

# Hormonotherapie in de oncologie

Impact van hormonale therapie in de oncologie bij de  
behandeling van het prostaatcarcinoom:  
indicaties, voordelen & nadelen

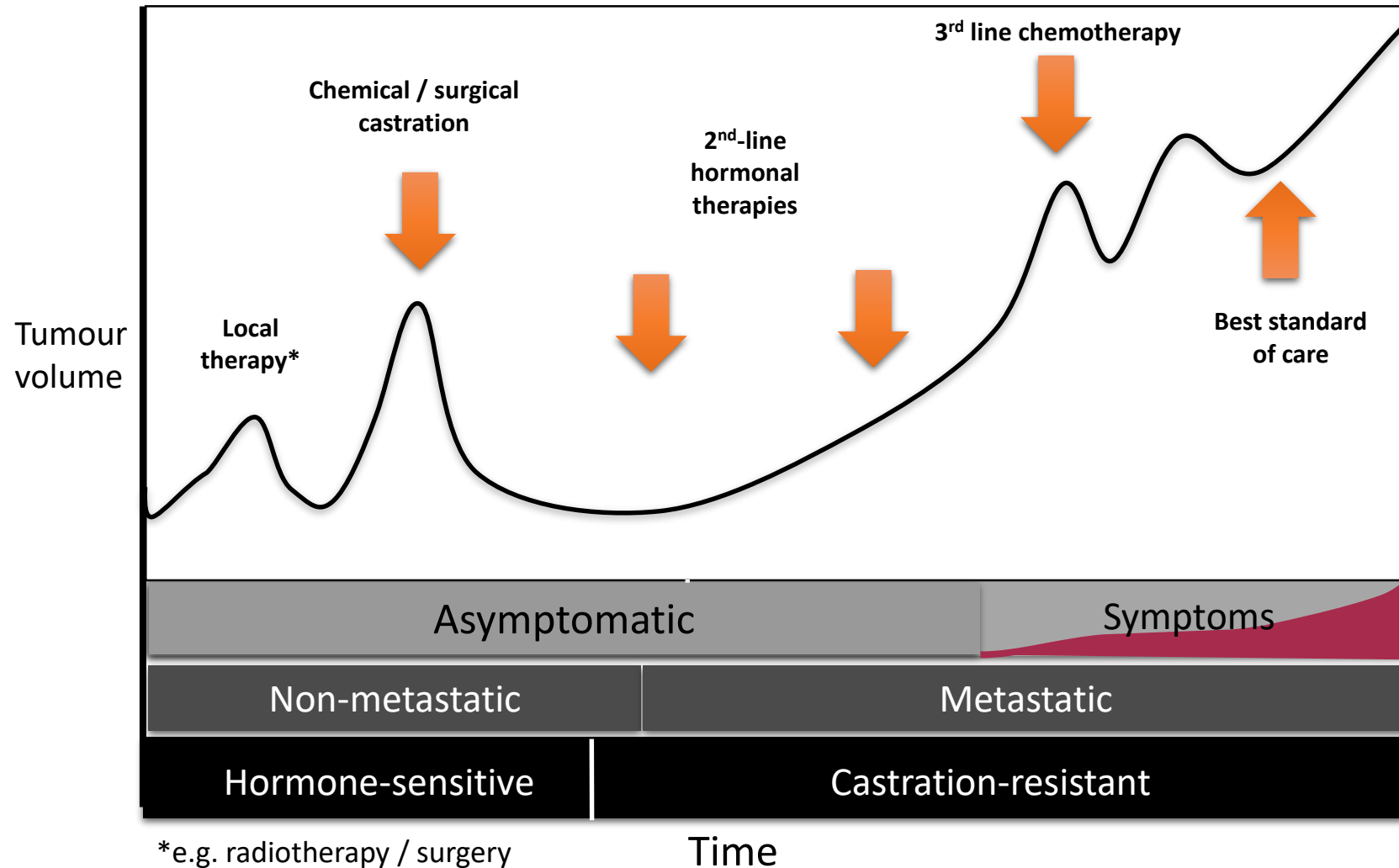
Prof. Valérie Fonteyne  
Radiotherapie-oncologie UZ Gent

Alumni avondcolloquia

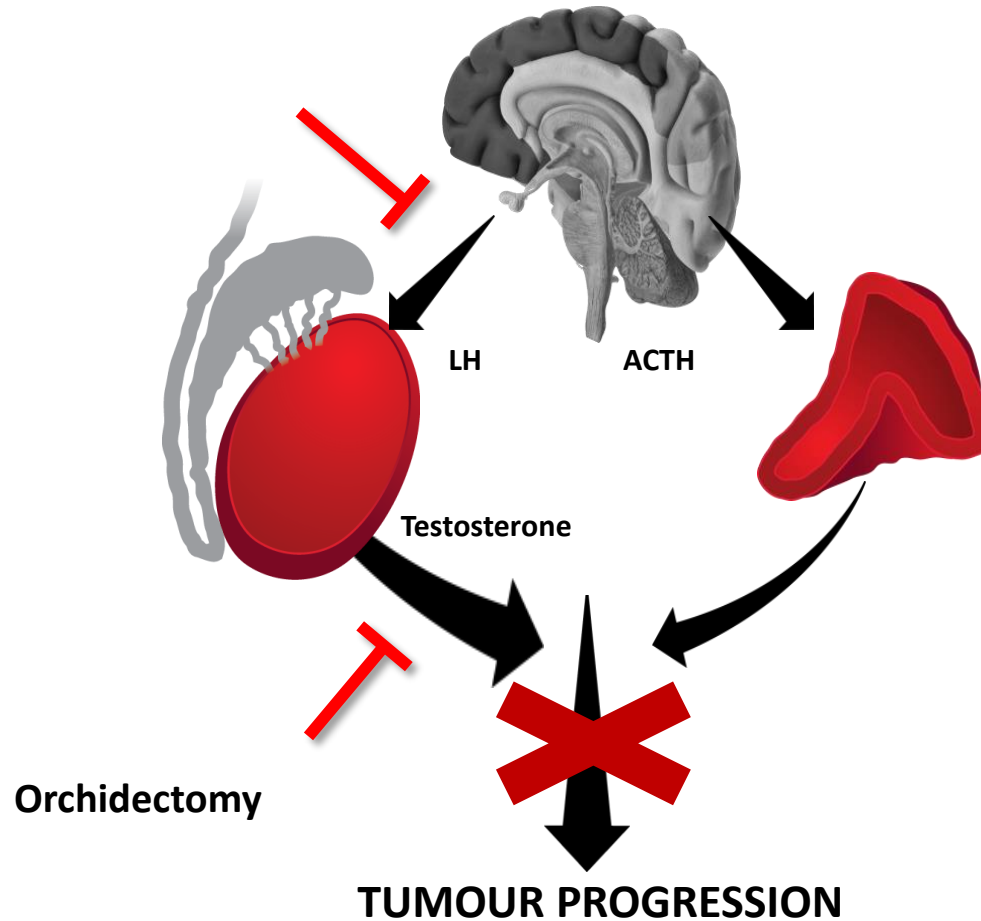
1/03/2023

**INLEIDING**

# Prostaatkanker: continuum van verschillende stadia



# Hormonale therapie = hoeksteen van de therapie



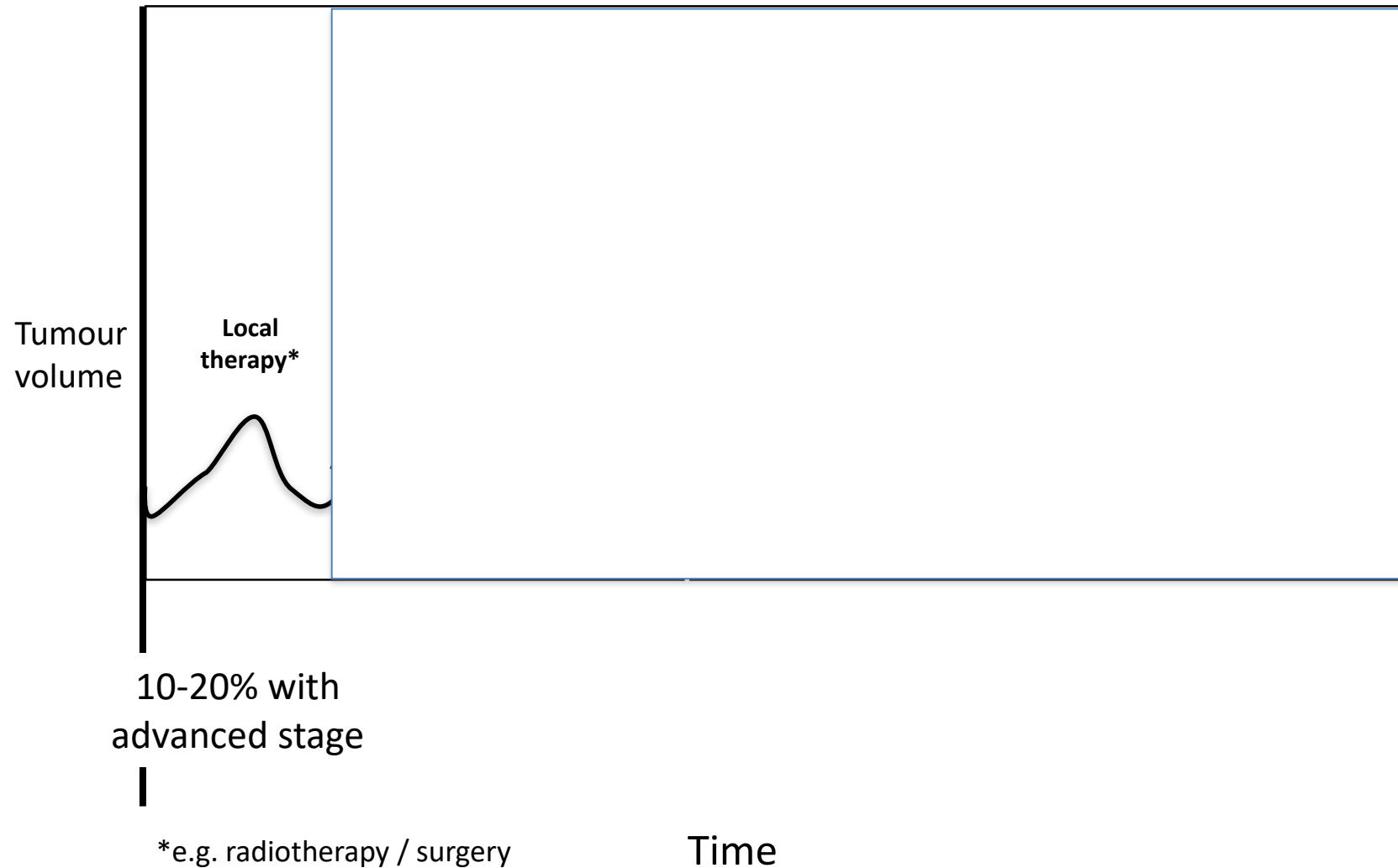
Door de hormonale therapie daalt het testosteroone met 90-95%

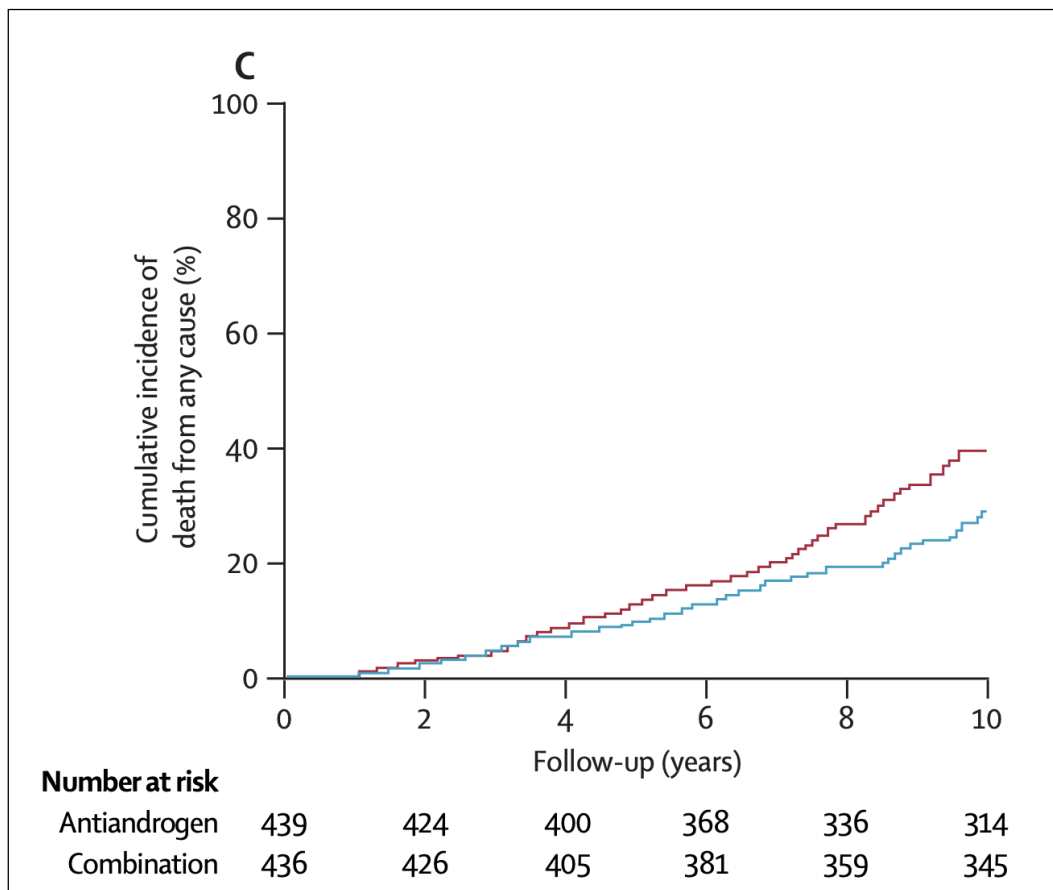
# 'EERSTE' LIJNS HORMONALE THERAPIE

# *'EERSTE' LIJNS HORMONALE THERAPIE*

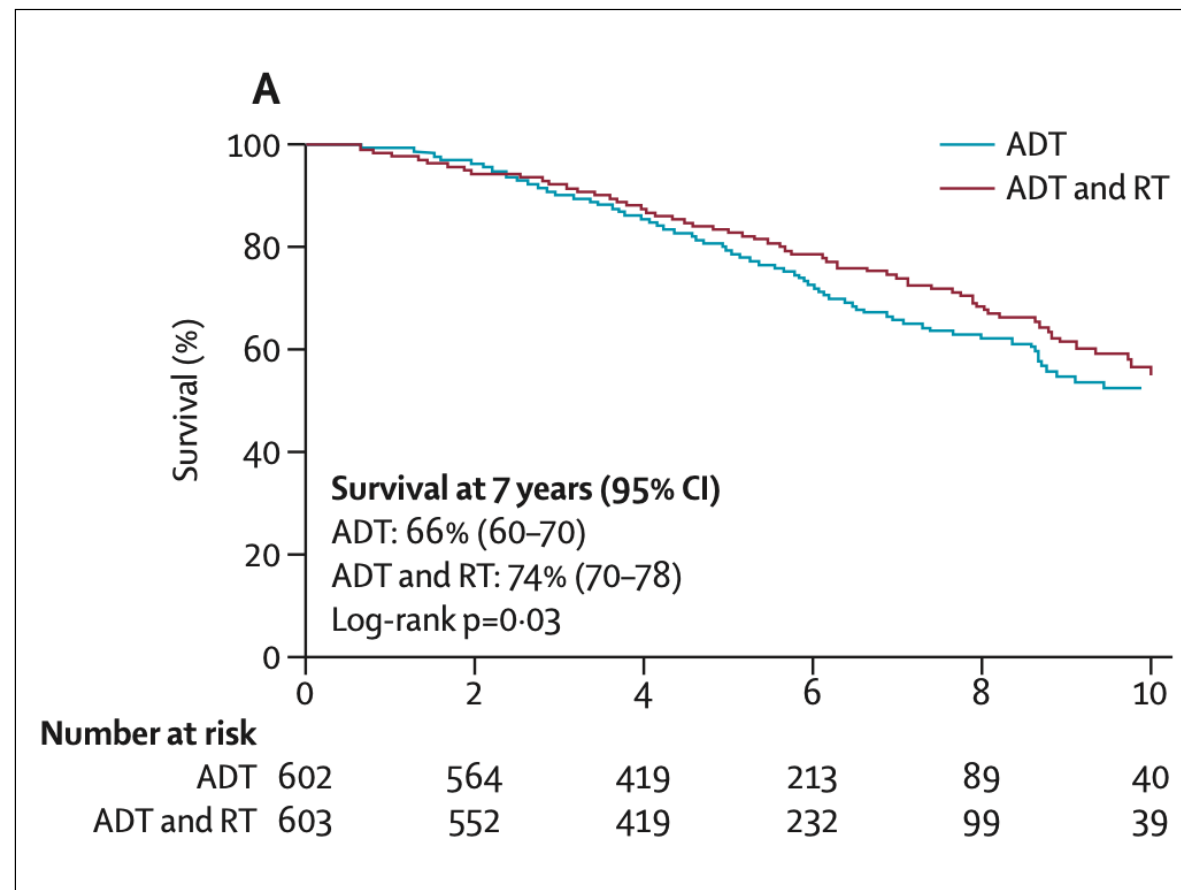
## INDICATIES

# Prostaatkanker: continuum van verschillende stadia





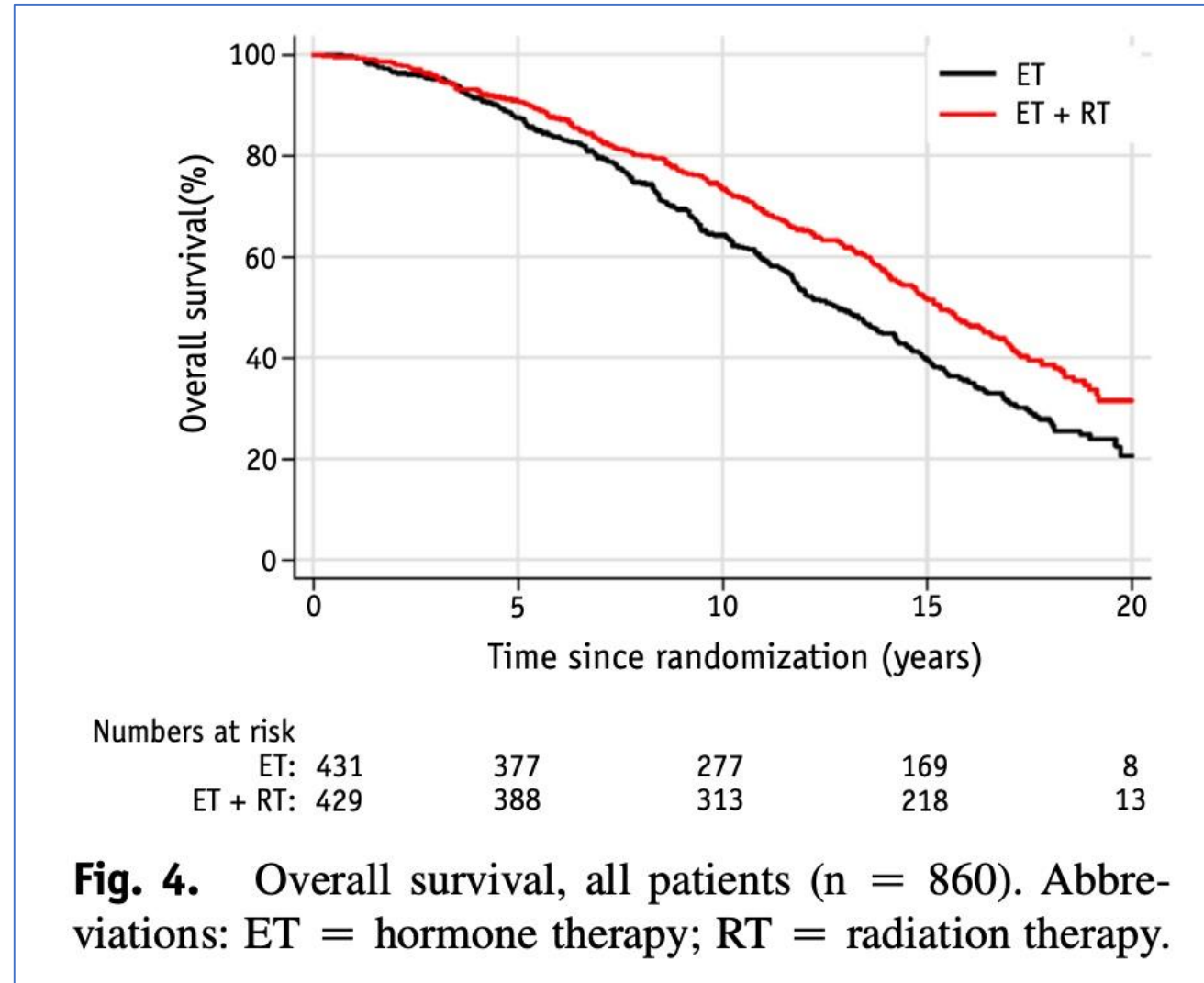
Widmark et al. Lancet 2009

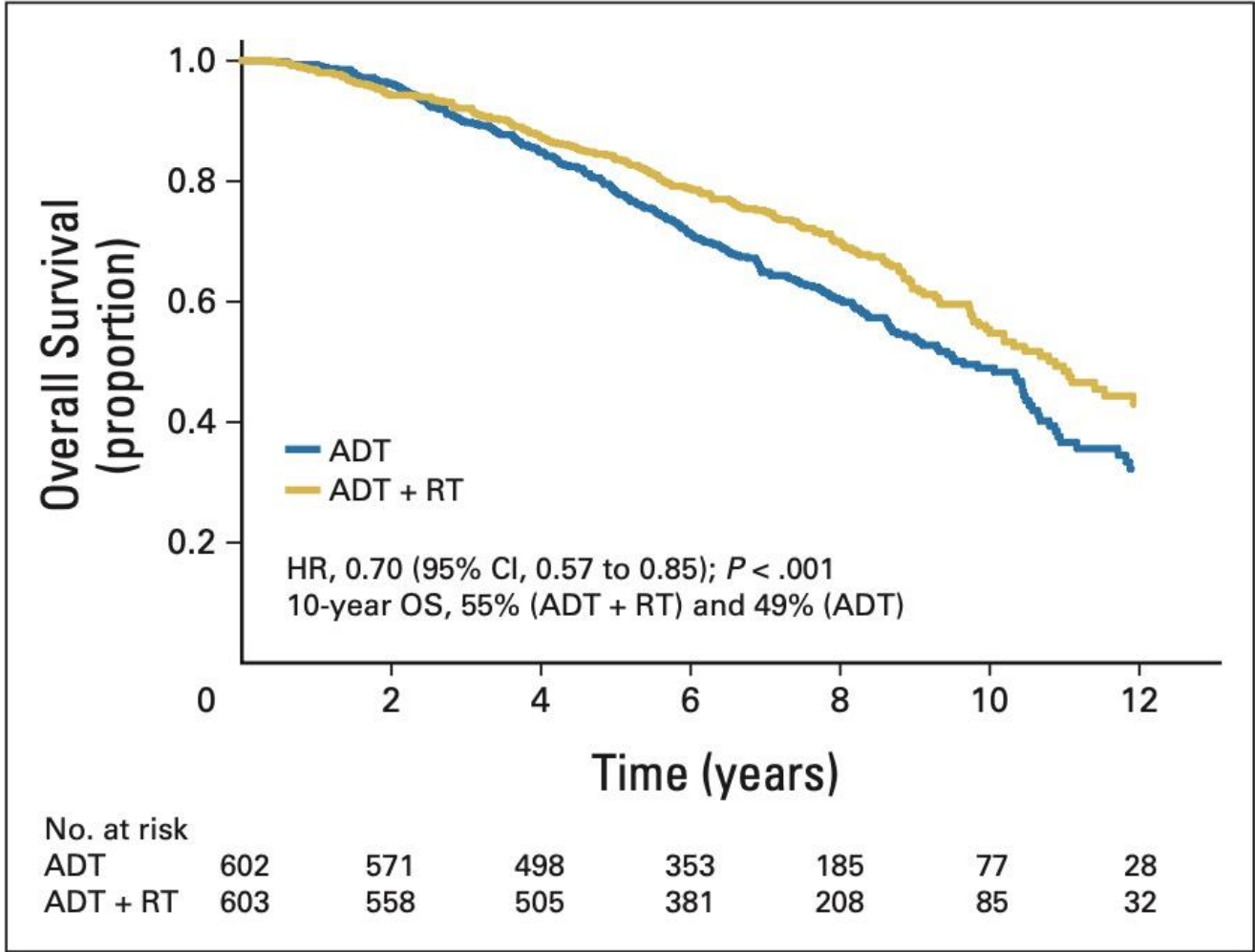


Warde et al. Lancet 2011



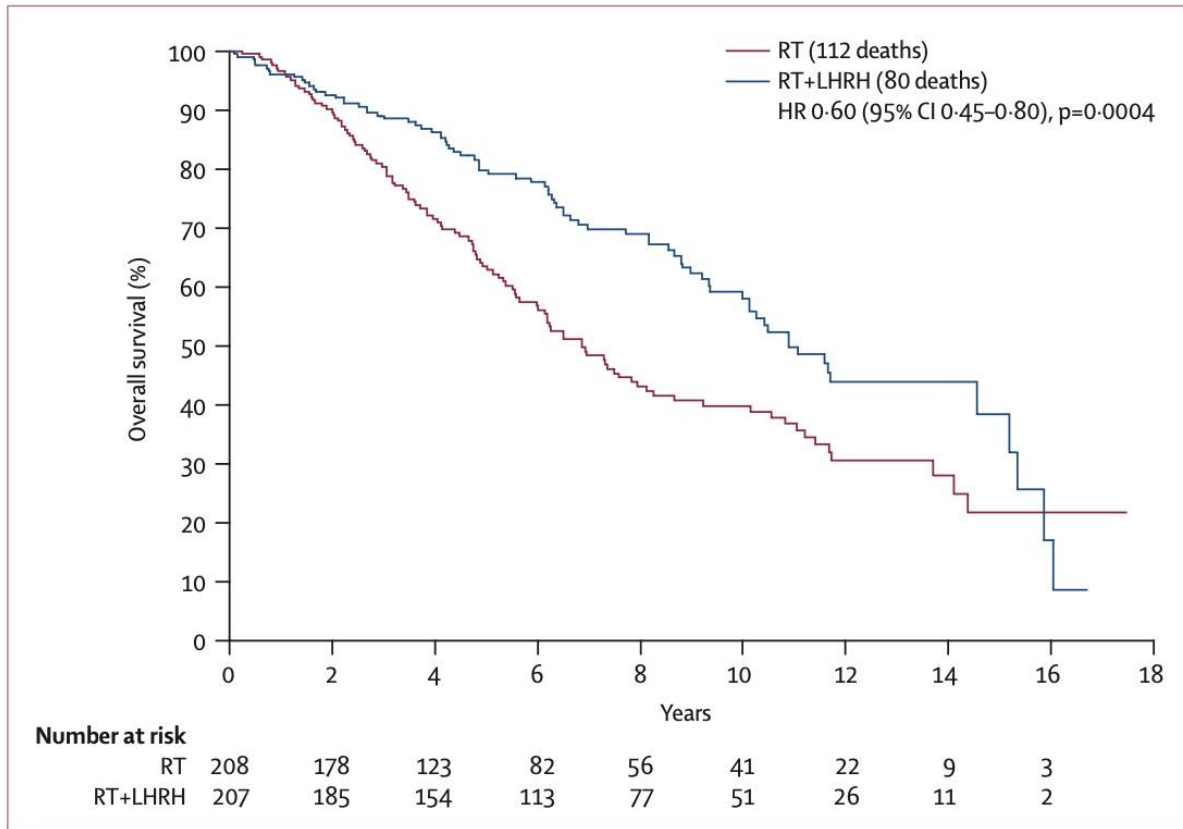
# SPCG7





**Fig 2.** Overall survival (OS). ADT, androgen-deprivation therapy; HR, hazard ratio; RT, radiotherapy.

# Bolla RT +/- ADT



**Figure 3: Overall survival**

RT=radiotherapy. LHRH=luteinising-hormone-releasing hormone.

	Radiation only (N=208)	Radiation plus androgen suppression (N=207)
Any clinical progression	104 (50%)	44 (21%)
Local	19 (9%)	9 (4%)
Local and regional	3 (1%)	0
Distant progression	58 (28%)	31 (15%)
Local and distant	20 (10%)	4 (2%)
Local, regional, and distant	4 (2%)	0

Data are number (%).

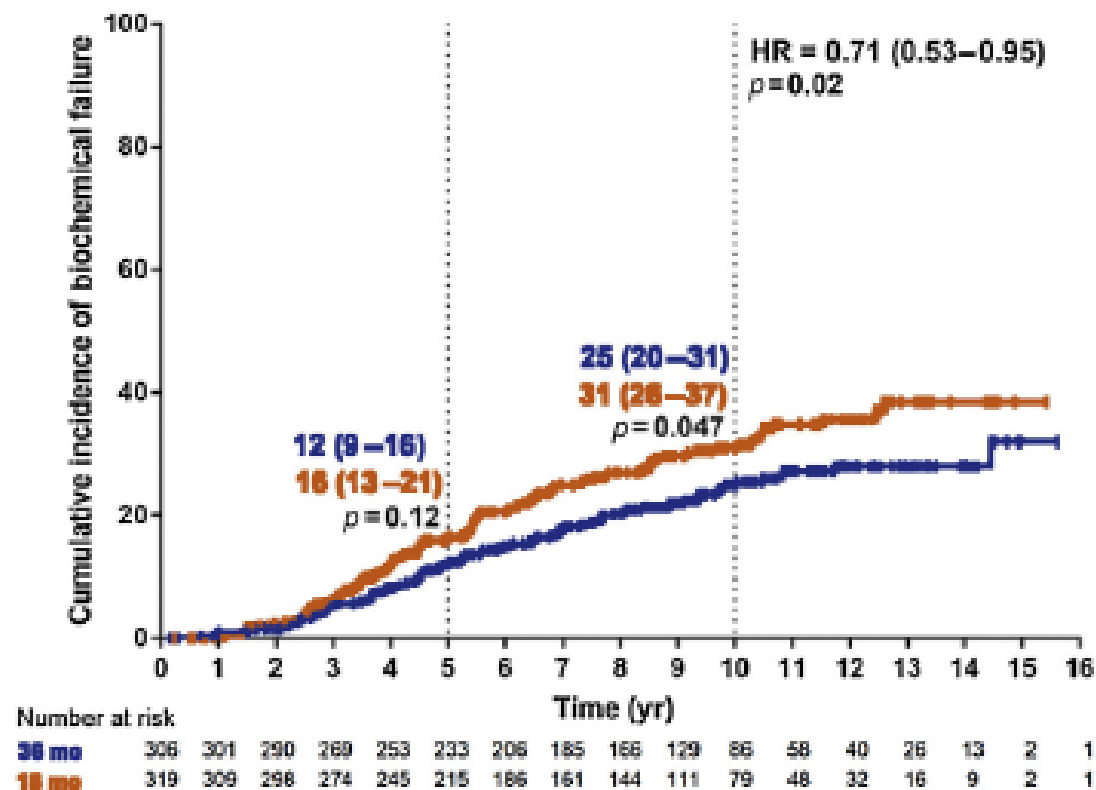
**Table 2: Sites of disease progression**

630 patients randomized

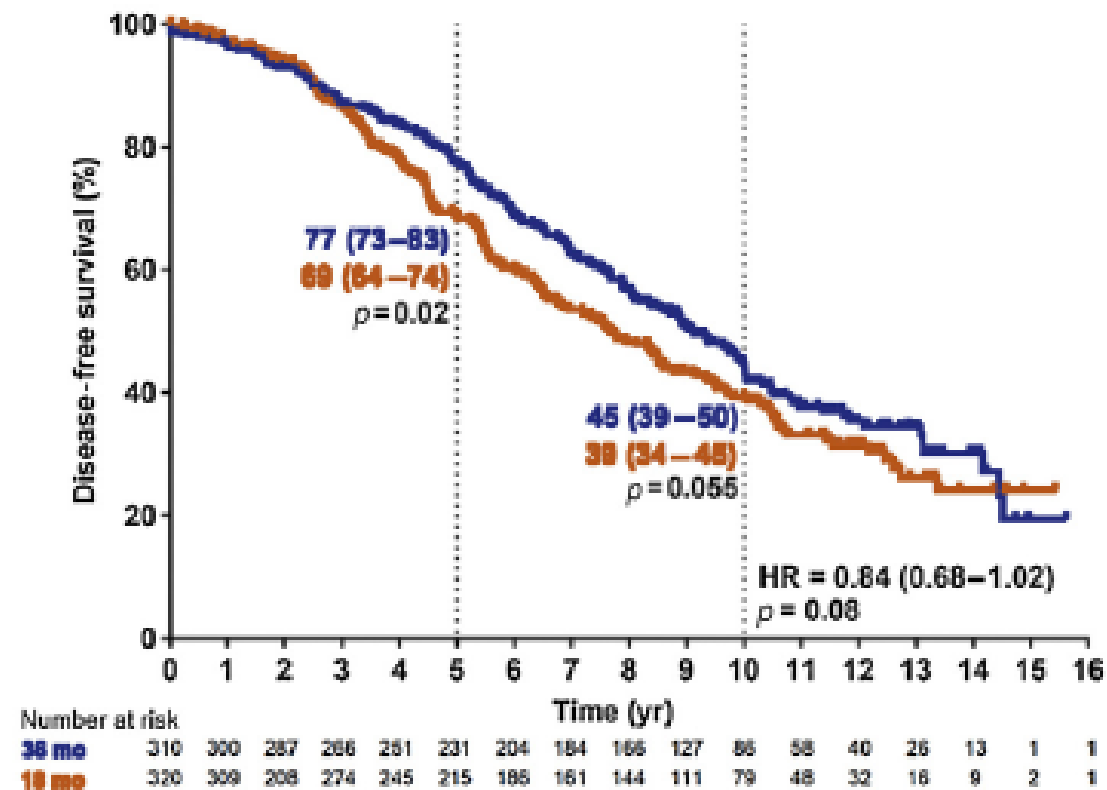
Long arm (36 mo): 310 patients

Short arm (18 mo): 320 patients

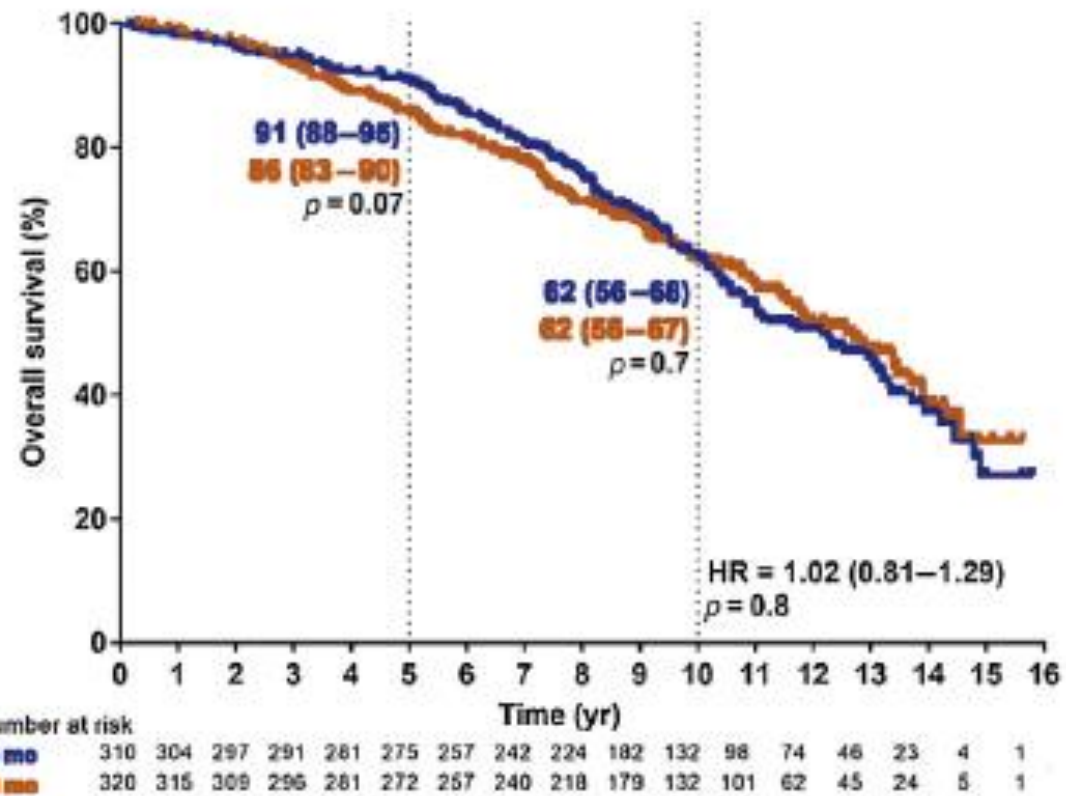
### C Biochemical failure



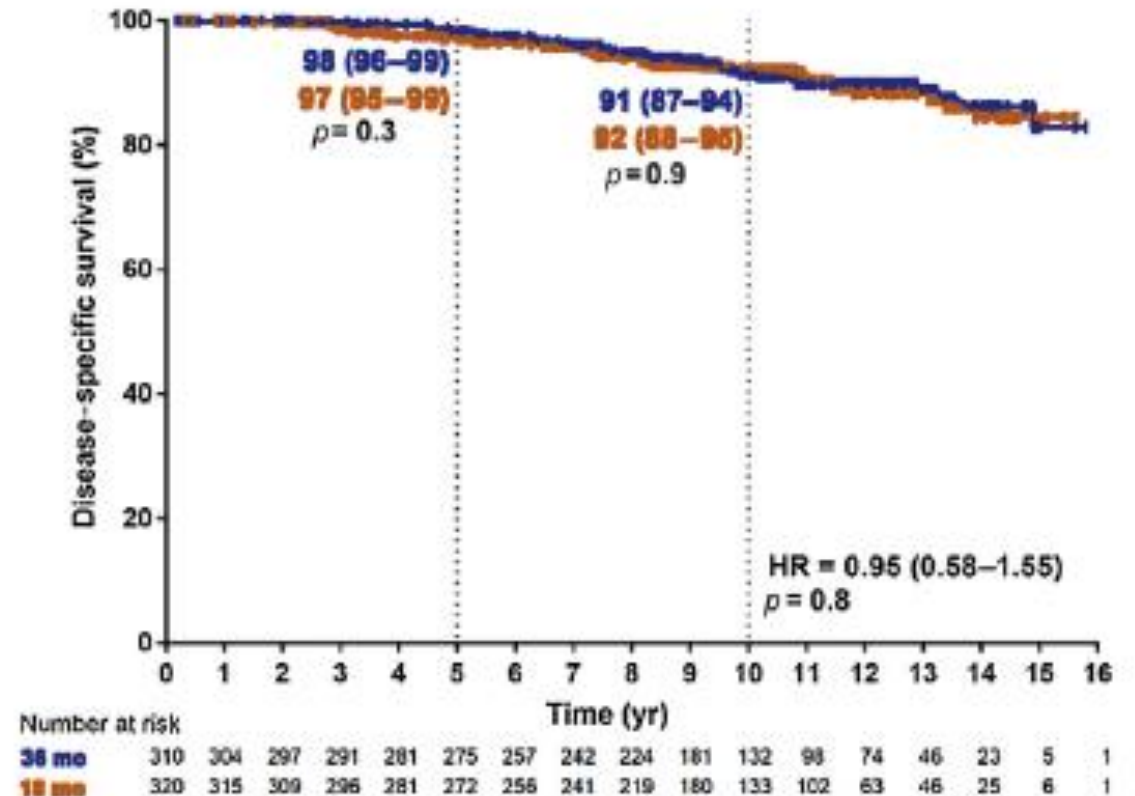
### D Disease-free survival



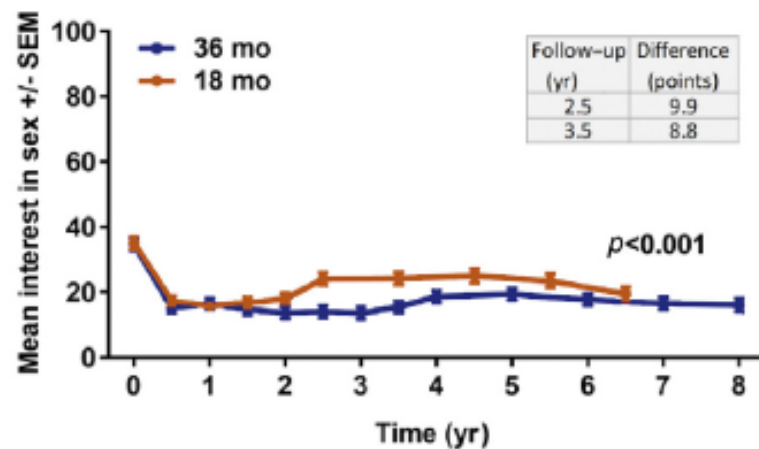
## A Overall survival



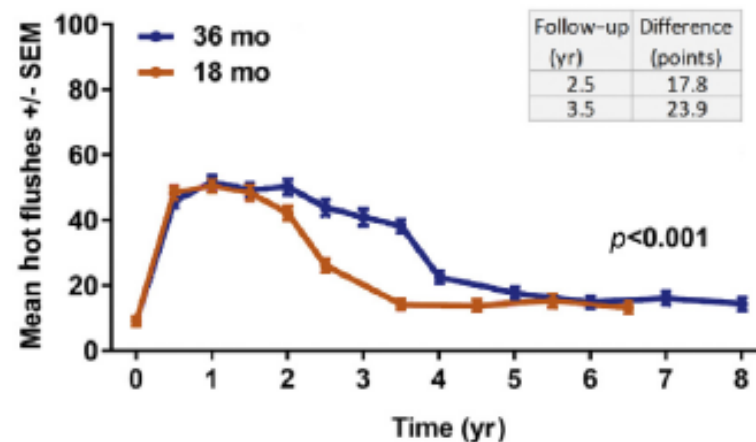
## B Disease-specific survival



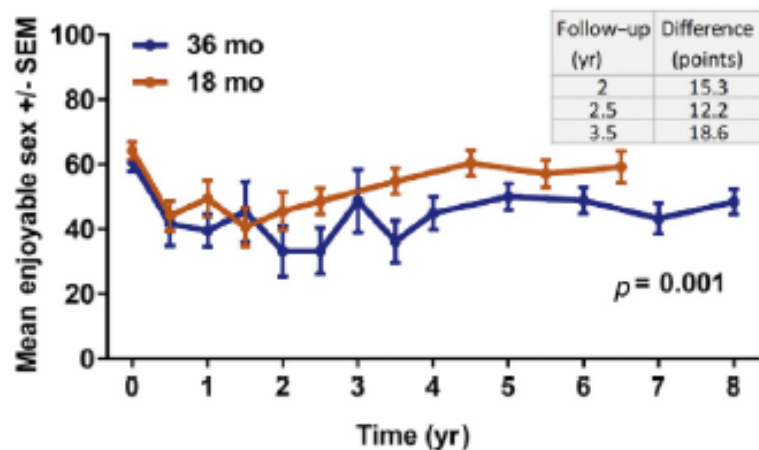
### C Interest in sex



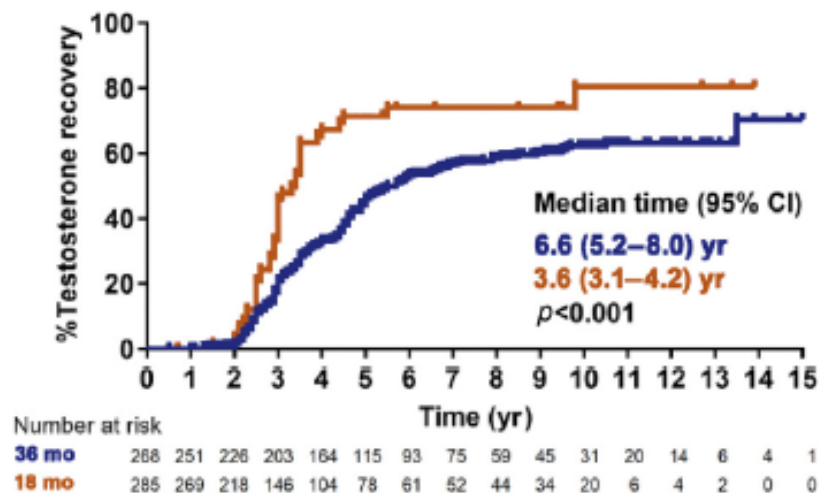
### D Hot flushes



### E Enjoyable sex



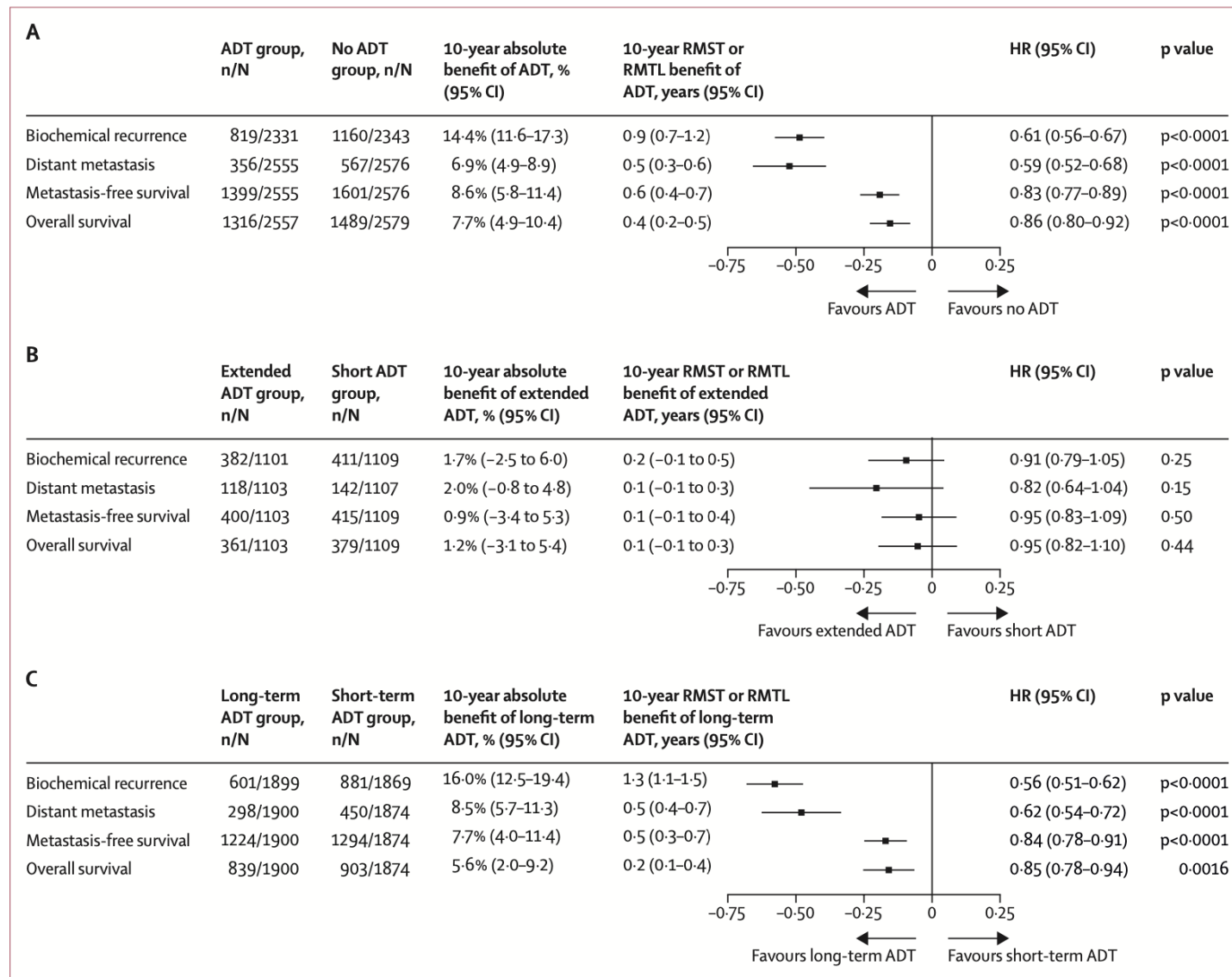
### F Normal testosterone recovery



## Hormonale therapie

## Neo-adjuvante hormonale therapie

## Adjuvante hormonale therapie



**Figure 3: Forest plots showing effects of ADT use (A), neoadjuvant ADT extension (B), and adjuvant ADT prolongation (C) on biochemical recurrence, distant metastasis, metastasis-free survival, and overall survival**

ADT=androgen deprivation therapy. HR=hazard ratio. RMST=restricted mean survival time. RMTL=restricted mean time lost.

# DADSPORT

Trial	Accrual period	Number of men	Duration of HT
<b>GETUG-AFU 16</b> (Carrie et al 2016, 2019)	2006-2010	743	None vs 6m
<b>NRG/RTOG 0534</b> (Pollack et al 2022)	2008-2015	1142	None vs 6m
<b>NRG/RTOG 9601</b> (Shipley et al 2017, Dess et al 2020)	1998-2003	760	None vs 24m
<b>RADICALS-HD</b> (Unpublished)	2007-2015	2839	None vs 6m None vs 6m vs 24m 6m vs 24m

3 trial comparisons - None vs 6m HT, 3364 men

2 trial comparisons - None vs 24m HT, 1088 men



# APCCC 2022

Grade Group (GS)	Pre-SRT PSA (ng/mL)			
	0.1-0.49	0.5-0.99	1.0-1.5	>1.5
1 (6)	RT alone (+STADT if Int-High GC or neg margin and multiple high RF)	RT + STADT	RT + STADT (Discuss LTADT if Int-High GC or multiple high RF)	RT + STADT (+LTADT if High GC and multiple high RF)
2, 3 (7)	RT alone if pos margin or low GC (+STADT if Int-High GC or multiple high RF)	RT + STADT	RT + STADT (Discuss LTADT if High GC or multiple risk factors)	RT + LTADT (STADT if pos margin and low GC)
4,5 (8-10)	RT + STADT (consider RT alone if low GC & only 1 high RF)	RT + STADT (Discuss LTADT with neg margins & multiple high RF)	RT + LTADT (Discuss STADT if margin positive & low GC; consider systemic therapy intensification with multiple high RF)	RT + LTADT (consider systemic therapy intensification with multiple high RF)

Clinical Trial Preferred Approach  
Whenever Possible

# *'EERSTE' LIJNS HORMONALE THERAPIE*

## BIJWERKINGEN

# 1) *CARDIOVASCULAIR*

- LHRH agonisten (Decapeptyl, Depo-Eligard, Zoladex):

- ↑ LDL
- ↑ triglyceriden
- ↑ visceraal vet
- ↑ insuline resistentie
- ↓ glucose tolerantie



**Induceren atherosclerose en  
coronair lijden**

≈ thrombo-embolische events, AMI, hartfalen, arythmie

# *1) CARDIOVASCULAIRE*

- RR op cardiovasculair event: 0.93-1.37
- ! Voorgeschiedenis van cardiovasculaire events
- Antagonisten (Firmagon): potentieel een lager risico

# *PREVENTIE: CARDIOVASCULAIR*

## *VOOR START HORMONALE THERAPIE:*

- Navragen of er cardiovasculaire events zijn geweest
- Labo: lipiden en glycemie
- ECG
- Bloeddruk
- BMI

## 2) *BOTDENSITEIT*

- ↑ botresorptie
- ↑ osteoclasten activatie



Verlies in BMD van 4-6%/jaar met een sneller verlies eerste jaar van hormonale therapie

- Kwalitatieve schade thv de trabeculaire microstructuur

## 2) *BOTDENSITEIT*

- RR op fractuur: 1.23
- RR op heupfractuur met nood aan hospitalisatie: 1.82

# *PREVENTIE: BOTDENSITEIT*

## *VOOR START HORMONALE THERAPIE:*

- Start Calcium (1200 mg/dag) + Vitamine D (800-2000 IU/dag)
- Aanpassingen levensstijl: rookstop, verminderde alcohol inname, meer fysieke activiteit
- Overweeg gebruik van botversterkers bij:
  - T score  $< 2$  of  $\geq 2$  risico factoren ( $> 65$  jaar, T score  $< -1.5$ , roker, BMI  $< 24$ , familiale VG van heupfractuur, inname van glucocorticoïene  $> 6$  maanden)



# *PREVENTIE: BOTDENSITEIT*

## *Tijdens en na HORMONALE THERAPIE:*

- Botdensitometrie alle 1-2 jaar zolang onder hormonale therapie
- Na afwerken van hormonale therapie: nieuwe botdensitometrie

### *3) COGNITIEVE STOORNISSEN*

- ↓ concentratie
- Geheugenstoornissen
- Dementie
- Depressie

# *PREVENTIE: COGNITIEVE STOORNISSEN*

## *VOOR START HORMONALE THERAPIE:*

- Screening voor cognitieve dysfunctie
- Psychiatrische of geriatrisch evaluatie zo VG van depressie of dementie
- Monitoring van cognitieve functies

## 4) *Hot flashes*

- Verstoring in thermoregulatie systeem

# *PREVENTIE: HOT FLASHES*

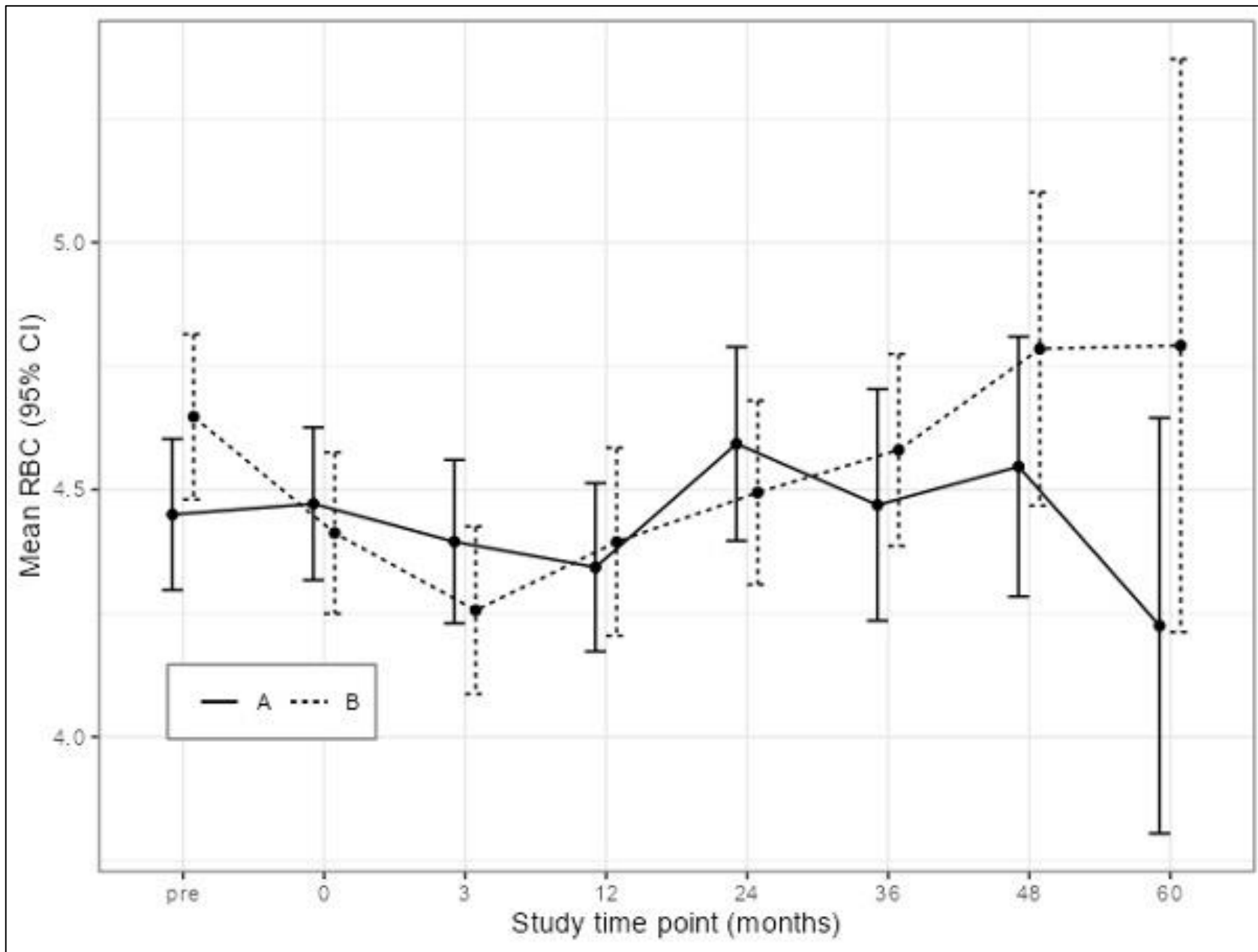
- Vermijden van te heet of gekruid eten
- Hormonale therapie o.v.v. megestrol of cyproterone acetate
- Gabapentine, venlafaxine of acupunctuur
- Salie

## *5) Vermoeidheid en anemie*

- ↓ testosteron geïnduceerde erythropoïesis
- ↓ testosteron geïnduceerde renale productie van erythropoïetine

# *PREVENTIE: VERMOEIDHEID EN ANEMIE*

- Fysieke activiteit en dieet
- Behandel andere oorzaken van anemie
- Monitor Hb levels



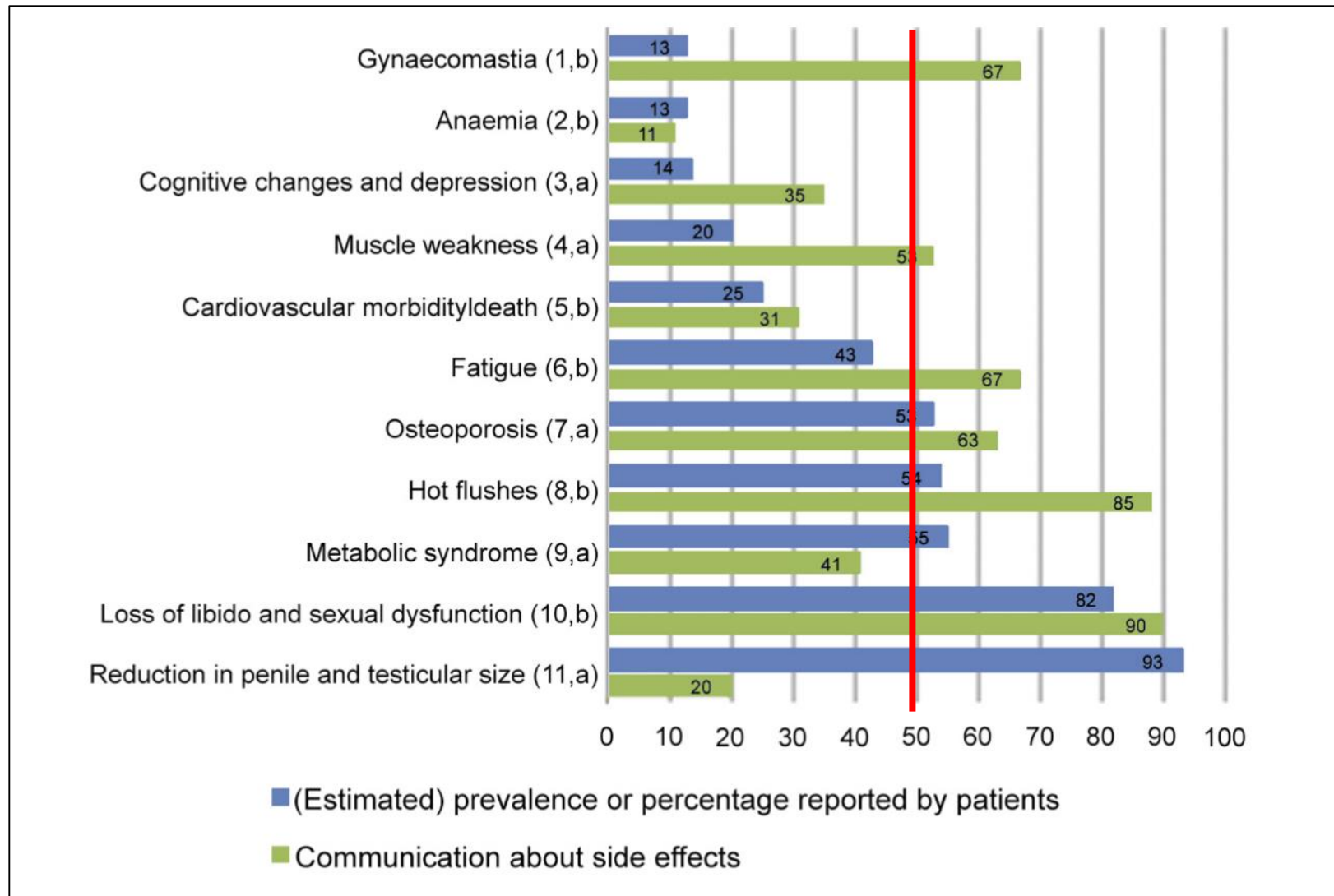


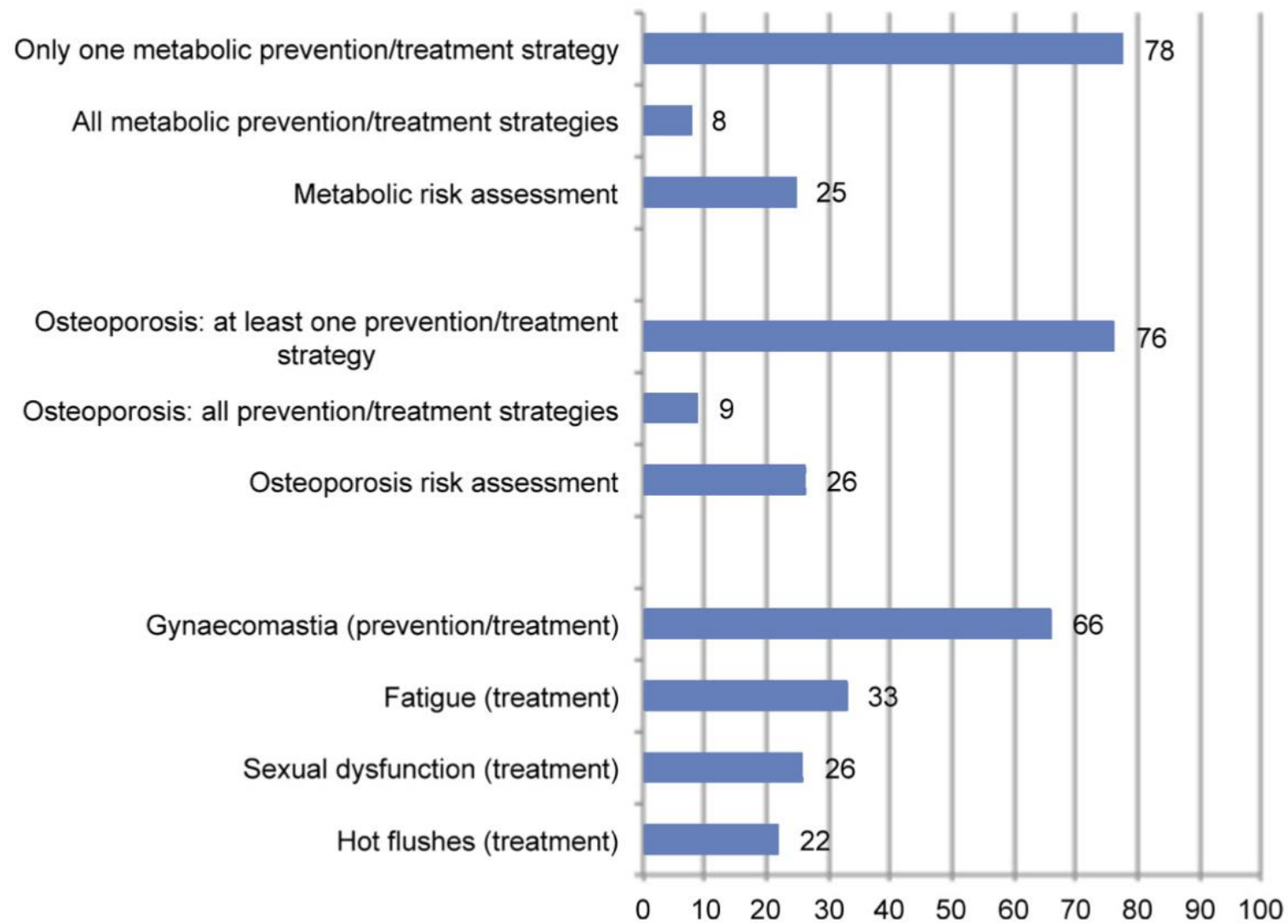
## 6) *Potentie en erectieverlies*

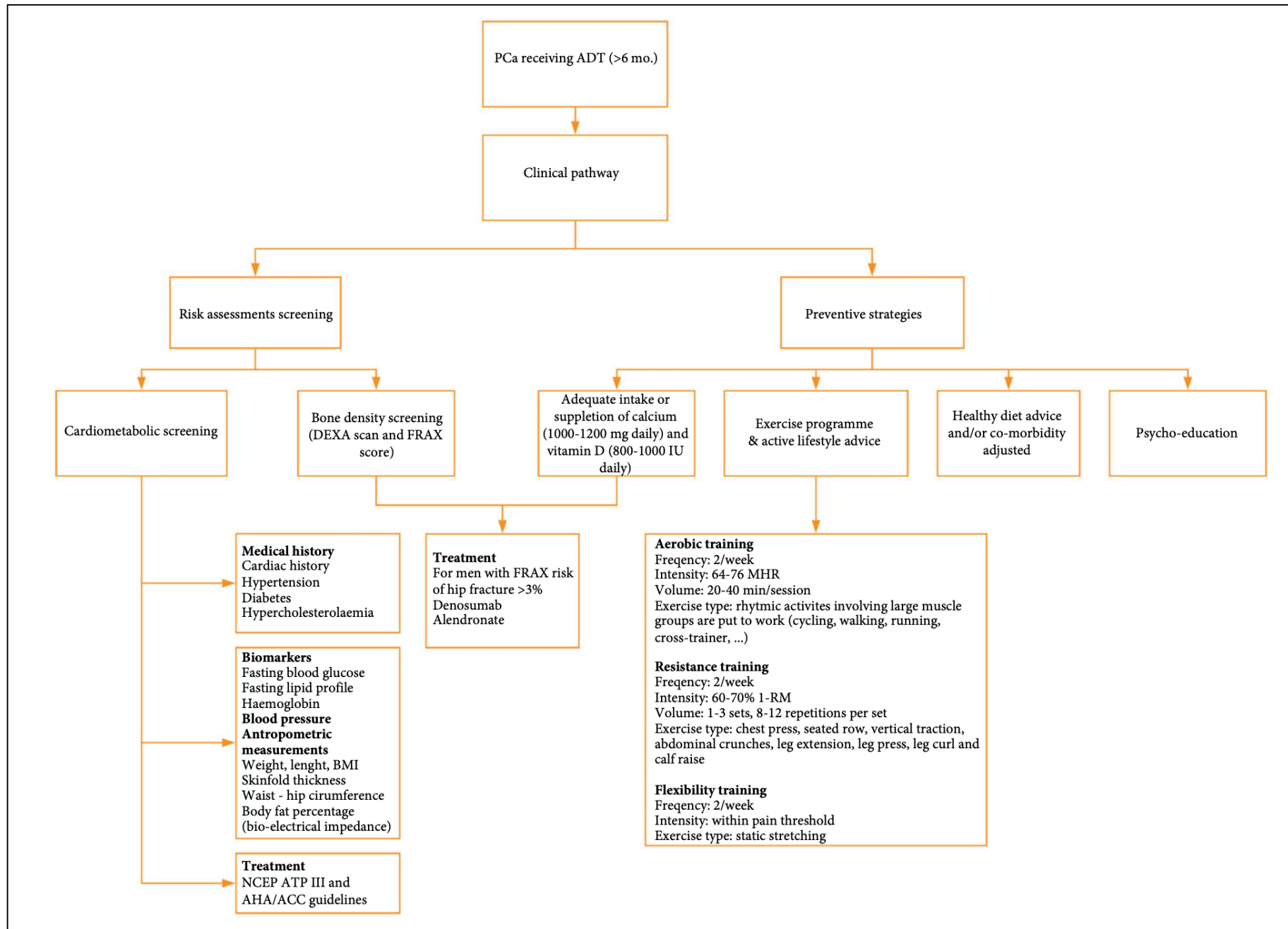
- ↓ peniele en testiculaire grootte
- Verlies libido
- ↓ gevoeligheid voor sexuele prikkels
- Erectiele dysfunctie

# *PREVENTIE: POTENTIE EN ERECTIEVERLIES*

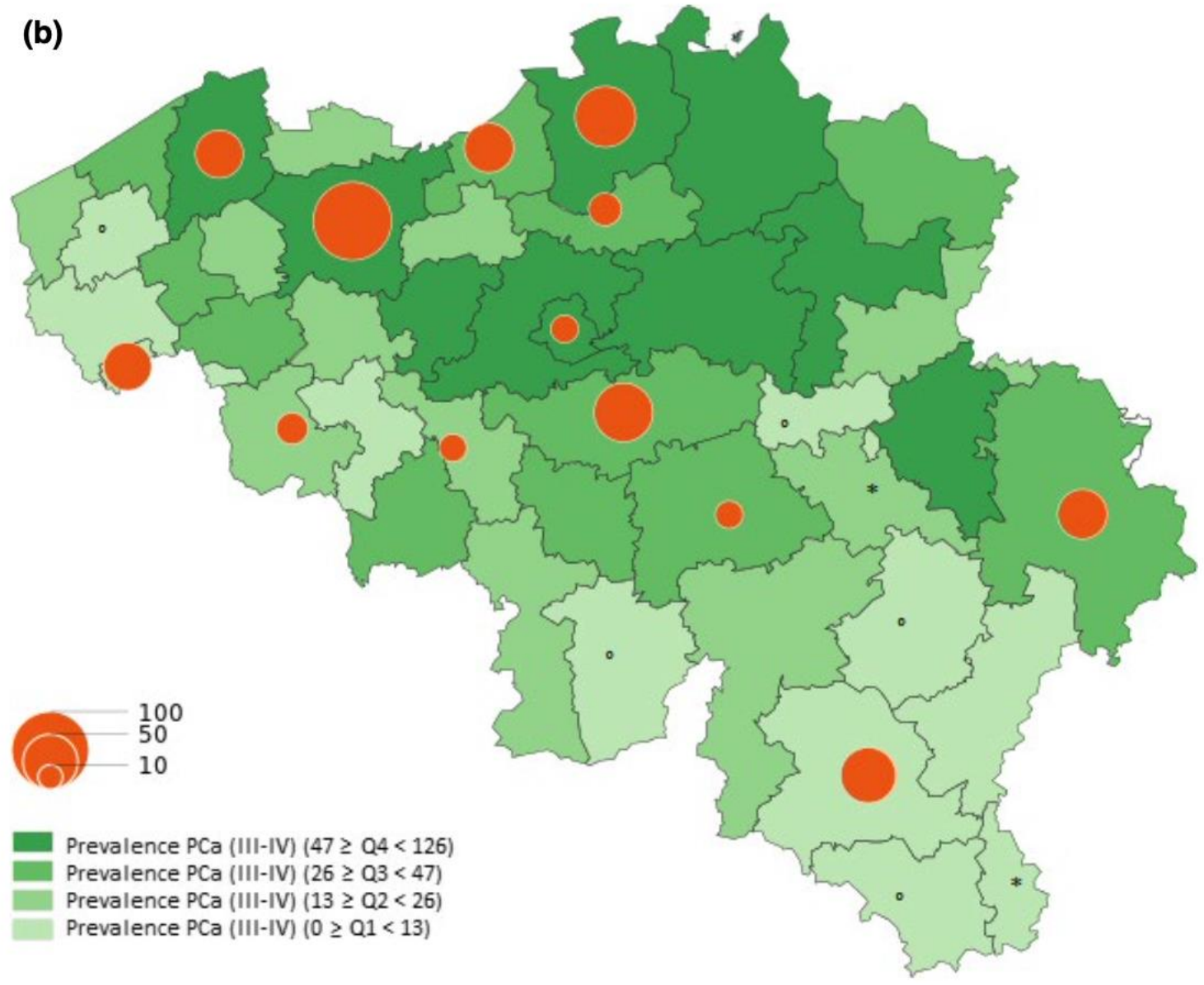
- Counselling
- Overweeg psychologische hulp
- Overweeg intermittente hormonale therapie



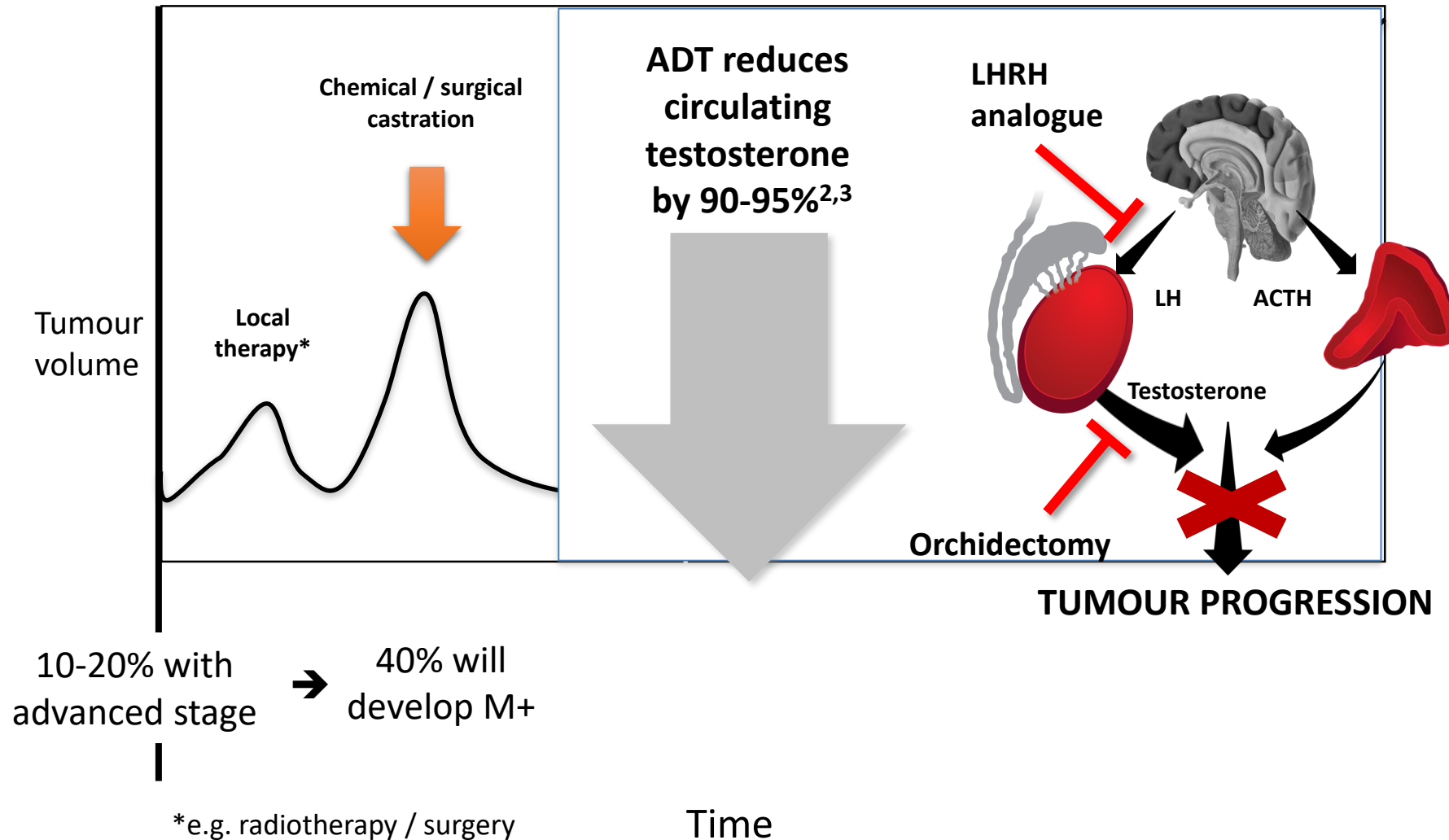




(b)



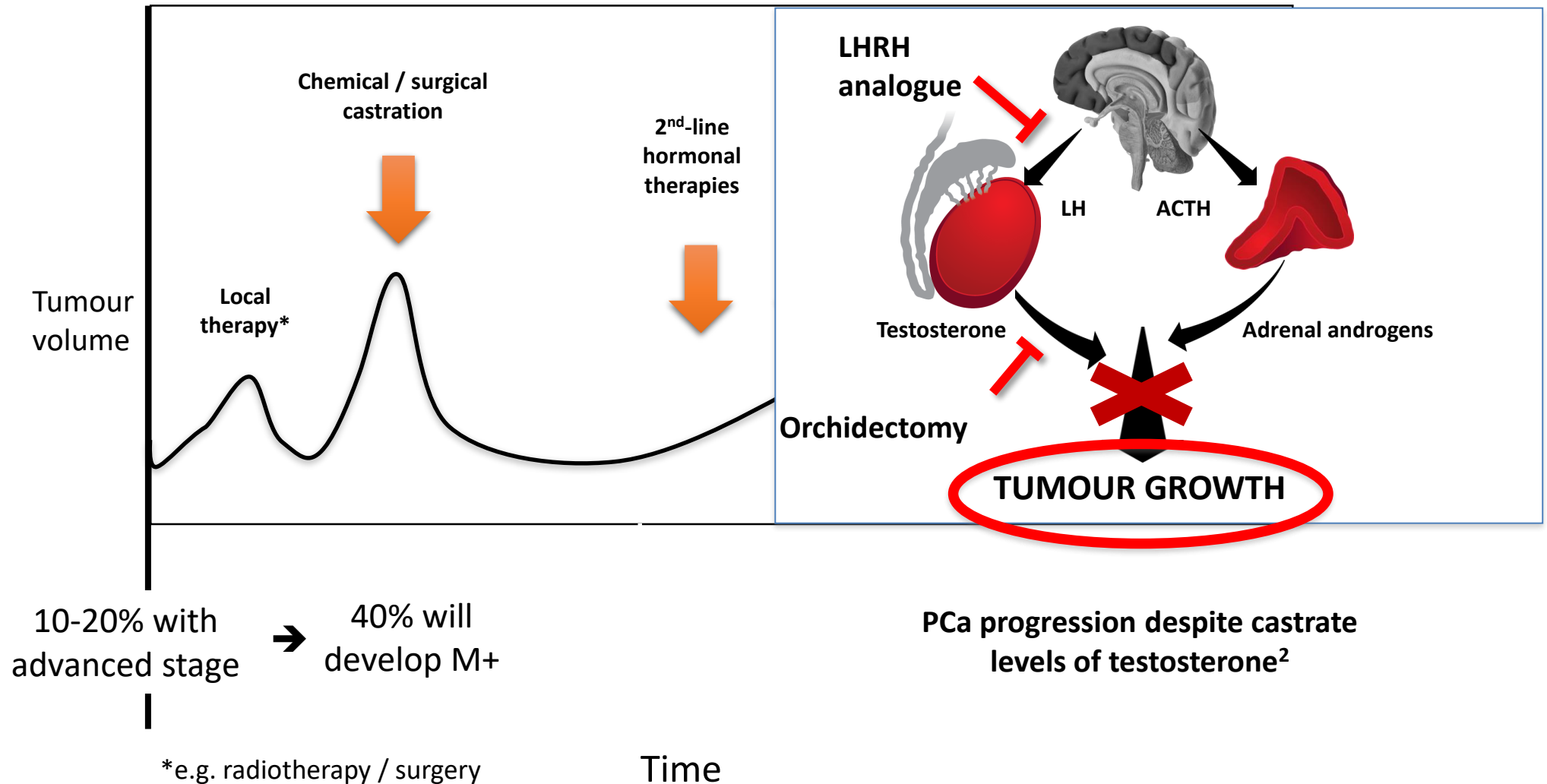
# Prostaatkanker: continuum van verschillende stadia



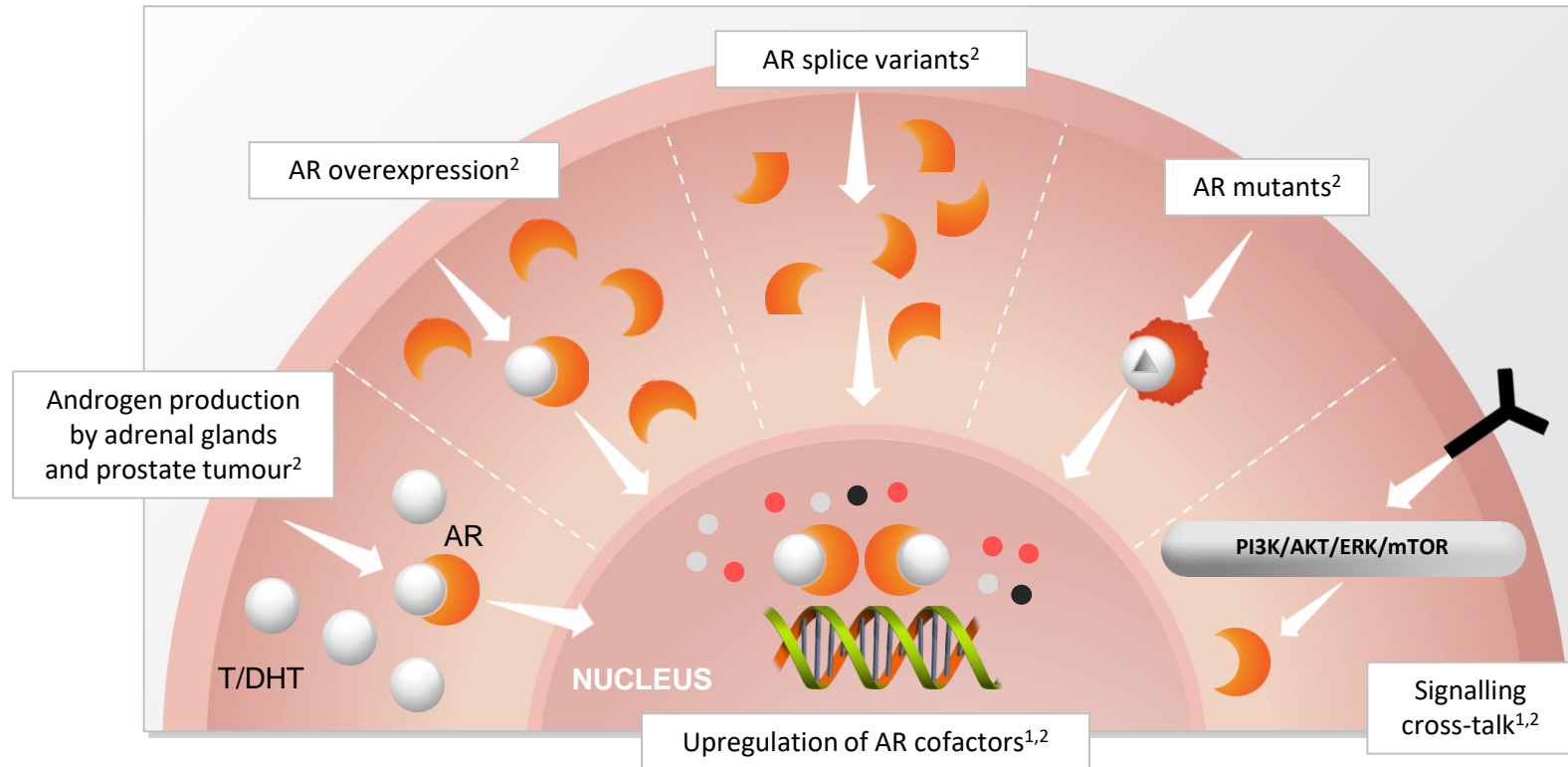
# 'TWEEDE' LIJNS HORMONALE THERAPIE



# Prostaatkanker: continuum van verschillende stadia



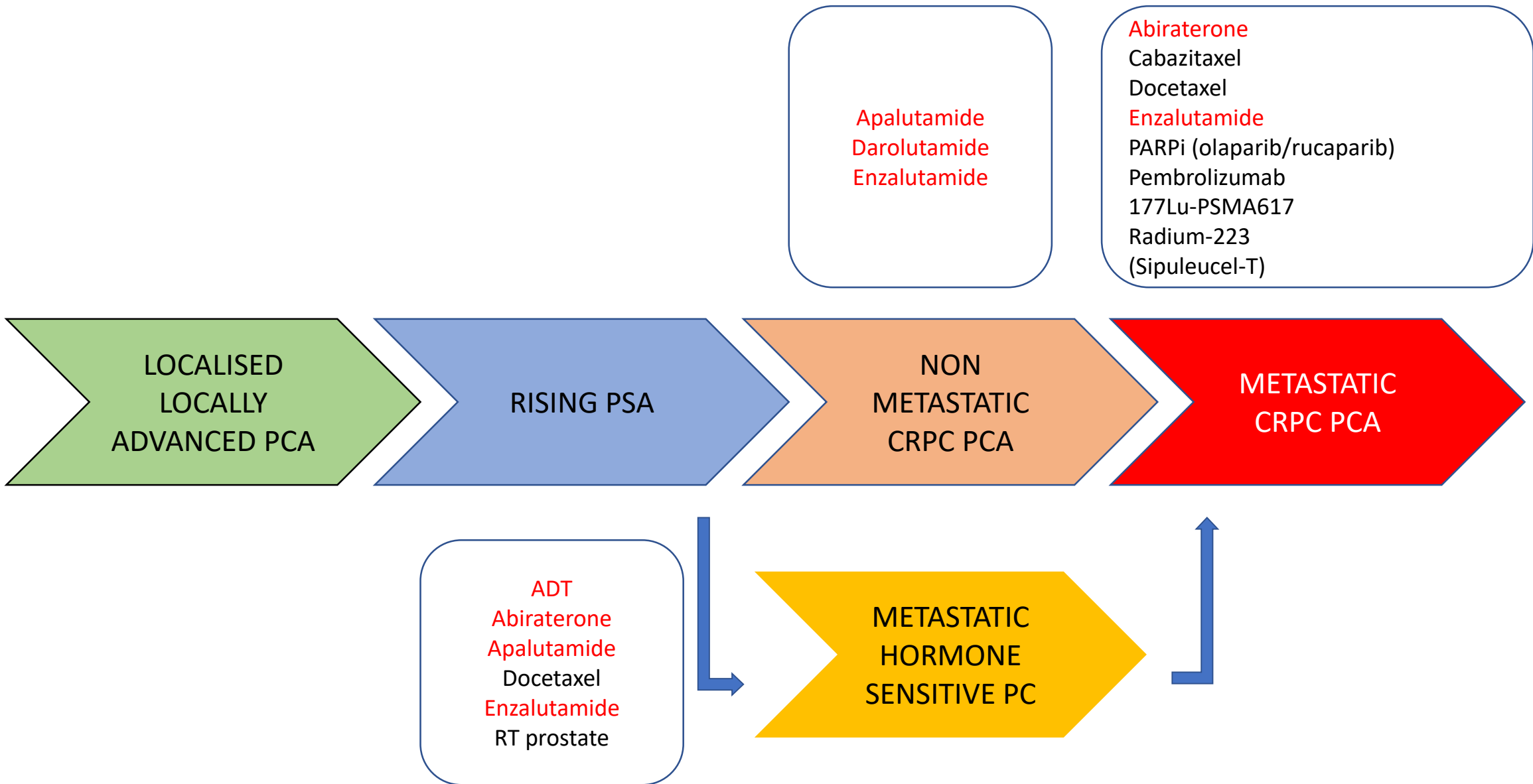
# De androgeen receptor is een logische target



1. Heinlein CA, Chang C. Endocr Rev 2004;25:276-308; 2. Hu R et al. Expert Rev Endocrinol Metab 2010;5:753-64

# *'TWEEDE' LIJNS HORMONALE THERAPIE*

## INDICATIES

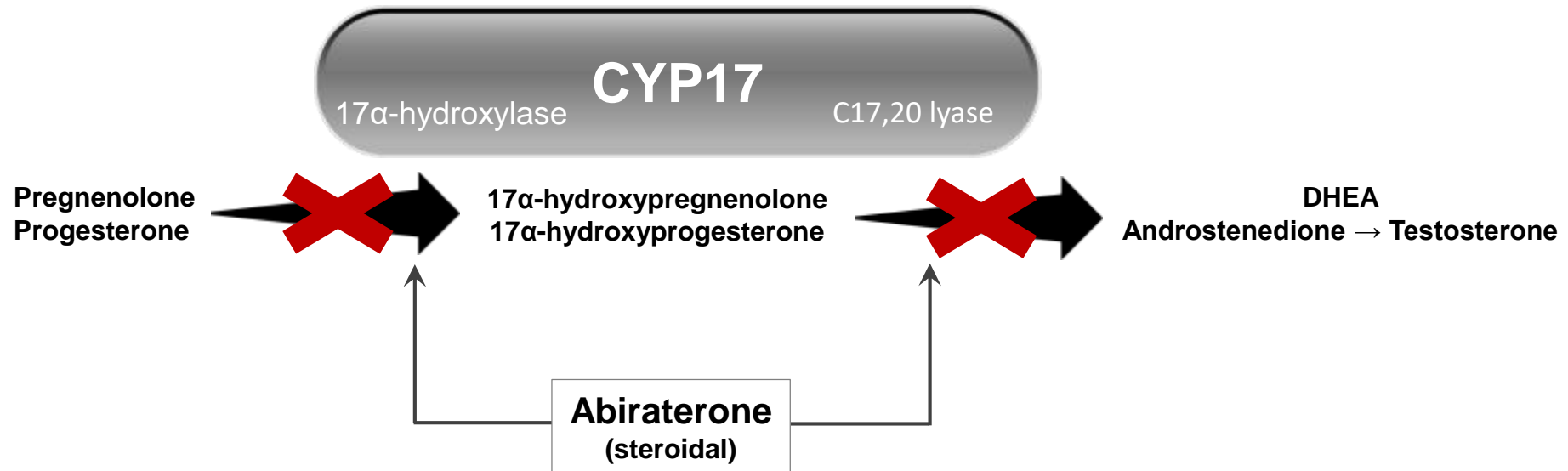


# *'TWEEDE' LIJNS HORMONALE THERAPIE*

## WERKINGSMECHANISME

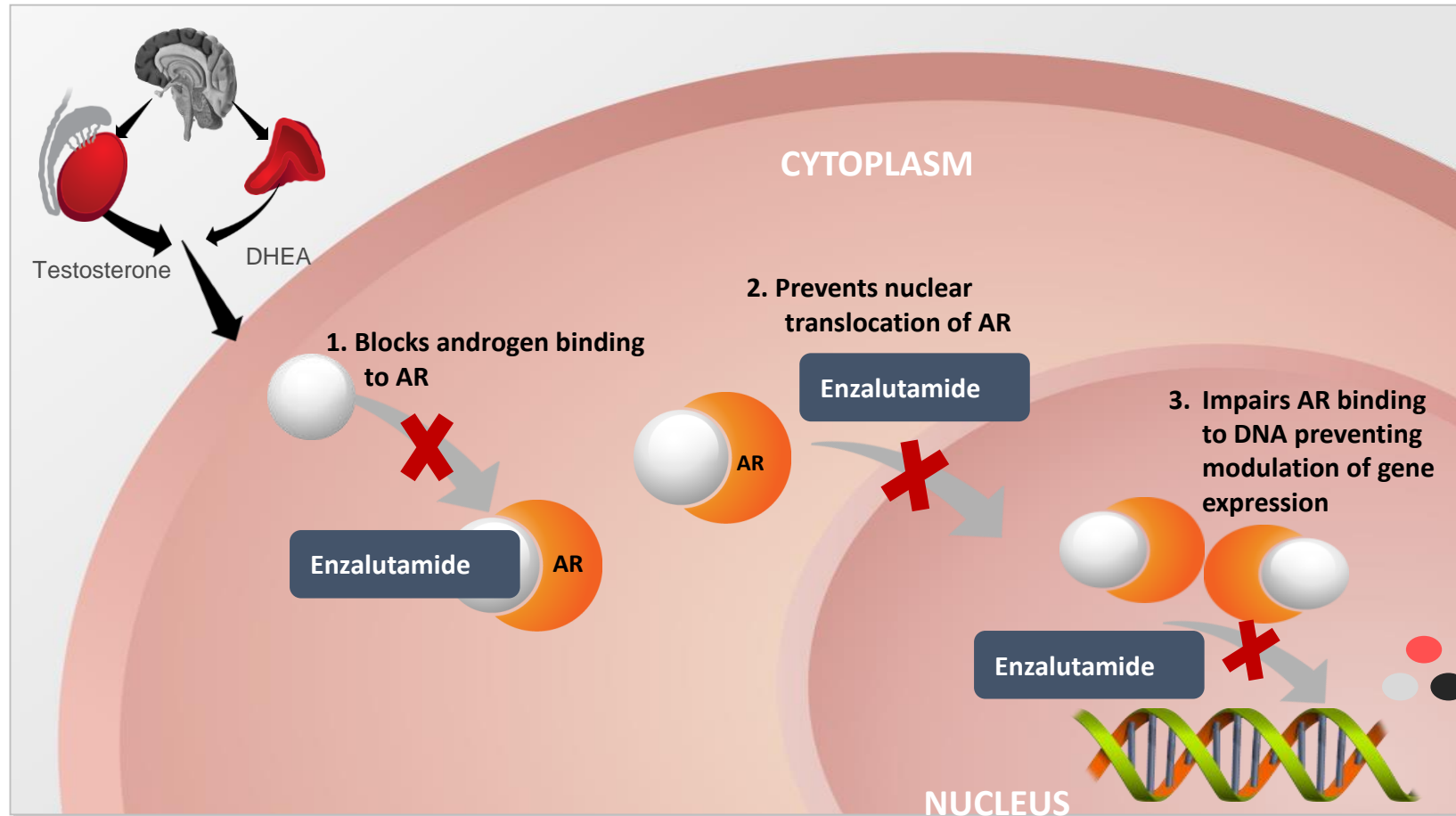
# Abiraterone

- Irreversible inhibitor of CYP17A: inhibits testosterone production in testis, adrenal glands, and prostate



# Enzalutamide

- Enzalutamide directly targets three key stages of the AR signalling pathway<sup>1,2</sup>



1. Tran C et al. Science 2009;324:787-90; 2. Hu R et al. Expert Rev Endocrinol Metab 2010;5:753-64

# *'TWEEDE' LIJNS HORMONALE THERAPIE*

## BIJWERKINGEN



**Table 2** Summary of ARPI-Specific Adverse Events and Their Management

ARPI	Specific Adverse Event	Physiopathology	Managemnt
Abiraterone	<ul style="list-style-type: none"> <li>● Hypokalemia</li> <li>● Hypertension</li> <li>● Peripheral edema</li> <li>● Congestive heart fail</li> <li>● Liver function impairment</li> </ul>	<ul style="list-style-type: none"> <li>● Inhibition of CYP17A1</li> </ul>	<ol style="list-style-type: none"> <li>1. Glucocorticoid replacement therapy with low-dose prednisone (5–10mg/day)</li> <li>2. Monitor potassium and liver function values during treatment</li> <li>3. Carefully consider the use of abiraterone in patients with cardiovascular comorbidities</li> <li>4. Reduce the dose or discontinue treatment in case of severe adverse events</li> </ol>
Enzalutamide	<ul style="list-style-type: none"> <li>● Hypertension</li> <li>● Fatigue</li> <li>● Seizures</li> </ul>	<ul style="list-style-type: none"> <li>● Passage through the blood–brain barrier</li> <li>● Off-target activity to induce inhibition of GABA-A receptors</li> </ul>	<ol style="list-style-type: none"> <li>1. Avoid the use of enzalutamide in patients with a predisposition to develop seizures</li> <li>2. Reduce the dose or discontinue treatment in case of severe adverse events</li> </ol>
Apalutamide	<ul style="list-style-type: none"> <li>● Hypertension</li> <li>● Fatigue</li> <li>● Seizures</li> <li>● Hypothyroidism</li> <li>● Skin rash</li> </ul>	<ul style="list-style-type: none"> <li>● Passage through the blood–brain barrier</li> <li>● Off-target activity to induce inhibition of GABA-A receptors</li> <li>● Interacts with thyroxine and levothyroxine</li> </ul>	<ol style="list-style-type: none"> <li>1. Avoid the use of apalutamide in patients with a predisposition to develop seizures</li> <li>2. Corticosteroids and oral antihistamines for skin rash</li> <li>3. Start or optimize treatment with levothyroxine</li> <li>4. Reduce the dose or discontinue treatment in case of severe adverse events</li> </ol>
Darolutamide	<ul style="list-style-type: none"> <li>● No increase in adverse events compared to placebo</li> </ul>	<ul style="list-style-type: none"> <li>● Less ability to pass the blood–brain barrier</li> </ul>	<ol style="list-style-type: none"> <li>1. Reduce the dose or discontinue treatment in case of severe adverse events</li> </ol>

**Abbreviations:** ADT, androgen deprivation therapy; ARPI, androgen receptor pathway inhibitors; BMI, body mass index; BPA, bisphosphonates; BMD, bone mineral density; ECG, electrocardiogram; GABA-A, gamma-aminobutyric acid-A; Hb, hemoglobin; LHRH, luteinizing hormone releasing hormone; mCRPC, metastatic castration-resistant prostate cancer.

**TABLE 3** Subgroup analysis of second-line hormonal therapy

Outcome	Abiraterone (n = 180)	Enzalutamide (n = 108)	1st ADT (n = 1575)	Abiraterone vs. 1st ADT		Enzalutamide vs. 1st ADT	
				HR (95% CI)	p Value	HR (95% CI)	p Value
Acute coronary syndrome							
Event rate	2.34%	1.28%	0.69%	6.91 (2.99–16.00)	<.01*	4.12 (1.81–9.37)	<.01*
Incidence density <sup>a</sup>	34.04	15.94	4.71				
Ischemic stroke							
Event rate	2.61%	1.26%	1.75%	3.43 (1.82–6.49)	<.01*	0.63 (0.24–1.62)	.34
Incidence density	39.36	15.38	11.92				
Heart failure							
Event rate	1.53%	1.06%	1.33%	3.12 (1.62–6.00)	<.01*	2.01 (0.82–4.93)	.13
Incidence density	18.97	15.43	8.99				
MACE							
Event rate	3.73%	2.33%	2.22%	4.12 (2.30–7.34)	<.01*	1.05 (0.79–1.51)	.99
Incidence density	55.18	33.87	15.27				

Note: \* $p < .05$ .

Abbreviations: ADT, androgen deprivation therapy; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MACE, major adverse cardiovascular events.

<sup>a</sup>Incidence density: event numbers per 1000 person-years.

**Table 1.** Comorbidities requiring pharmacologic treatment during the last 12 months (as diagnosed by a physician) at any age in at least 10% of men aged 65 years or older.

Comorbidity	Age		
	65–74 years	75–84 years	>85 years
Hypertension	49.8%	53.0%	44.5%
Hypercholesterolemia	41.4%	39.2%	24.1%
Chronic back pain	39.1%	43.3%	50.6%
Cervical	15.5%	18.4%	23.0%
Lumbar	23.6%	24.9%	27.6%
Arthrosis (excluding arthritis)	26.8%	38.7%	49.1%
Diabetes	25.0%	25.9%	22.7%
CV disease	18.8%	26.8%	35.1%
Myocardial infarction	1.6%	2.5%	3.0%
Angina pectoris/Coronary disease	2.4%	4.1%	6.3%
Stroke*	2.6%	1.7%	3.6%
Other <sup>†</sup>	12.2%	18.5%	22.2%
Prostate problems <sup>†</sup>	18.4%	28.2%	30.9%
Mental disorders	12.6%	16.9%	17.0%
Depression	6.5%	7.2%	6.1%
Anxiety (chronic)	4.3%	4.9%	3.5%
Other <sup>†</sup>	1.8%	4.8%	7.4%
Chronic allergy <sup>‡</sup>	10.0%	7.7%	7.7%
Chronic bronchitis, emphysema, COPD	8.7%	12.3%	16.4%
Urinary incontinence <sup>#</sup>	7.3%	17.9%	27.6%
Kidney disorders <sup>†</sup>	4.9%	7.9%	11.3%
Chronic constipation	3.4%	5.0%	14.2%

Adapted from the National Health Survey 2017. Ministerio de Sanidad, Consumo y Bienestar Social. Gobierno de España[30]. This survey was carried out using a closed questionnaire. The answers were reported by participants and no confirmed diagnosis is available.

\*Includes embolism, cerebral infarction, brain hemorrhage.

<sup>†</sup>Not specified in the original document.

<sup>‡</sup>Includes rhinitis, conjunctivitis, food allergies, and other allergies except allergic asthma.

<sup>#</sup>Includes urine control problems.

COPD, chronic obstructive pulmonary disease.

**Table 2.** DDIs between ARIs and frequent treatments for common metabolic disorders in men with nmCRPC receiving ADT.

Condition	Drug class	Common treatments	Effect of ARIs on comedication exposure ('perpetrators')			Effect of comedications on ARI exposure ('victims')			
			Apalutamide	Enzalutamide	Darolutamide	Apalutamide	Enzalutamide	Darolutamide	
Hypertension	Ca channel blocker	Diltiazem	↓↓/↓↓	↓/↓↓	-/-	-/-	-/-	-/-	
		Nifedipine	↓↓/↓↓	↓/↓↓↓	-/-	-/-	-/-	-/-	
		Verapamil	↓↓/↓↓	↓/↓/-	-/-	-/-	-/↑	-/-	
		Amlodipine	↓/↓↓	↓/↓↓	-/-	-/-	-/-	-/-	
	ARB	Losartan	↓/↓	↓/↓	-/-	-/-	-/-	-/-	
		Valsartan	-/↓	-/-	-/↑	-/-	-/-	-/-	
	Beta-blocker	Atenolol	-/-	-/-	-/-	-/-	-/-	-/-	
		Propranolol	-/↓	-/↓	-/-	-/-	-/-	-/-	
		Bisoprolol	↓/-	↓/-	-/-	-/-	-/-	-/-	
	ACE inhibitor	Enalapril	-/-	-/-	-/-	-/-	-/-	-/-	
		Captopril	-/-	-/-	-/-	-/-	-/-	-/-	
	Diuretics	Furosemide	-/-	-/-	-/-	-/-	-/-	-/-	
		Hydrochlorothiazide	-/-	-/-	-/-	-/-	-/-	-/-	
		Spirolactone	-/-	-/-	-/-	-/-	-/-	-/-	
Dyslipidaemia	Statins	Rosuvastatin	↓/↓	-/-	↑↑/↑↑	-/-	-/-	-/-	
		Atorvastatin	↓/↓	↓/↓	-/↑	-/-	-/-	-/-	
		Simvastatin	-/↓	-/↓	-/↑	-/-	-/-	-/-	
		Fluvastatin	-/↓	↓/↓	-/↑	-/-	-/-	-/-	
		Pravastatin	-/↓	-/-	-/↑	-/-	-/-	-/-	
		Pitavastatin	-/↓	-/-	-/↑	-/-	-/-	-/-	
		Lovastatin	-/↓	-/↓	-/↑	-/-	-/-	-/-	
	Fibrates	Gemfibrozil	-/-	-/-	-/-	↑/↑	↑↑/↑↑	-/-	
	Diabetes mellitus	Biguanides	Metformin	-/-	-/-	-/-	-/-	-/-	-/-
		Sulfonylureas	Gliclazide	-/↓	↓/↓	-/-	-/-	-/-	-/-
			Glimepiride	-/↓	↓/↓	-/-	-/-	-/-	-/-
			Glyburide	-/↓	↓/↓	-/↑	-/-	-/-	-/-
		DPP-4 inhibitors	Linagliptin	↓↓/↓	↓↓/↓	-/-	-/-	-/-	-/-
			Saxagliptin	↓/↓	↓/↓	-/-	-/-	-/-	-/-
Meglitinides		Repaglinide	↓/↓	↓/↓	-/↑	-/-	-/-	-/-	
Insulin		Insulin	-/-	-/-	-/-	-/-	-/-	-/-	

**Table 3.** DDIs between ARIs and frequent treatments for common cardiovascular diseases in men with nmCRPC receiving ADT.

Condition	Drug class	Common treatments	Effect of ARIs on comedication exposure ('perpetrators')			Effect of comedications on ARI exposure ('victims')			
			Apalutamide	Enzalutamide	Darolutamide	Apalutamide	Enzalutamide	Darolutamide	
CV disease <sup>†</sup> , deep vein thrombosis, atrial fibrillation	Antithrombotics	Warfarin	↓/↓	↓↓/↓	-/-	-/-	-/-	-/-	
		Acenocoumarin	↓/↓	↓↓/↓	-/-	-/-	-/-	-/-	
		Heparin	-/-	-/-	-/-	-/-	-/-	-/-	
		Dabigatran	X(↓↓↓)/↓	-/↓	-/-	-/-	-/-	-/-	
		Rivaroxaban	X(↓↓↓)/↓↓	↓↓/↓↓	-/↑	-/-	-/-	-/-	
		Apixaban	X(↓↓↓)/↓↓	↓↓/↓↓	-/-	-/-	-/-	-/-	
		Edoxaban	↓↓/↓	↓↓/↓	-/-	-/-	-/-	-/-	
		Antiplatelet agents	ASA	-/-	-/-	-/-	-/-	-/-	-/-
			Clopidogrel	↓↓/-	↓/↓	-/-	-/-	-/-	-/-
			Ticagrelor	X(↓↓↓)/↓↓	X(↓↓↓)/↓↓	-/-	-/-	-/-	-/-
Cardiac arrhythmia, HF	Cardiac glycosides Antiarrhythmics	Digoxin	↓/↓	-/↓	-/-	-/-	-/-	-/-	
		Amiodarone	↓/↓↓	↓/↓↓	-/-	-/-	-/-	-/-	
		Dronedarone	X(↓↓↓)/↓↓	X(↓↓↓)/↓↓	-/-	-/-	-/-	-/-	

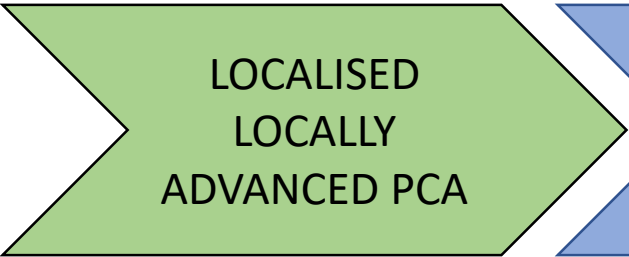
**CONCLUSIE**

Active surveillance  
Watchful waiting  
Local therapy ± ADT  
(ADT)

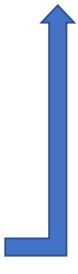
Salvage local therapy  
± ADT

Apalutamide  
Darolutamide  
Enzalutamide

Abiraterone  
Cabazitaxel  
Docetaxel  
Enzalutamide  
PARPi (olaparib/rucaparib)  
Pembrolizumab  
177Lu-PSMA617  
Radium-223  
(Sipuleucel-T)



ADT  
Abiraterone  
Apalutamide  
Docetaxel  
Enzalutamide  
RT prostate



- De hormonale therapie is essentieel in de behandeling van prostaatkanker
- MAAR niet zonder bijwerkingen
- Screening!
- Inclusie in zorgpad
- CAVE drug-drug interactie