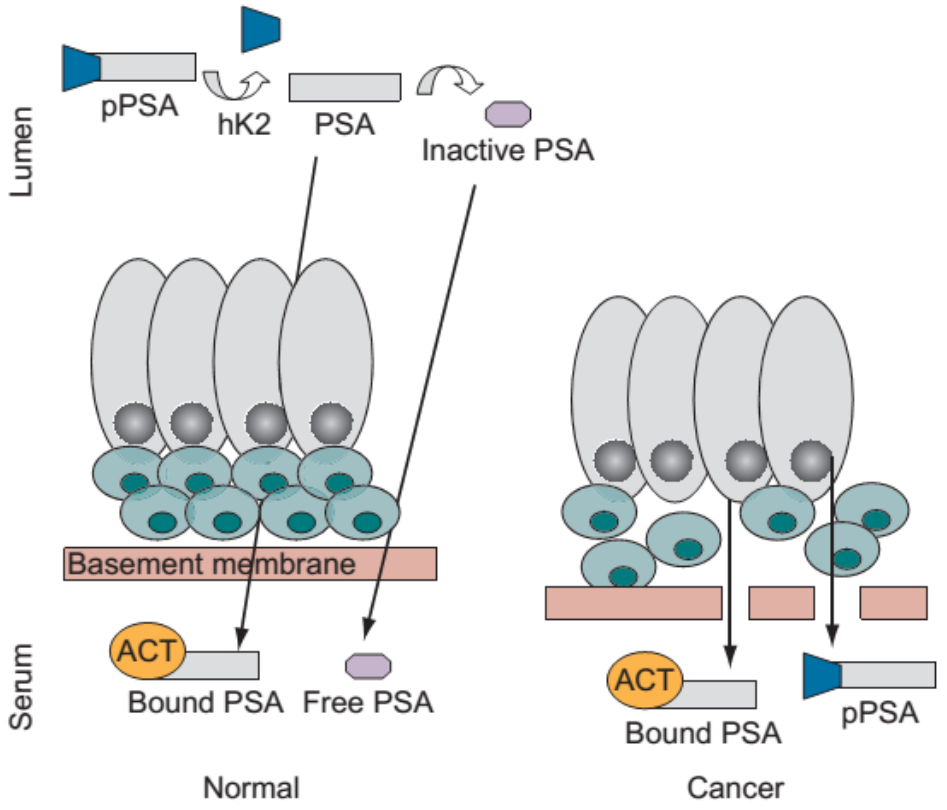


Figure 108-6. Prostate-specific antigen (PSA) synthesis in normal versus cancer tissue. ProPSA is secreted into the lumen, where the 7–amino acid leader sequence is cleaved by hK2 to yield active PSA. Some of the active PSA diffuses into the serum, where it is bound to proteases such as α_1-antichymotrypsin (ACT). The luminal active PSA undergoes proteolysis, and the resulting inactive PSA also may enter the circulation to circulate in the unbound or free state. In prostate cancer, loss of the tissue architecture may permit a relative increase in bound PSA and proPSA in serum.

PROSTATE HEALTH INDEX (PHI)

- A new formula that combines all 3 forms (**total PSA, free PSA and [-2] form of proPSA (p2PSA)**) into a single score

- Formula: **([-2]proPSA/free PSA) × √PSA**

- **For PSA 4-10,**
  - AUC: **PHI 0.698**, fPSA% (0.59-) 0.654, PSA 0.549
  - **FDA proven for: > 50 yrs men, PSA 4-10, DRE (-)**

Clinical Significance of “phi” score

phi RANGE*	PROBABILITY OF CANCER	95% CONFIDENCE INTERVAL
0–26.9	9.8%	5.2%–15.4%
27.0–35.9	16.8%	11.3%–22.2%
36.0–54.9	33.3%	26.8%–39.9%
55.0+	50.1%	39.8%–61.0%

Table. Probability of prostate cancer based on *phi* results.[1]

*The phi results are intended to be used as an aid in distinguishing prostate cancer from benign prostatic conditions in men 50 years of age and older with total PSA results in the 4–10 ng/mL range and negative digital rectal examination (DRE) findings.

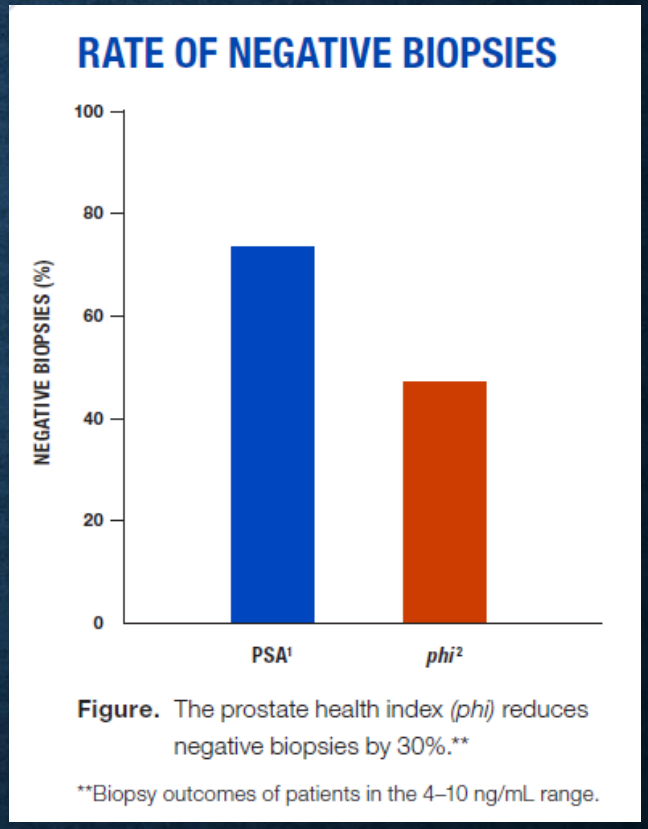


Figure. The prostate health index *(phi)* reduces negative biopsies by 30%.**

**Biopsy outcomes of patients in the 4–10 ng/mL range.

- Sensitivity of **90%** !
- ↓ **30%** unnecessary biopsy !

PROSTATE CANCER DETECTION RATE (BY DRE/ PSA)

TABLE 111-1 Prostate Cancer Detection as a Function of Serum Prostate-Specific Antigen Level and Digital Rectal Examination Findings in Contemporary Series

PSA LEVEL (ng/mL)	DRE FINDINGS*	CANCER DETECTION RATE (%)†	CANCER YIELD ON BIOPSY (%)‡	RATE OF HIGH-GRADE CANCER ON BIOPSY (%)§
0-1	–		8.8	0.9
1-2	–		17.0	2.0
0-2	–		12	1.4
		0.7	8	
2-4	–		15-25	5.2
		2	21	
4-10	+	11	17-32	4.1
		11-27	45-51	11.7
>10	–	41	43-65	19.4
	+	31-76	70-90	50.5
<4	–		15	2.3
	+	1-3	13-17	
>4	–	14	23-38	5.8
	+	14-38	55-63	20.6

Table 5.2.1: Risk of PCa in relation to low PSA values

PSA level (ng/mL)	Risk of PCa (%)	Risk of Gleason ≥ 7 PCa (%)
0.0-0.5	6.6	0.8
0.6-1.0	10.1	1.0
1.1-2.0	17.0	2.0
2.1-3.0	23.9	4.6
3.1-4.0	26.9	6.7

PROSTATE CANCER - SCREENING & EARLY DETECTION

- **Risk factors:**
  - **Genetics**: 1st degree relatives (father/ brother 2-3X)
  - Chronic inflammation, smoking, diet (Western diet), obesity
- **Symptoms:**
  - Early stage: Asymptomatic, or lower urinary tract symptoms (like BPH)
- **Screening**
  - > 50 y/o: **DRE/ PSA** annually
  - **DO NOT SCREEN: > 70 y/o or life expectancy < 10 years**
- **Survival of prostate cancer**
  - Local disease - Median survival > 5 years
  - Metastatic disease- Median survival 2-3 years (individuals may survive >10 years)

PROSTATE CANCER - DIAGNOSIS

- **Diagnosis/ Screening: DRE + PSA**
  - DRE (digital rectal examination): hard nodule ➔ biopsy
  - **PSA: many confounding factors** (age, prostate size, inflammation, ejaculation, drugs)

    處理原則 (PSA threshold changes with age/ different risk groups)

    * < 4 ng/mL: 可視為無異

    * 4-10 ng/mL: gray zone

      ➔ 可參考PSA velocity (>0.75 /year), PSA density, free PSA % 決定切片與否

    * >10 ng/mL: 建議切片

  - **Prostate MRI: increasing role before prostate biopsy**

  - **BIOPSY: 唯一確診方式**
- Work-up: MRI/ bone scan (localized or metastatic)

PATHOLOGY OF PROSTATIC NEOPLASM

- Prostatic intraepithelial neoplasia (PIN)
  - Low grade (LGPIN): no clinical significance
  - **High grade (HGPIN):**
    - 1 core of Bx: unnecessary repeat Bx within 1yr
    - **≥ 2 cores of Bx:** repeat Bx within 1yr

- **Atypical** cell/ diagnosis of Bx: **REPEAT Bx !**
  (Cancer risk 40%!)

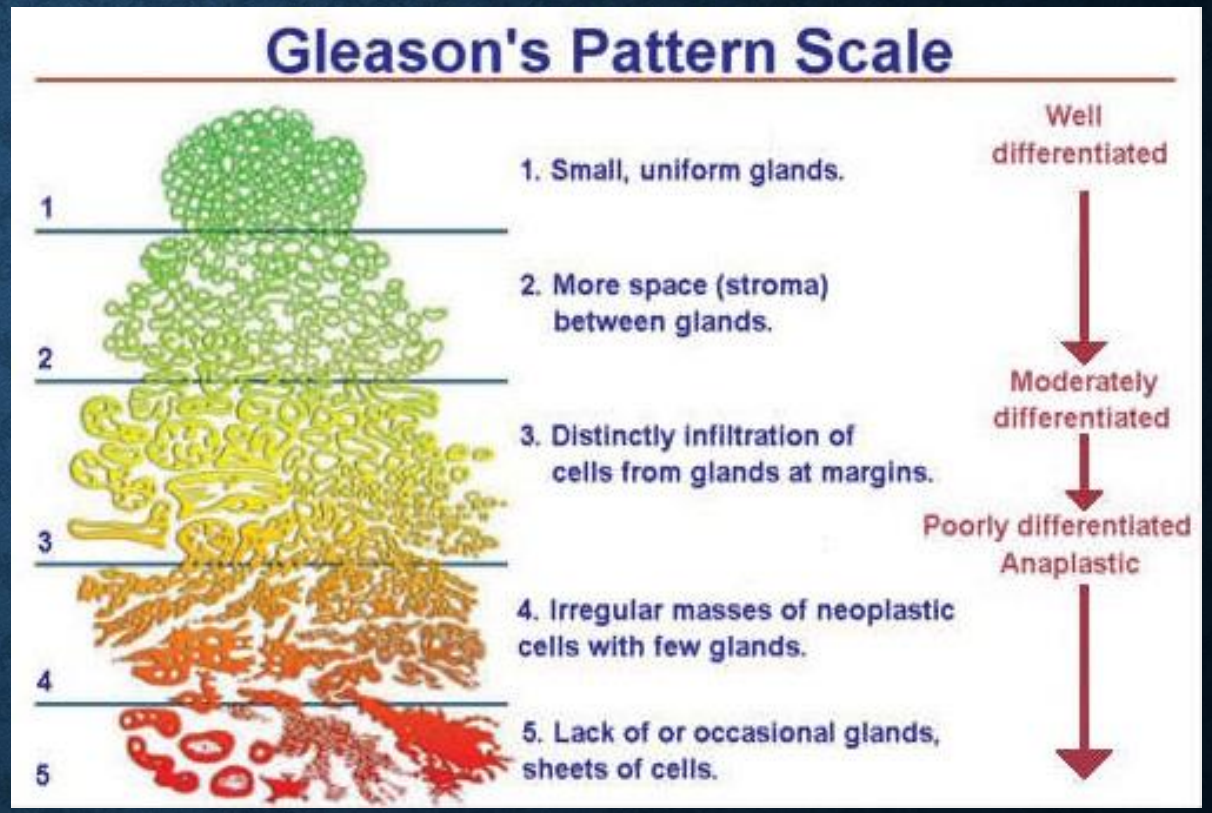
- Adenocarcinoma

PROSTATE CANCER - PATHOLOGY

- **Adenocarcinoma**
- **Gleason's score:**

最大面積分數 + 次大面積分數

- **Not recommended that G's 2 to 4** be assigned for adenocarcinoma of the prostate on needle biopsy
  - Most upgrading after review by expert
  - Poor reproducibility in diagnosis
  - Not favorable outcomes after RP
- **Favorable outcomes:** from Gr. I (most favorable) to Gr. V (least favorable)



Gleason score less than or equal to 6: Grade Group I
Gleason score 3 + 4 = 7: Grade Group II
Gleason score 4 + 3 = 7: Grade Group III
Gleason score 8: Grade Group IV
Gleason score 9 to 10: Grade Group V

American Joint Committee on Cancer (AJCC)
TNM Staging System For Prostate Cancer (8th ed., 2017)
***Table 1.* Definitions for T, N, M**
Clinical T (cT)

T	Primary Tumor
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Clinically inapparent tumor that is not palpable
T1a	Tumor incidental histologic finding in 5% or less of tissue resected
T1b	Tumor incidental histologic finding in more than 5% of tissue resected
T1c	Tumor identified by needle biopsy found in one or both sides, but not palpable
T2	Tumor is palpable and confined within prostate
T2a	Tumor involves one-half of one side or less
T2b	Tumor involves more than one-half of one side but not both sides
T2c	Tumor involves both sides
T3	Extraprostatic tumor that is not fixed or does not invade adjacent structures
T3a	Extraprostatic 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.

Pathological T (pT)

T	Primary Tumor
T2	Organ confined
T3	Extraprostatic extension
T3a	Extraprostatic extension (unilateral or bilateral) or microscopic invasion of bladder neck
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

Note: There is no pathological T1 classification.
Note: Positive surgical margin should be indicated by an R1 descriptor, indicating residual microscopic disease.

N	Regional Lymph Nodes
NX	Regional lymph nodes cannot be assessed
N0	No positive regional nodes
N1	Metastases in regional node(s)

M	Distant Metastasis
M0	No distant metastasis
M1	Distant metastasis
M1a	Nonregional lymph node(s)
M1b	Bone(s)
M1c	Other site(s) with or without bone disease

Note: When more than one site of metastasis is present, the most advanced category is used. M1c is most advanced.

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2021
Prostate Cancer

Adenocarcinoma, SqCC, Neuroendocrine carcinoma, sarcoma UC

Table 2. AJCC Prognostic Groups

Group	T	N	M	PSA (ng/mL)	Grade Group
Stage I	cT1a-c	N0	M0	PSA <10	1
	cT2a	N0	M0	PSA <10	1
	pT2	N0	M0	PSA <10	1
Stage IIA	cT1a-c	N0	M0	PSA ≥10 <20	1
	cT2a	N0	M0	PSA ≥10 <20	1
	pT2	N0	M0	PSA ≥10 <20	1
	cT2b	N0	M0	PSA <20	1
	cT2c	N0	M0	PSA <20	1
Stage IIB	T1-2	N0	M0	PSA <20	2
Stage IIC	T1-2	N0	M0	PSA <20	3
	T1-2	N0	M0	PSA <20	4
Stage IIIA	T1-2	N0	M0	PSA ≥20	1-4
Stage IIIB	T3-4	N0	M0	Any PSA	1-4
Stage IIIC	Any T	N0	M0	Any PSA	5
Stage IVA	Any T	N1	M0	Any PSA	Any
Stage IVB	Any T	Any N	M1	Any PSA	Any

Note: When either PSA or Grade Group is not available, grouping should be determined by T category and/or either PSA or Grade Group as available.

Histopathologic Type

This classification applies to adenocarcinomas and squamous carcinomas, but not to sarcoma or transitional cell (urothelial) carcinoma of the prostate. Adjectives used to describe histologic variants of adenocarcinomas of prostate include mucinous, signet ring cell, ductal, and neuroendocrine, including small cell carcinoma. There should be histologic confirmation of the disease.

Definition of Histologic Grade Group (G)

Recently, the Gleason system has been compressed into so-called Grade Groups.

Grade Group	Gleason Score	Gleason Pattern
1	≤6	≤3+3
2	7	3+4
3	7	4+3
4	8	4+4, 3+5, 5+3
5	9 or 10	4+5, 5+4, 5+5

Initial Risk Stratification for Clinically Localized Prostate Cancer

Risk Group	Clinical/Pathologic Features			Imaging[f,g]	Germline Testing[c]	Molecular/ Biomarker Analysis of Tumor[c]
Very low[d]	Has all of the following: • T1c • Grade Group 1 • PSA <10 ng/mL • Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core[e] • PSA density <0.15 ng/mL/g			• Consider confirmatory prostate biopsy ± mpMRI to establish candidacy for active surveillance	Recommended if family history positive See PROS-1	Not indicated
Low[d]	Has all of the following but does not qualify for very low risk: • T1–T2a • Grade Group 1 • PSA <10 ng/mL			• Consider confirmatory prostate biopsy ± mpMRI to establish candidacy for active surveillance	Recommended if family history positive See PROS-1	Consider if life expectancy ≥10 y[j]
Intermediate[d]	Has all of the following: • No high-risk group features • No very-high-risk group features • Has one or more intermediate risk factors (IRF): ▸ T2b–T2c ▸ Grade Group 2 or 3 ▸ PSA 10–20 ng/mL	Favorable intermediate	Has all of the following: • 1 IRF • Grade Group 1 or 2 • <50% biopsy cores positive[e]	• Consider confirmatory prostate biopsy ± mpMRI to establish candidacy for active surveillance • Bone imaging[h]: not recommended for staging • Pelvic ± abdominal imaging[i]: recommended if nomogram predicts >10% probability of pelvic lymph node involvement • If regional or distant metastases are found, see PROS-8	Recommended if family history positive or intraductal/cribriform histology See PROS-1	Consider if life expectancy ≥10 y[j]
		Unfavorable intermediate	Has one or more of the following: • 2 or 3 IRFs • Grade Group 3 • ≥ 50% biopsy cores positive[e]	• Bone imaging[h]: recommended if T2 and PSA >10 ng/mL • Pelvic ± abdominal imaging[i]: recommended if nomogram predicts >10% probability of pelvic lymph node involvement • If regional or distant metastases are found, see PROS-8	Recommended if family history positive or intraductal/cribriform histology See PROS-1	Consider if life expectancy ≥10 y[j]
High	Has no very-high-risk features and has exactly one high-risk feature: • T3a OR • Grade Group 4 or Grade Group 5 OR • PSA >20 ng/mL			• Bone imaging[h]: recommended • Pelvic ± abdominal imaging[i]: recommended • If regional or distant metastases are found, see PROS-8	Recommended	Consider if life expectancy ≥10 y[j]
Very high	Has at least one of the following: • T3b–T4 • Primary Gleason pattern 5 • 2 or 3 high-risk features • >4 cores with Grade Group 4 or 5			• Bone imaging[h]: recommended • Pelvic ± abdominal imaging[i]: recommended • If regional or distant metastases are found, see PROS-8	Recommended	Not routinely recommended

PROSTATE CANCER - PRINCIPLES OF TREATMENT

- Considering:
  - **Risk group stratification (clinical stage, PSA, pathology features)**
  - **Life expectency**

- **Localized prostate cancer (T1-2, within prostatic capsule):**
  - **Observation**: in low/ favorable intermediate risk patients with life expectancy < 10 yrs
  - **Active surveillance**: in low/ favorable intermediate risk patients with life expectancy > 10 yrs
  - **Radical prostatectomy**
  - **Radiotherapy (RT) +/- ADT** (androgen deprivation therapy)

- **Locally advanced prostate cancer (T3-4)**
  - **Radical prostatectomy + pelvic LN dissection**
  - **RT + ADT**

PROSTATE CANCER - PRINCIPLES OF TREATMENT

- **Regional risk group prostate cancer (any T, N1, M0)**
  - **RT + ADT**
  - If life < 5yr and asymptomatic: OBS or ADT

- **Metastatic prostate cancer**
  - **Systemic therapy: ADT (androgen deprivation therapy)**
  - **ADT + secondary hormone therapy** (abiraterone / in high risk, enzalutamide, apalutamide)
  - **ADT + chemotherapy** (Docetaxel) in high volume patients
  - **ADT + RT** in low volume patients

  - **Castration resistance prostate cancer**

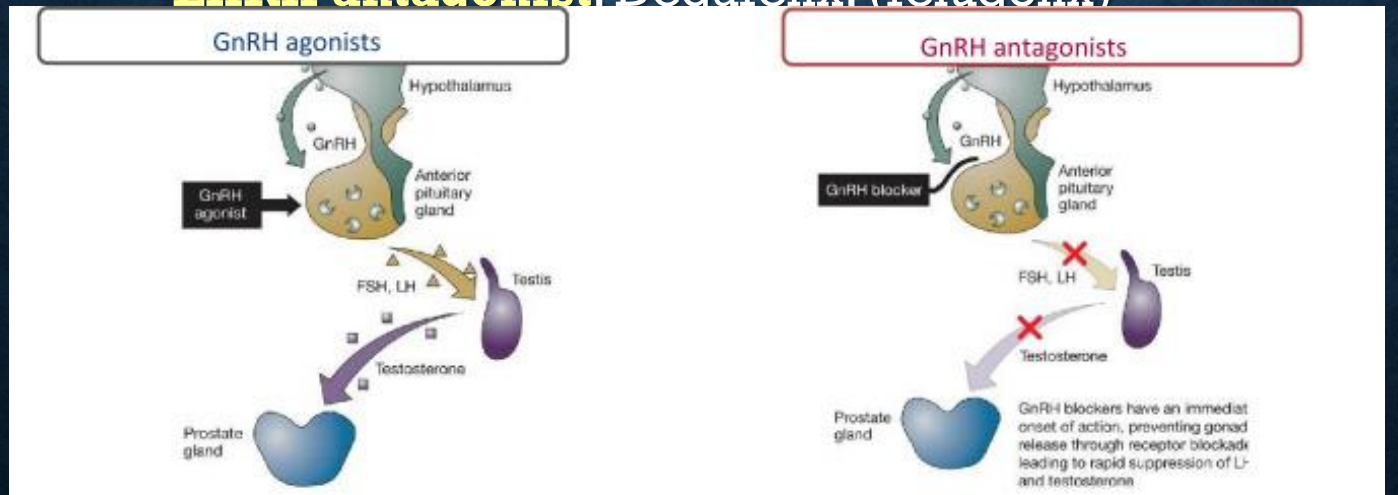
  →**ADT + secondary hormone therapy** or

  ADT + chemotherapy

ANDROGEN DEPRIVATION THERAPY (ADT)

- **Goals: castration** (testosterone < 50ng/dL) with adequate tumor control

- Surgical castration: **orchiectomy**
- Medical castration:
  - **LHRH agonist**: Leuprolide, Goserelin, Triptorelin
  - **LHRH antagonist**: Degarelix, (relugolix)



- Surge in FSH, LH and testosterone before suppression
- Microsurges in LH and testosterone on repeat injection
- FSH suppression, but not maintained long term

- Immediate suppression of FSH, LH and testosterone
- No microsurges
- Prolonged suppression of FSH, LH and testosterone

ACTIVE SURVEILLANCE VS OBSERVATION

- Active surveillance (AS)
  - **Actively** monitor the course of disease,

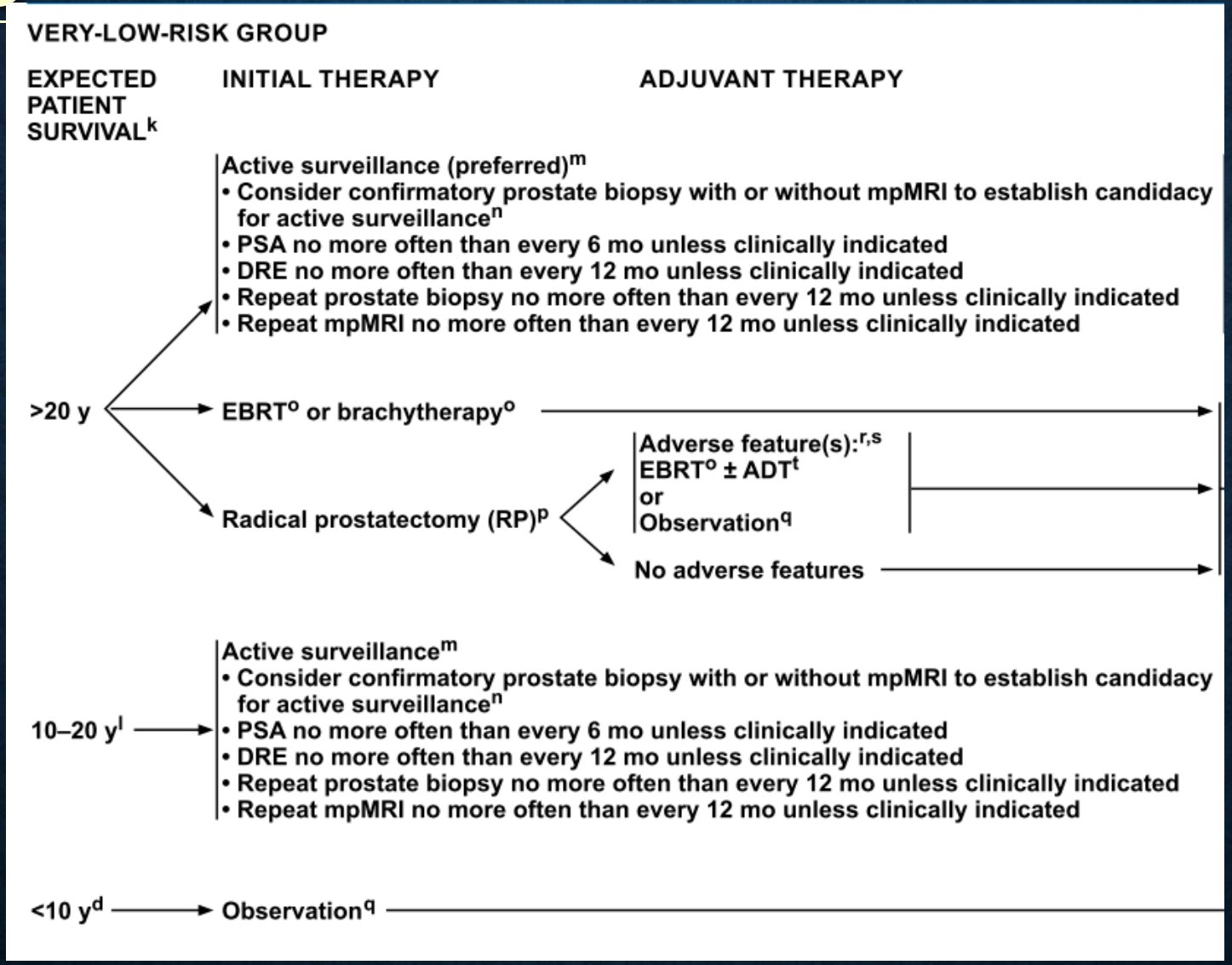
  with the expectation to deliver curative therapy if the cancer progresses

- Observation (OBS)
  - Monitor the clinical course,

  with the expectation to deliver palliative therapy for development of symptoms or change in exam or PSA

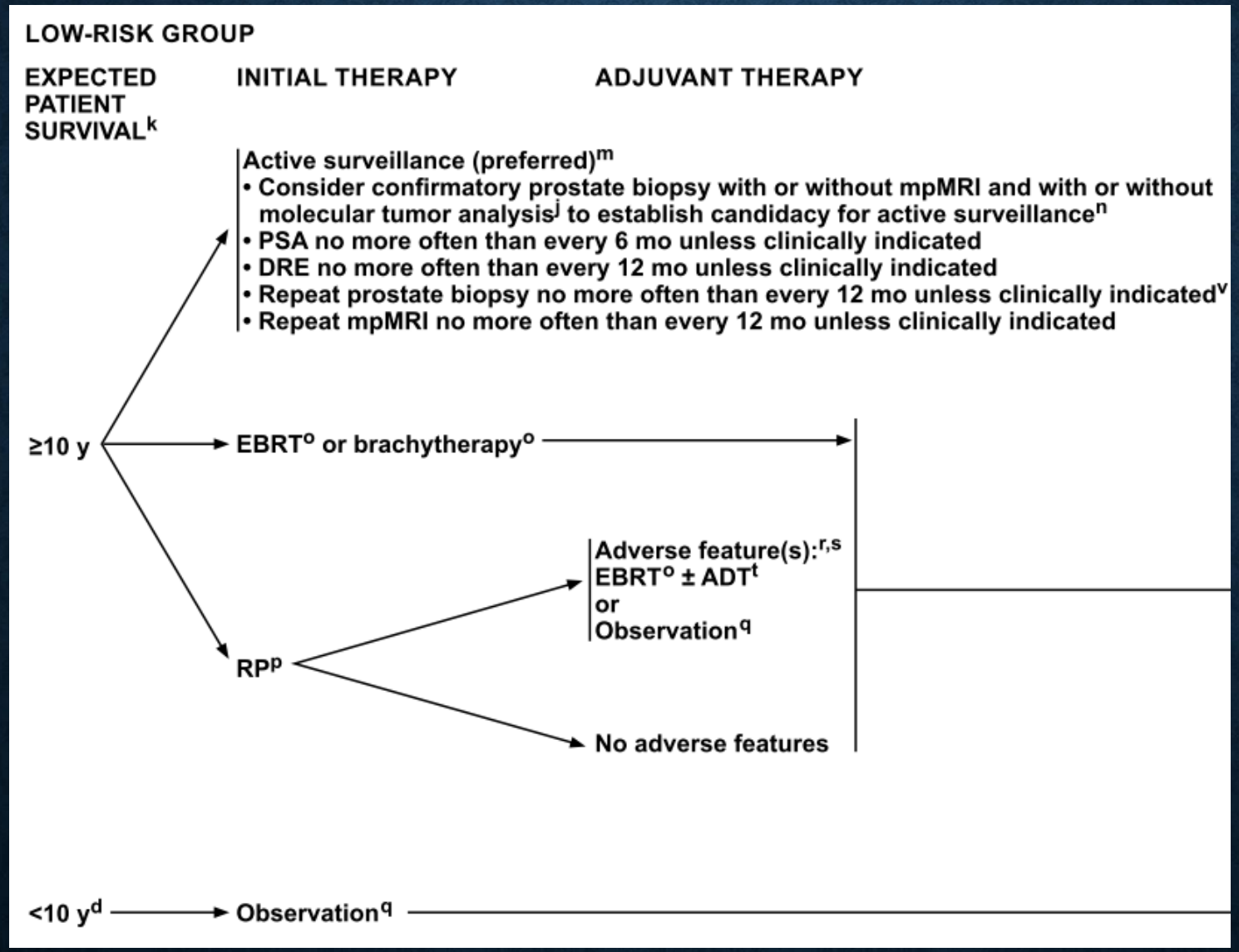
  - **Goal: maintain QoL** by avoiding non-curative treatment
  - **Advantage: avoidance of AE** of unnecessary treatments

MANAGEMENT OF VERY LOW RISK PC



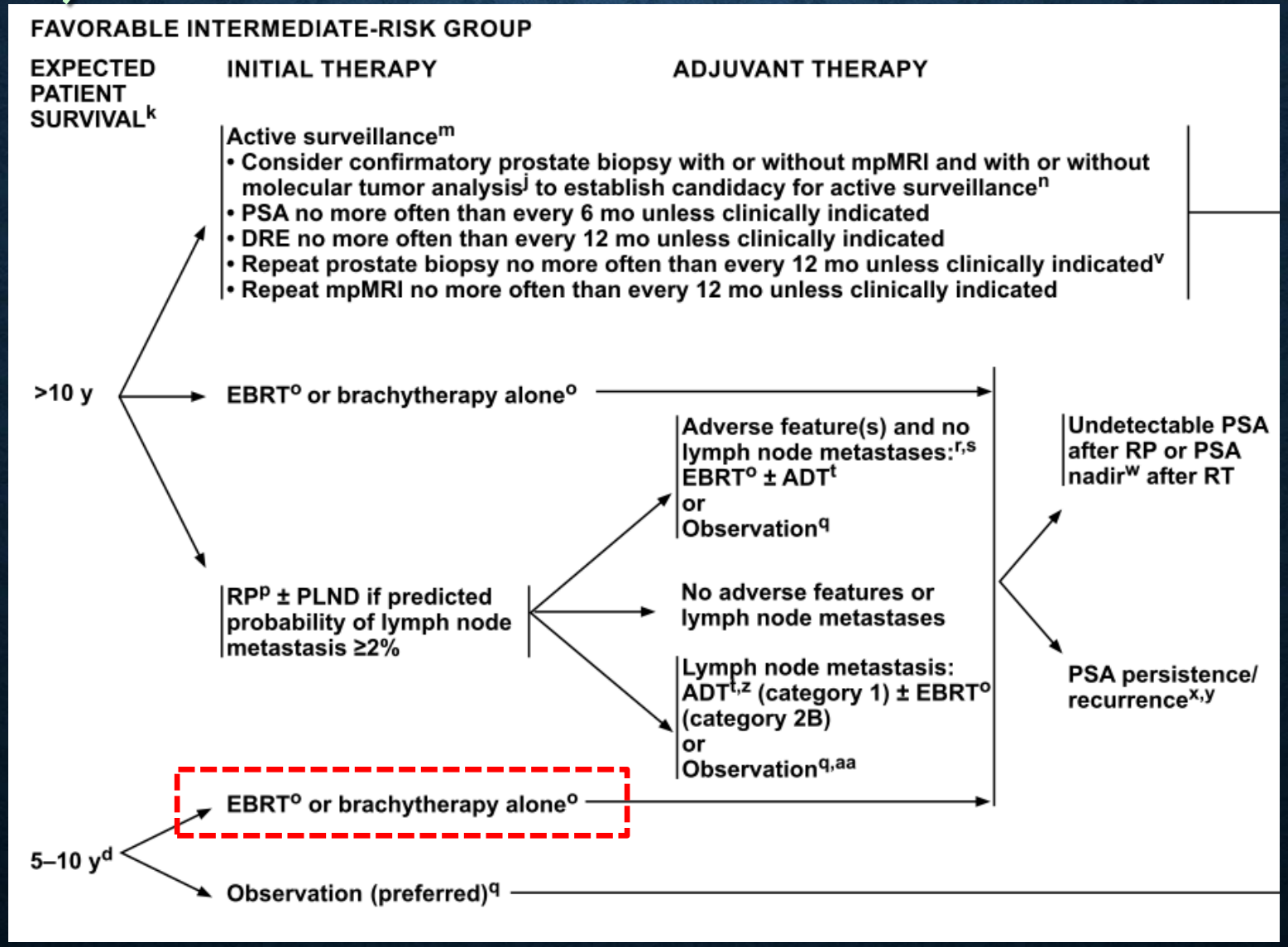
(in addition to **OP/ RT**, increasing roles of **AS** & **OBS**)

MANAGEMENT OF LOW RISK PC

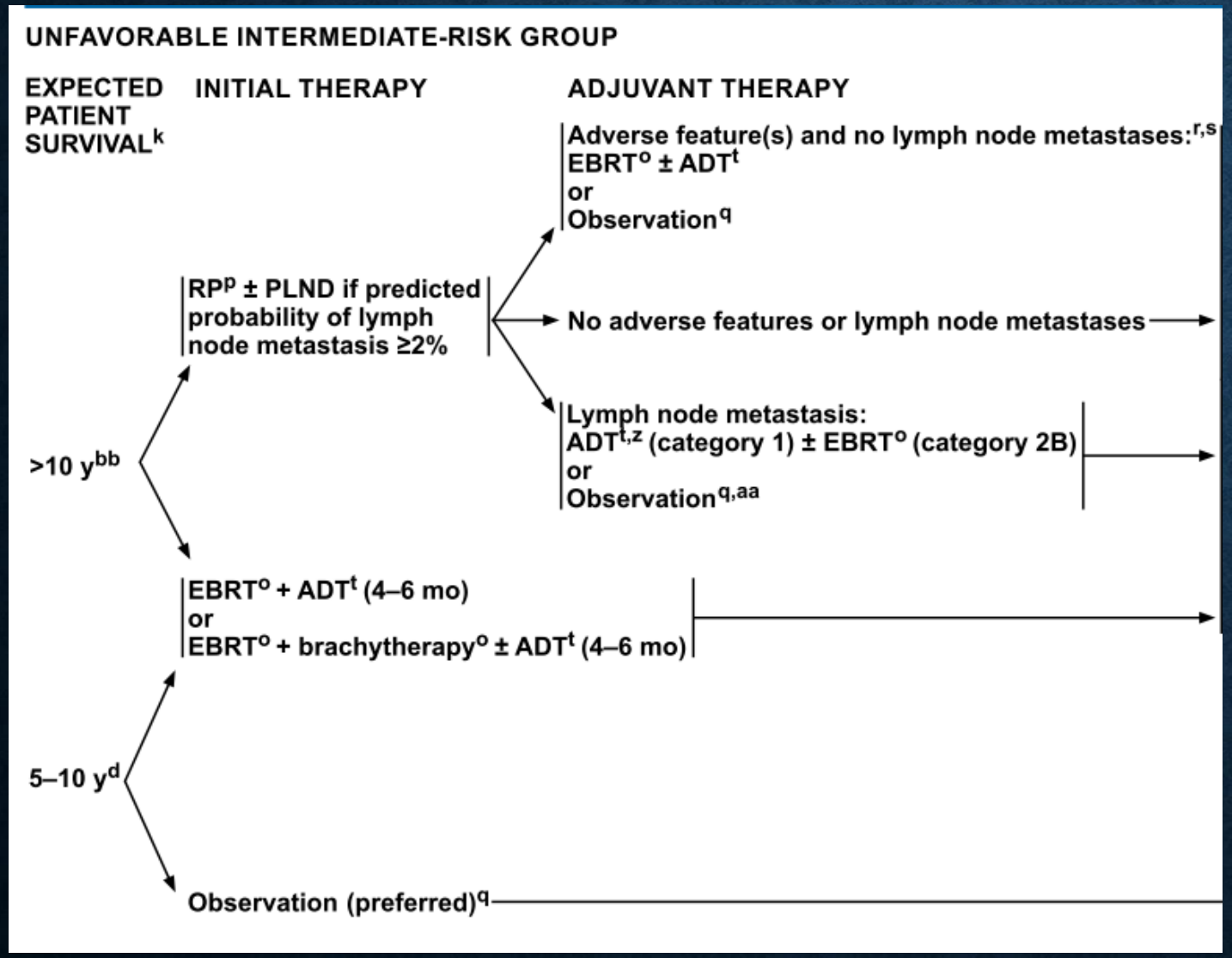


(in addition to **OP/ RT**, increasing roles of **AS** & **OBS**)

MANAGEMENT OF FAVORABLE INTERMEDIATE RISK PC (ALMOST = LOW RISK PC)

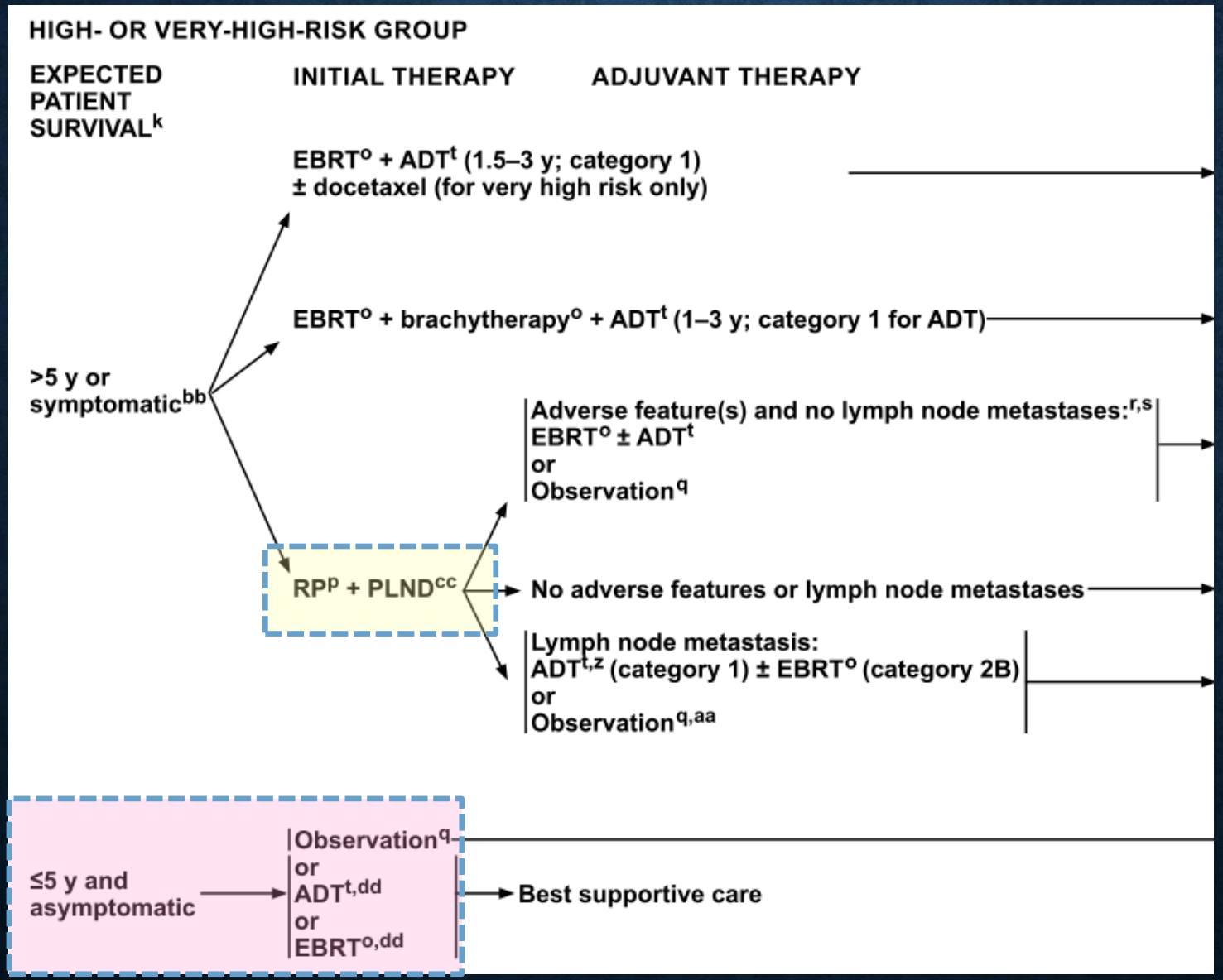


MANAGEMENT OF UNFAVORABLE INTERMEDIATE RISK PC

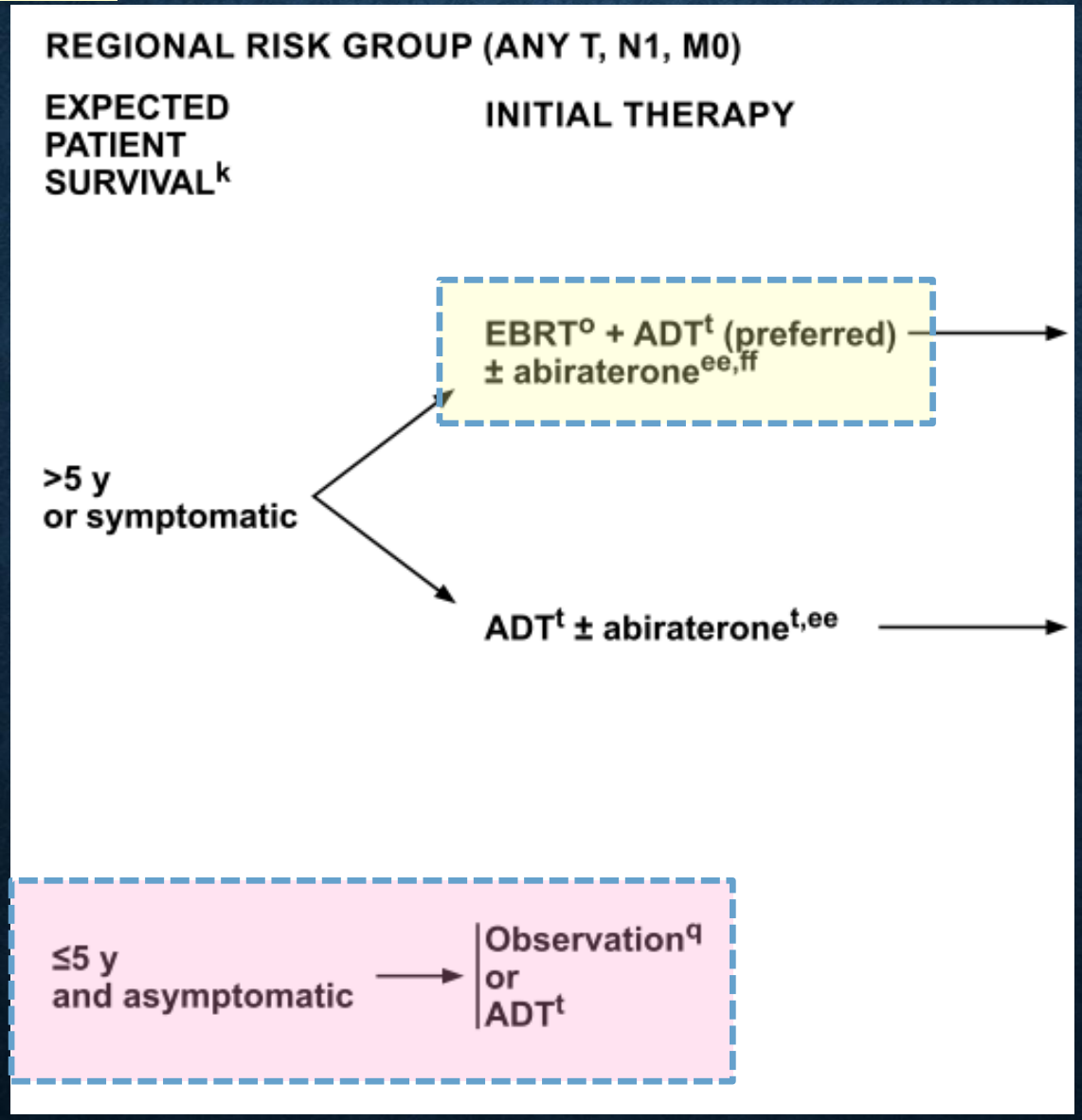


(Aggressive : OP/ RT+ ADT [4-6mo]; **↓roles of AS & OBS)**

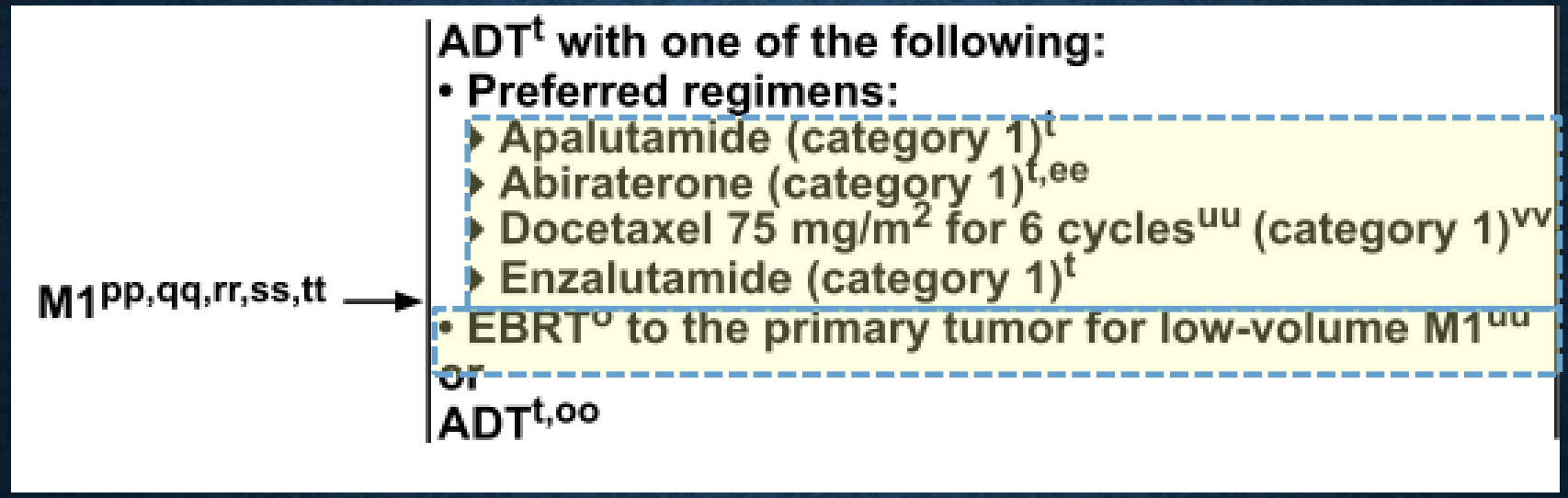
MANAGEMENT OF HIGH OR VERY HIGH RISK PC



MANAGEMENT OF REGIONAL (LN) RISK PC



MANAGEMENT OF METASTATIC PC (MCSPC)



* LOW VOLUME DISEASE: LESS CERTAIN BENEFITS FROM EARLY C/T+ ADT (HIGH VOLUME: VISCERAL METASTASIS AND/ OR ≥4 BONE META WITH ≥ 1 BEYOND PELVIS VERTEBRAL COLUMN)

Reported RCTs in mHSPC: High-Volume/High-Risk Disease

Trial[1]	Comparator Arm	Control Arm	N	HR for PFS (or Other Endpoint)	HR for OS
Docetaxel					
▪ CHAARTED[2]	ADT + Doc	ADT	513	0.58 (time to CRPC)	0.63
▪ GETUG-15[3]	ADT + Doc	ADT	183	NA	0.78
▪ STAMPEDE Arm C[4]	ADT + Doc	ADT	148	NA	0.81
AR Pathway Inhibitors					
▪ LATITUDE[5]	ADT + ABI + Pred	ADT	955	NA	0.62
▪ STAMPEDE Arm G[6]	ADT + ABI + Pred	ADT	473	0.31 (FFS)	0.54
▪ ENZAMET[7]	ADT + ENZA (± Doc)	ADT + NSAA (± Doc)	588	0.45	0.80
▪ ARCHES[8]	ADT + ENZA*	ADT*	727	0.43 (rPFS)	TBD
▪ TITAN[9]	ADT + APA*	ADT*	660	0.53	0.68
RT					
▪ STAMPEDE Arm H[10]	ADT + RT to prostate	ADT (+ DOC possible)	1120	NA	1.07
▪ HORRAD[11]	ADT + RT to prostate	ADT	272	NA	1.06

*Prior DOC allowed.

1. VanderWeele. JCO. 2019;37:2961. 2. Kyriakopoulos. JCO. 2018;36:1080. 3. Gravis. Eur Urol. 2016;70:256. 4. Clark. Ann Oncol. 2019;30:1992. 5. Fizazi. Lancet Oncol. 2019;20:686. 6. Hoyle. Eur Urol. 2019;76:719. 7. Davis. NEJM. 2019;381:121. 8. Armstrong. JCO. 2019;37:2974. 9. Chi. NEJM. 2019;381:13. 10. Parker. Lancet. 2018;392:2353. 11. Boevé. Eur Urol. 2019;75:410.

Any Question?