Parameter identification of a model for prostate cancer treated by intermittent therapy

Clément Draghi
Biomedical Engineer

Fabrice Denis
oncologist

Alain Tolédano
oncologist

&

Christophe Letellier

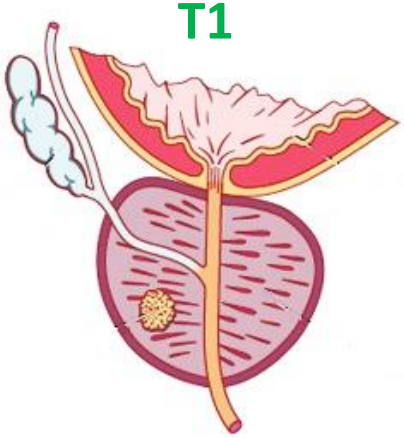
Institut Rafaël
Maison de l'après cancer

iLC
Institut inter-régional de Cancérologie

Normandie Université

➢ Evolution of prostate cancer: Tumor, Node, Metastasis Classification

T1

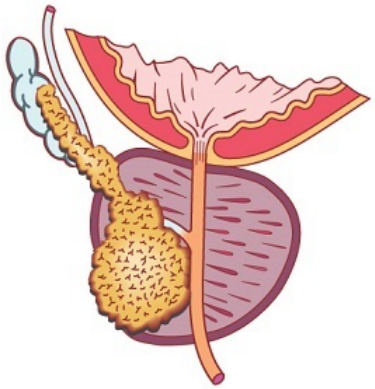


Clinically **inapparent** tumor

T2

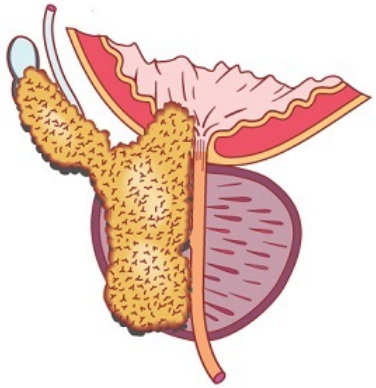
Tumor confined **within** prostate

T3

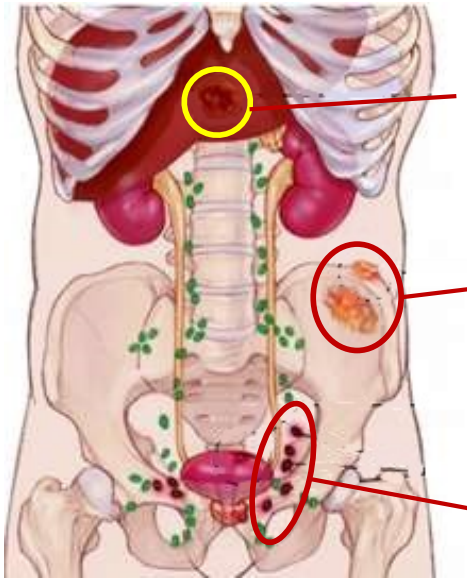


Tumor **extends through** the prostatic capsule

T4



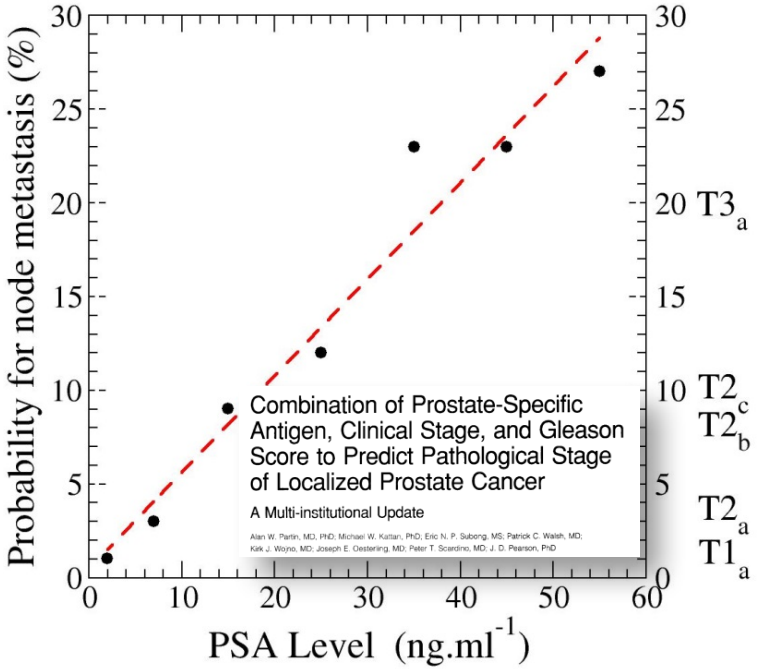
Tumor **fixed or invades adjacent** structures other than seminal vesicles

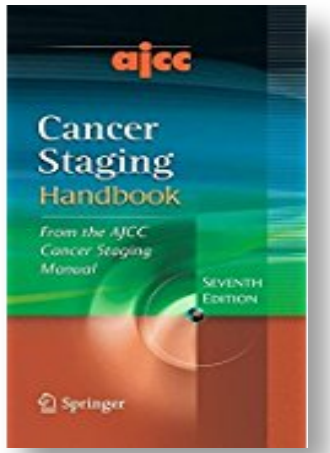


Liver **metastasis**

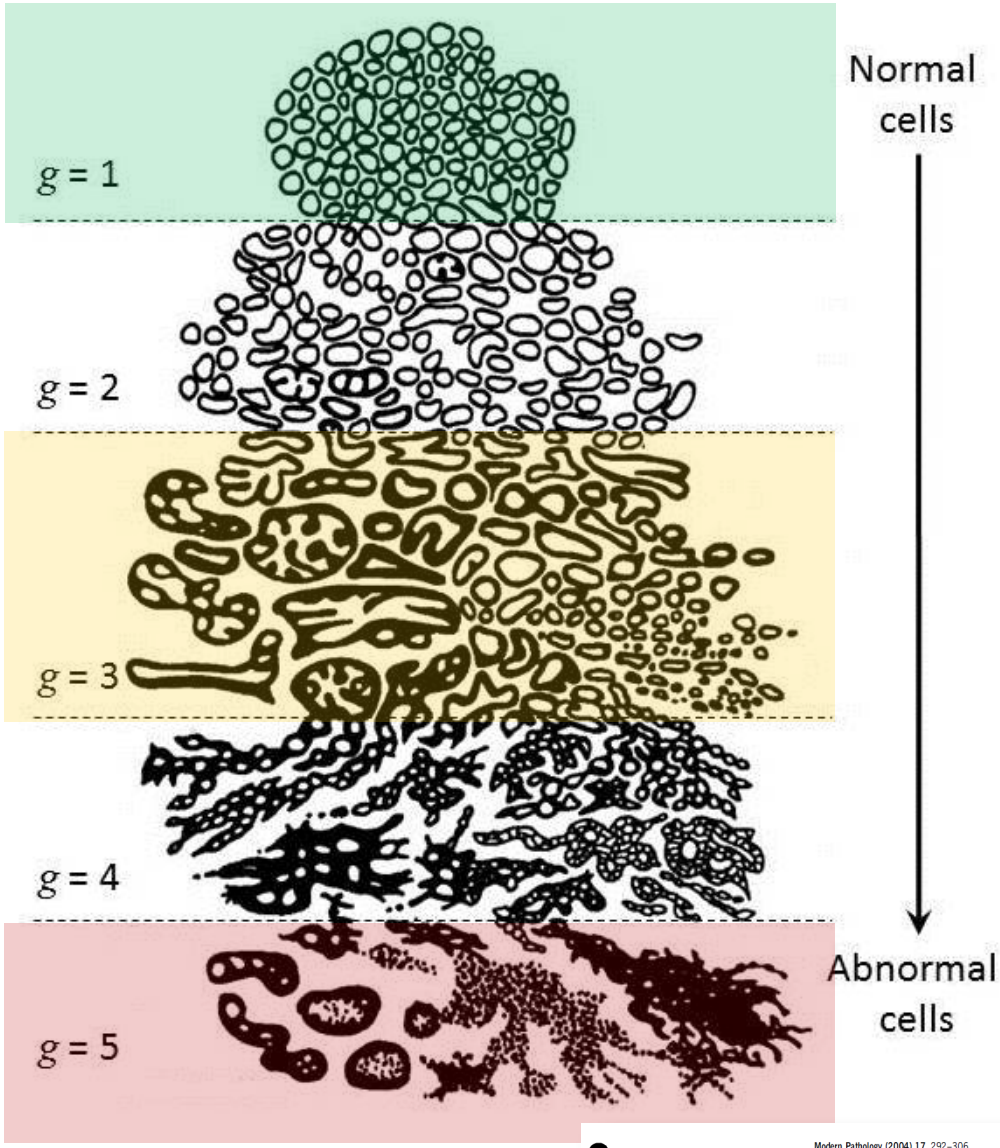
Bone **metastasis**

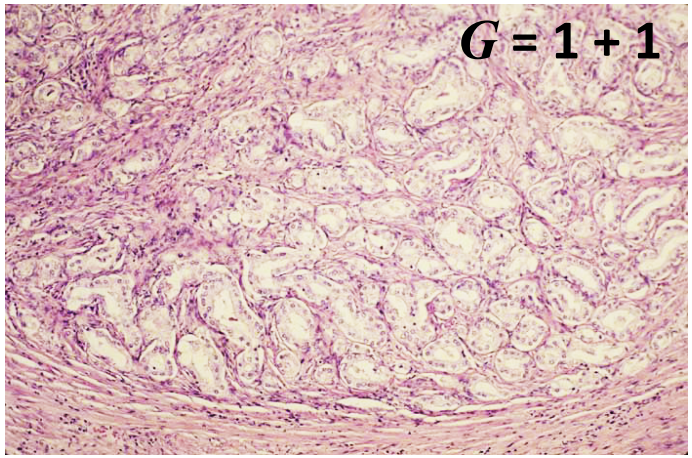
Lymph node **metastasis**

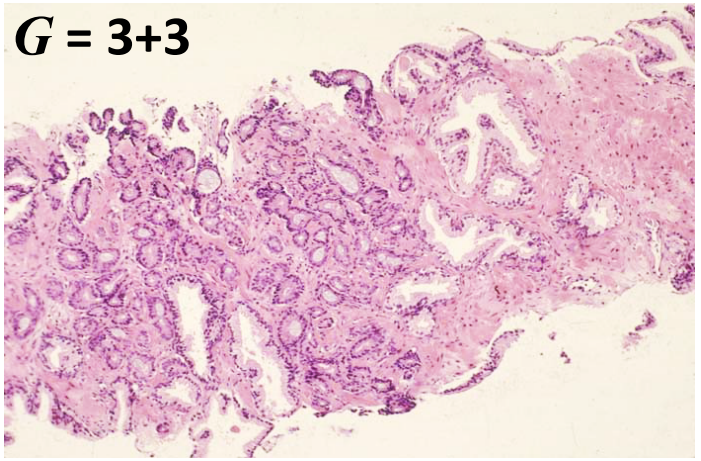


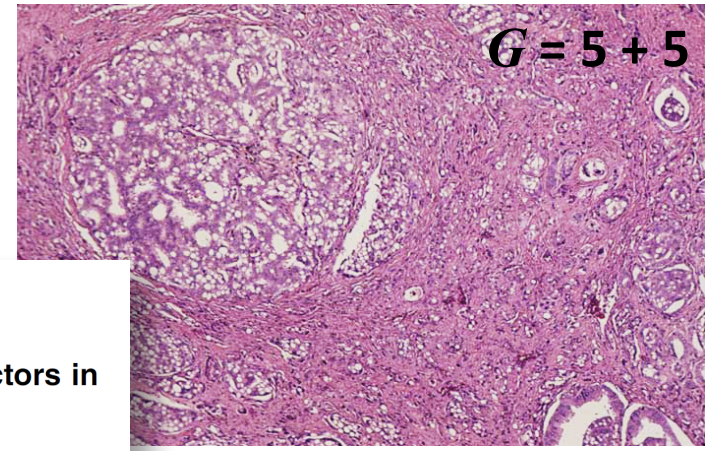


➢ **Prognosis factor**: Gleason score









Modern Pathology (2004) 17, 292–306
© 2004 USCAP, Inc All rights reserved 0893-3952/04 $25.00
www.modernpathology.org

Gleason grading and prognostic factors in carcinoma of the prostate

Peter A Humphrey

➢ **Prognosis factor** for survival

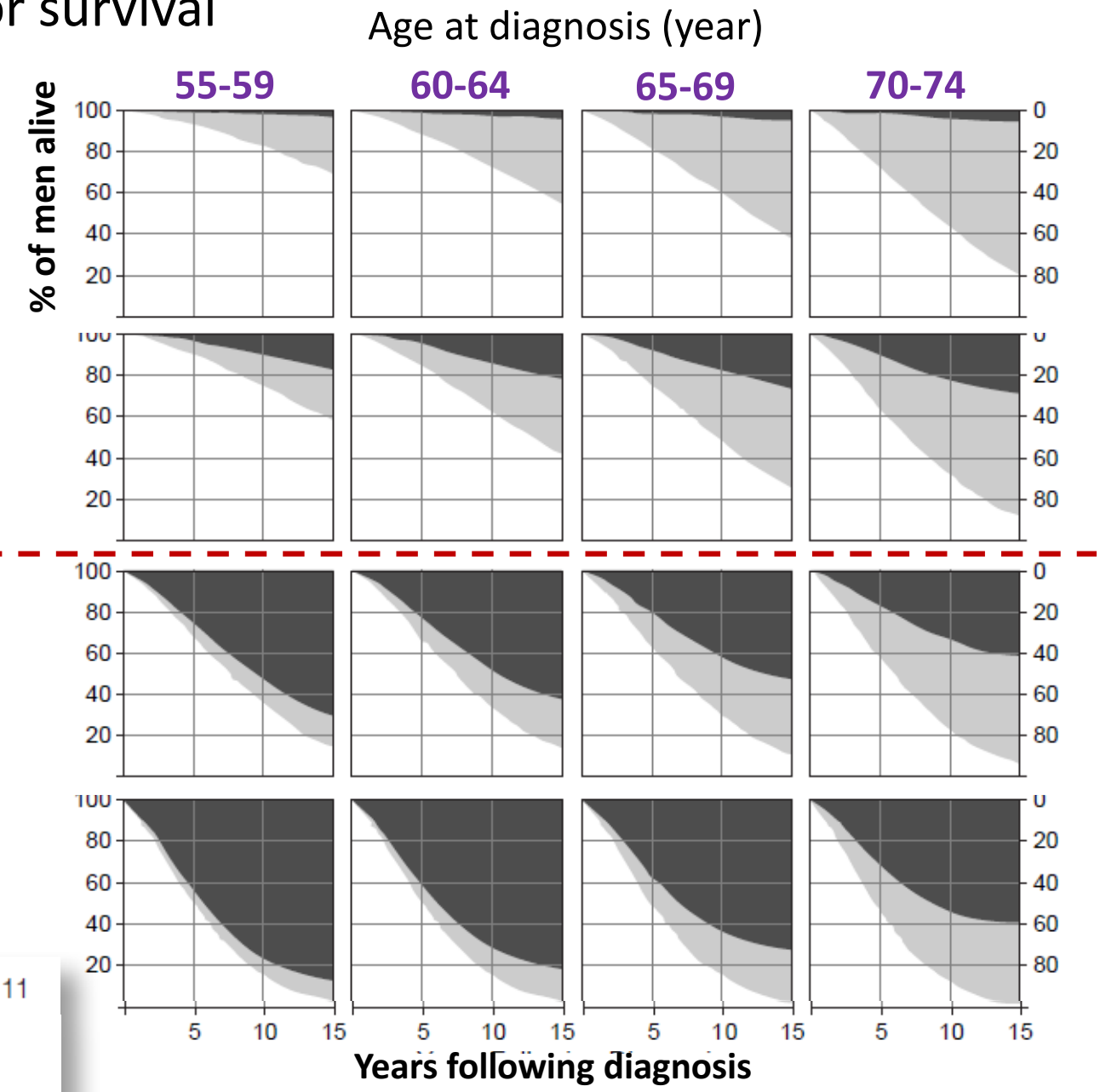
Gleason score

$2 \leq G \leq 4$

$G = 6$

$G = 7$

$8 \leq G \leq 10$



% of men deceased from **prostate cancer**

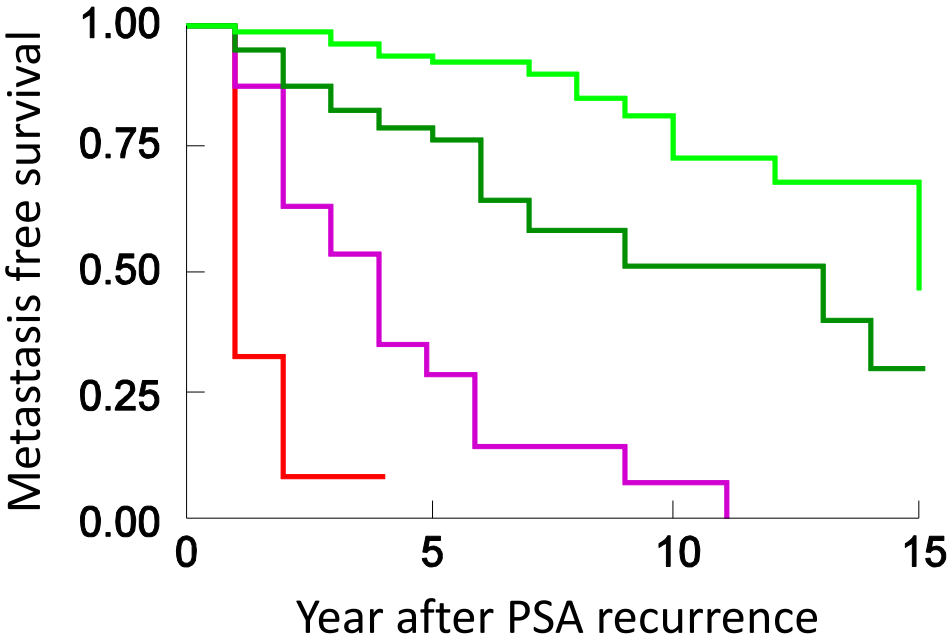
% of men deceased from **other causes**

JAMA, September 16, 1998—Vol 280, No. 11

Competing Risk Analysis of Men Aged 55 to 74 Years at Diagnosis Managed Conservatively for Clinically Localized Prostate Cancer

Peter C. Albertsen, MD; James A. Hanley, PhD; Donald F. Gleason, MD, PhD; Michael J. Barry, MD

- The **doubling duration τ_{PSA} of PSA level** is also a prognosis factor



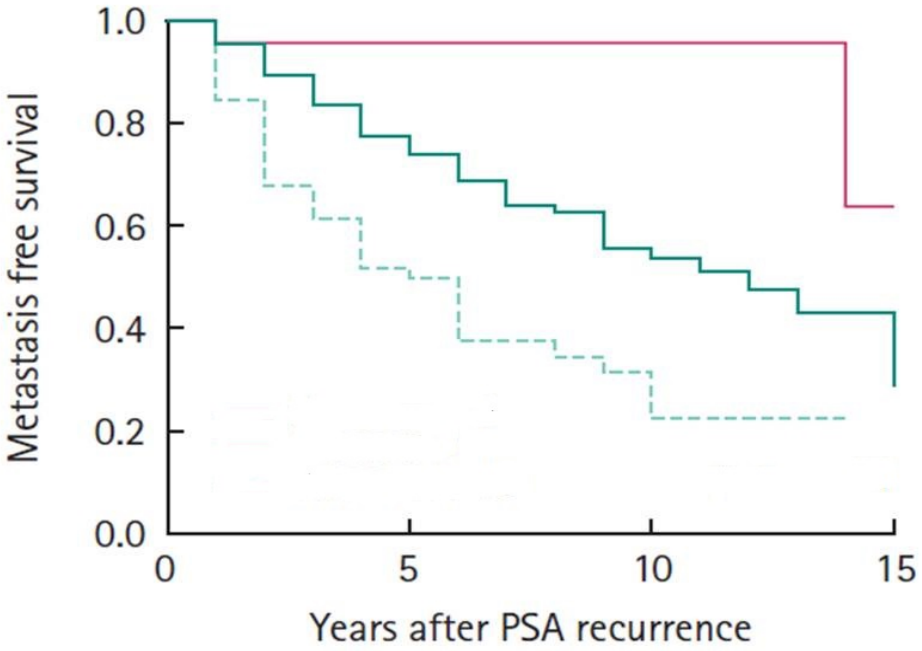
$\tau_{PSA} > 15$ months

$9 < \tau_{PSA} < 15$ months

$3 < \tau_{PSA} < 9$ months

$\tau_{PSA} < 3$ months

- As the **Gleasone score G**



$4 \leq G \leq 6$

$G = 7$

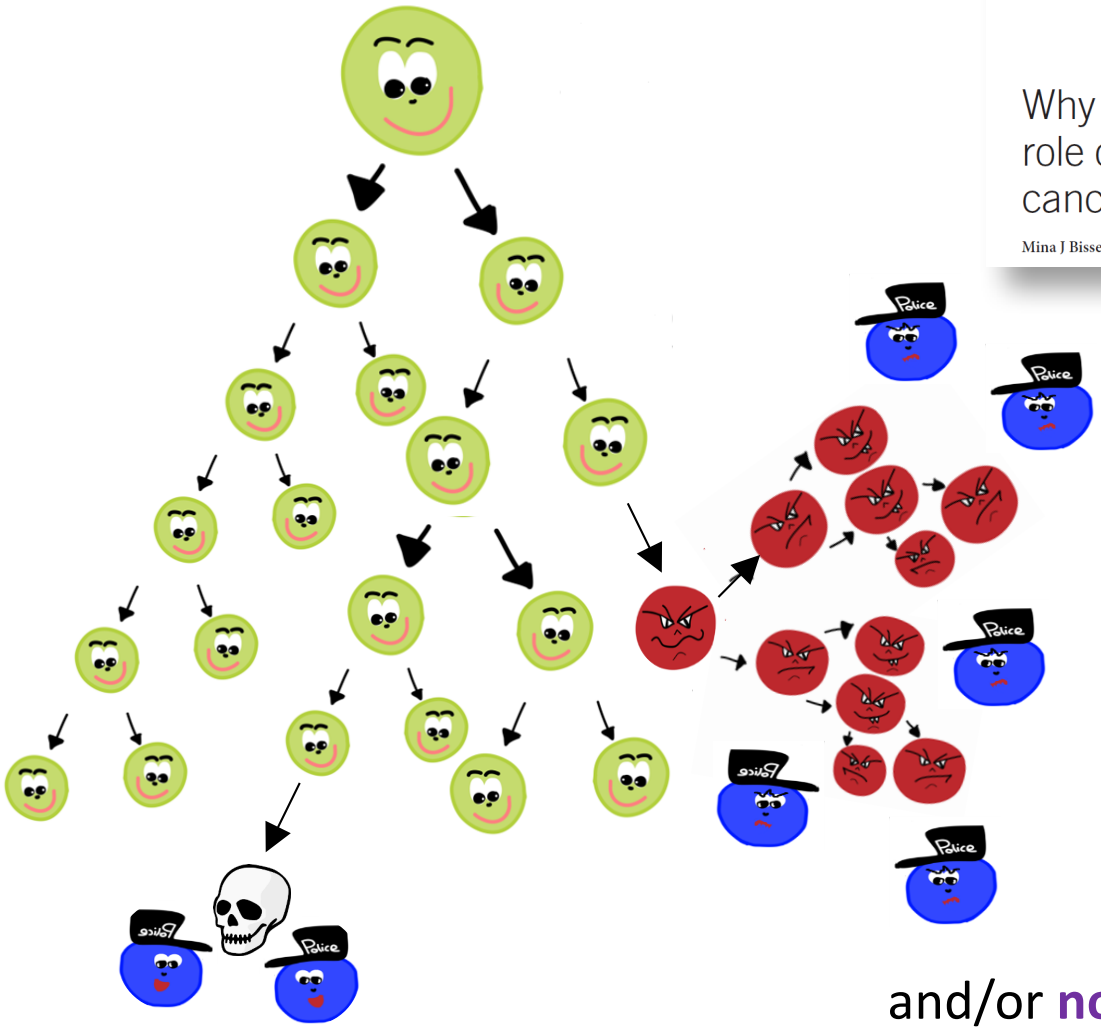
$8 \leq G \leq 10$

BJUI

The natural history of metastatic progression in men with prostate-specific antigen recurrence after radical prostatectomy: long-term follow-up

Emmanuel S. Antonarakis, Zhaoyong Feng*, Bruce J. Trock*, Elizabeth B. Humphreys*, Michael A. Carducci, Alan W. Partin*, Patrick C. Walsh* and Mario A. Eisenberger

➢ **Biology of cancer** in 2 min…

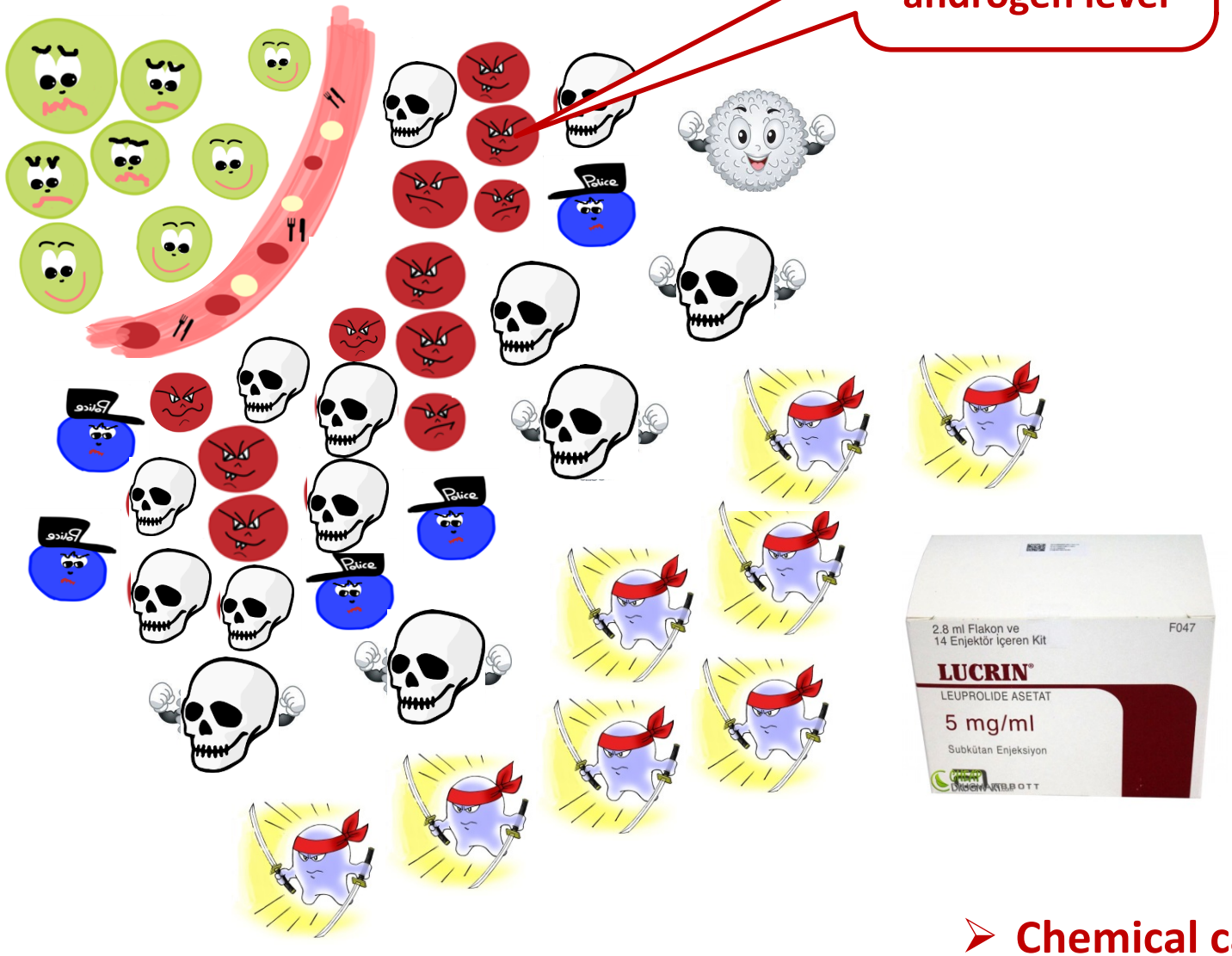


Efficient immune system
and/or **competitive** host tissue
= **strong barriers** against tumor growth

Inefficient
immune system
and/or **noncompetitive** host tissue
= **weak barriers** against tumor growth

➢ **Biology of cancer** in 2 min…

➢ **Weakly competitive** host tissue



➢ **Chemical castration**

✓ Evolution of prostate cancer

- ❖ **Hormone-dependent tumor cells** ➢ **LHRH analogs**
- ❖ **Hormone-hypersensitive tumor cells** ➢ **Anti-androgen drug**

- ❖ **Hormone-independent tumor cells** ➢ **Chemotherapy**

Hormone evasion

✓ A model for prostate cancer

$$
\begin{cases}
\dot{p} = \rho_p\, p(1-p) - \alpha_{pa}\,(1-a)p - \delta_{pB}\, p\, \mathrm{B}(t) \\
\dot{a} = \rho_a a(1-a) - \delta_{aL}\, a\, \mathrm{L}(t) \\
\dot{t}_\mathrm{d} = \rho_\mathrm{d} t_\mathrm{d} - [\delta_{da}(a) + \delta_{dB}\, \mathrm{B}(t)]\; t_\mathrm{d}^2 - \alpha_{dp}\, t_\mathrm{d}\, p - \epsilon(1-a)\, t_\mathrm{d} \\
\dot{t}_\mathrm{i} = \rho_\mathrm{i}\, t_\mathrm{i} - \alpha_{ip}\, t_\mathrm{i}\, p + \epsilon(1-a) t_\mathrm{d}
\end{cases}
$$

Patient global status

Androgen level

Hormone-dependent

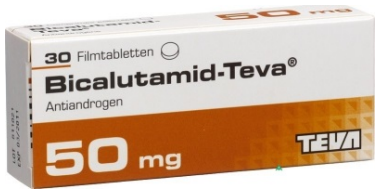
Hormone-hypersensitive

mutation

LHRH analogs

➢ **Reduce the level of androgens**

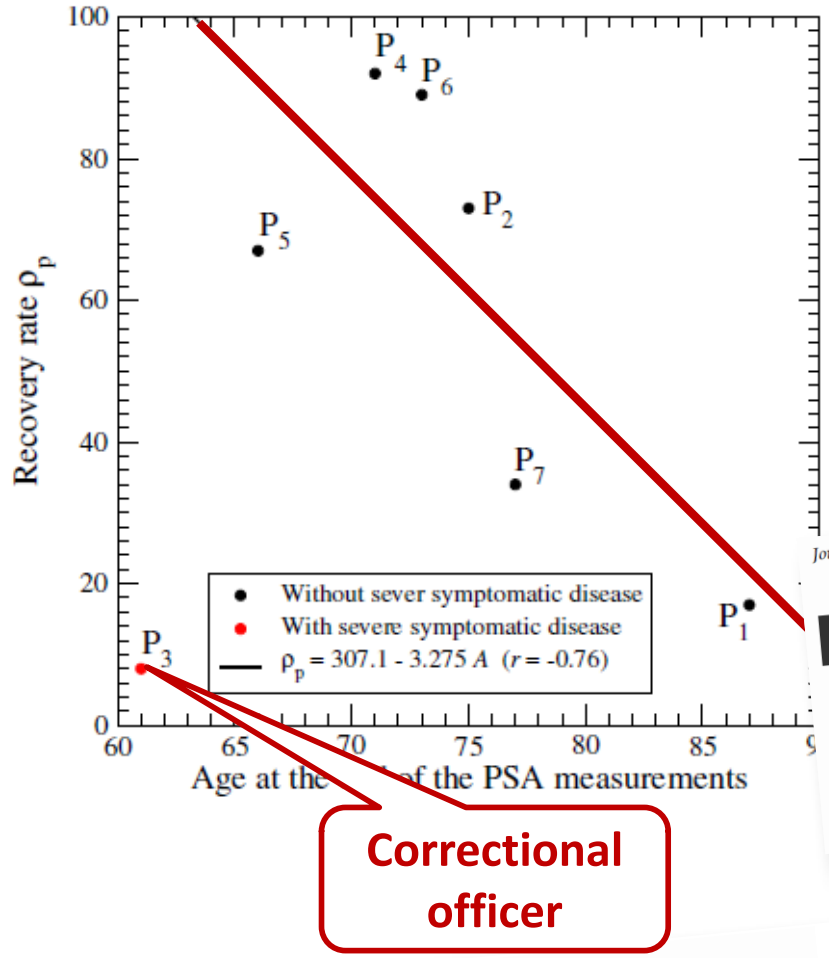
Anti-androgen drug



➢ **Prevent the effects of androgens**

✓ **Parameter identification** performed using a **genetic algorithm**

✓ **Recovery rate** ρ_p of patient's **global status**



- characterizes the **ability of the body to react against any aggression**
- **decreases with age**

Review series

Causes, consequences, and reversal of immune system aging

Encarnacion Montecino-Rodriguez, Beata Berent-Maoz, and Kenneth Dorshkind

Journal of Internal Medicine 2000; 247: 159–167

21st CENTURY REVIEW

Ageing and medicine

Nuffield Department of Clinical Medicine, University of Oxford, Oxford, UK

European Heart Journal (2008) 29, 640–648
doi:10.1093/eurheartj/ehm584

CLINICAL RESEARCH
Prevention and epidemiology

Work stress and coronary heart disease: what are the mechanisms?

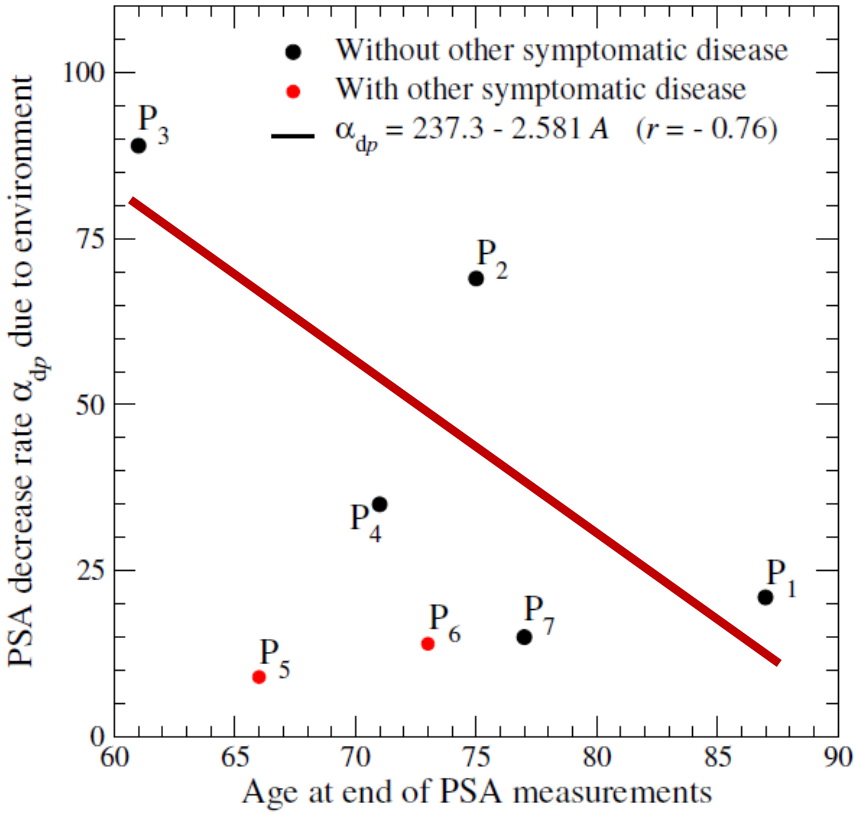
Tarani Chandola[1]*, Annie Britton[1], Eric Brunner[1], Harry Hemingway[1], Marek Malik[2], Meena Kumari[1], Ellena Badrick[1], Mika Kivimaki[1], and Michael Marmot[1]

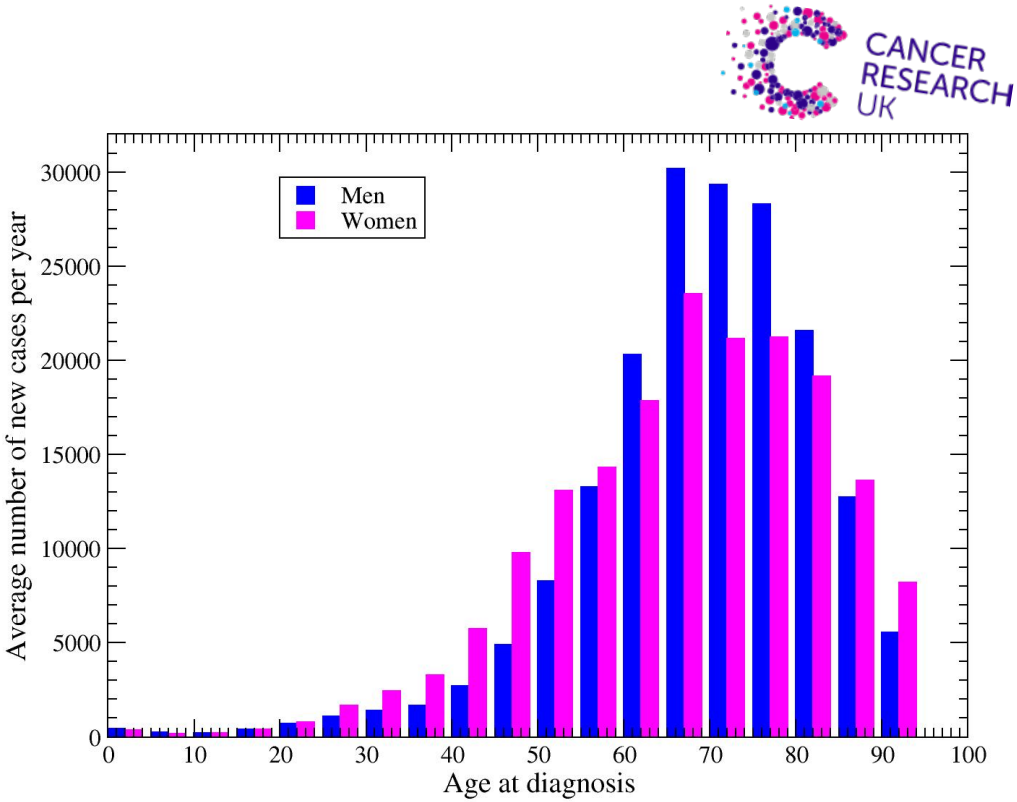
Psychological Stress and Disease

Sheldon Cohen, PhD
Denise Janicki-Deverts, PhD
Gregory E. Miller, PhD

JAMA, October 10, 2007—Vol 298, No. 14

✓ **Decrease rate α_{dp} in the PSA level due to the environment**



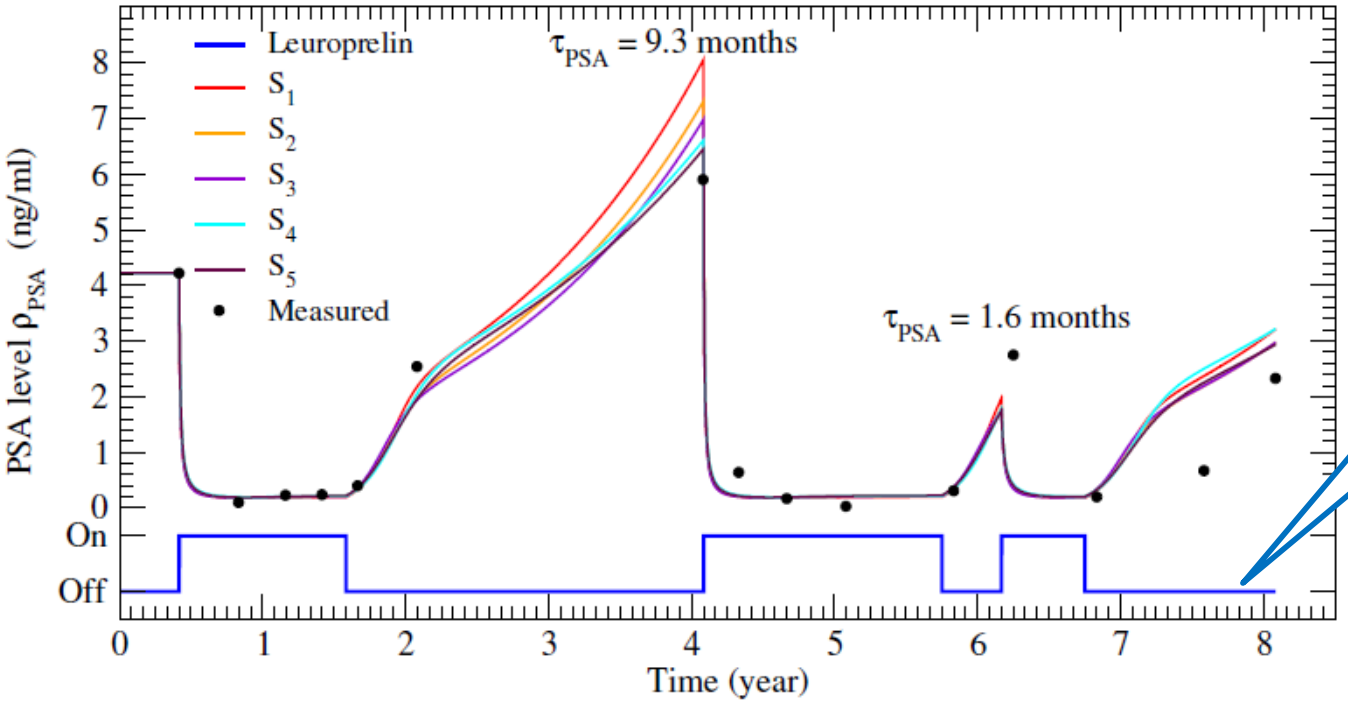


CANCER RESEARCH UK

- The **strength of barriers** against tumor progression **decreases with the age**
- Correlated to the increase in **cancer incidence with the age**

✓ An easy case

75 years old
Gleason score = **6**
No particular medical history



LHRH analogs

➢ Model parameter values

	ρ_p	α_{pa}	ρ_a	ρ_d	δ_{da}	α_{dp}	ρ_i	α_{ip}	ϵ
Patient P_2 (75 years, $G = 6$): $\delta_{aL} = 300$, Er = 15%									
1	89	81	159	64	275	59	0	0	0
2	75	60	185	71	255	66	0	0	0
3	76	52	196	89	293	84	0	0	0
4	72	59	130	62	222	58	0	0	0
5	53	36	199	80	234	76	0	0	0

No hormone-hypersensitive tumor cells

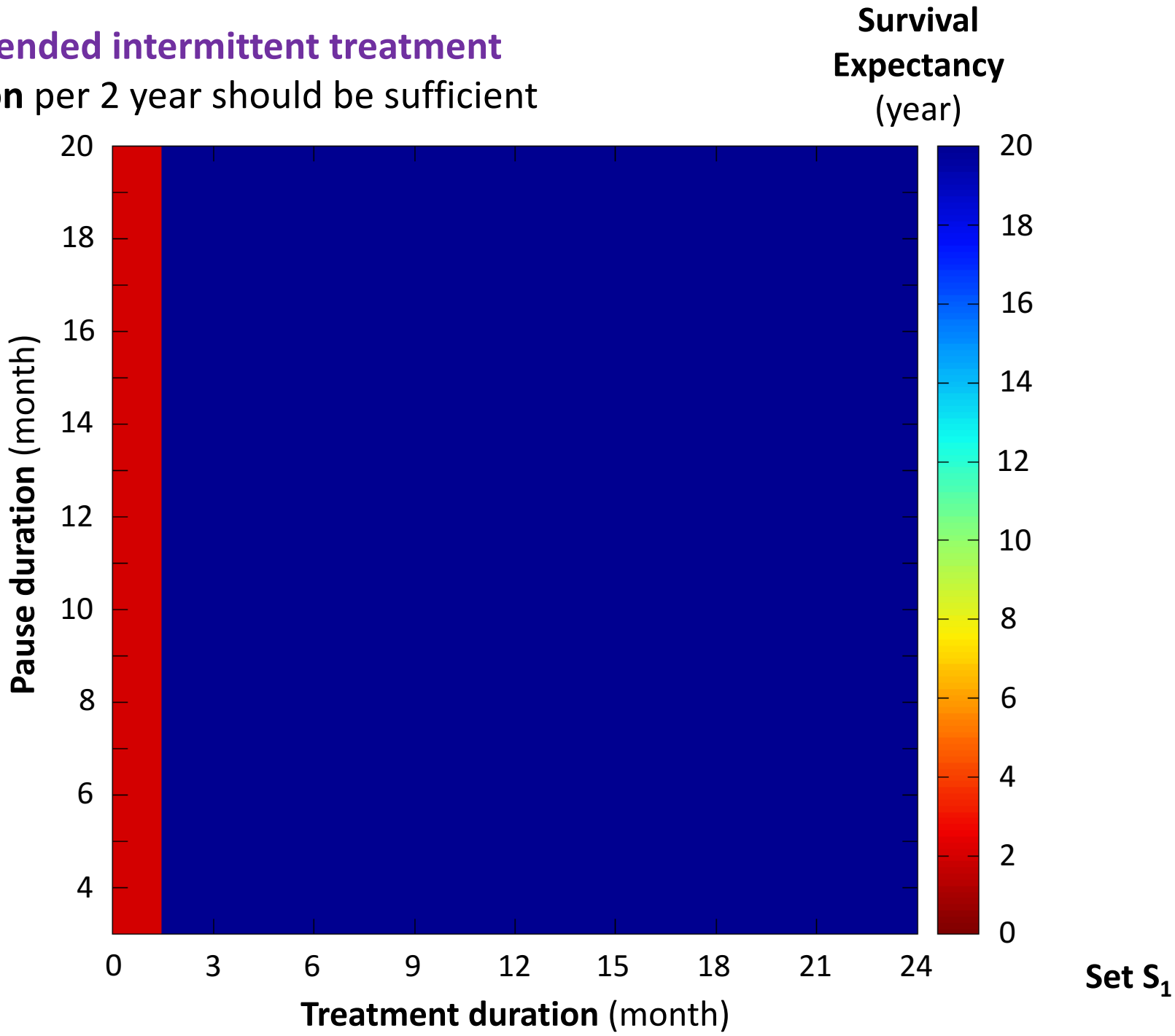
➢ **Aggressive cancer strongly dependent on androgens**

Balanced by a

➢ **Strong environment**

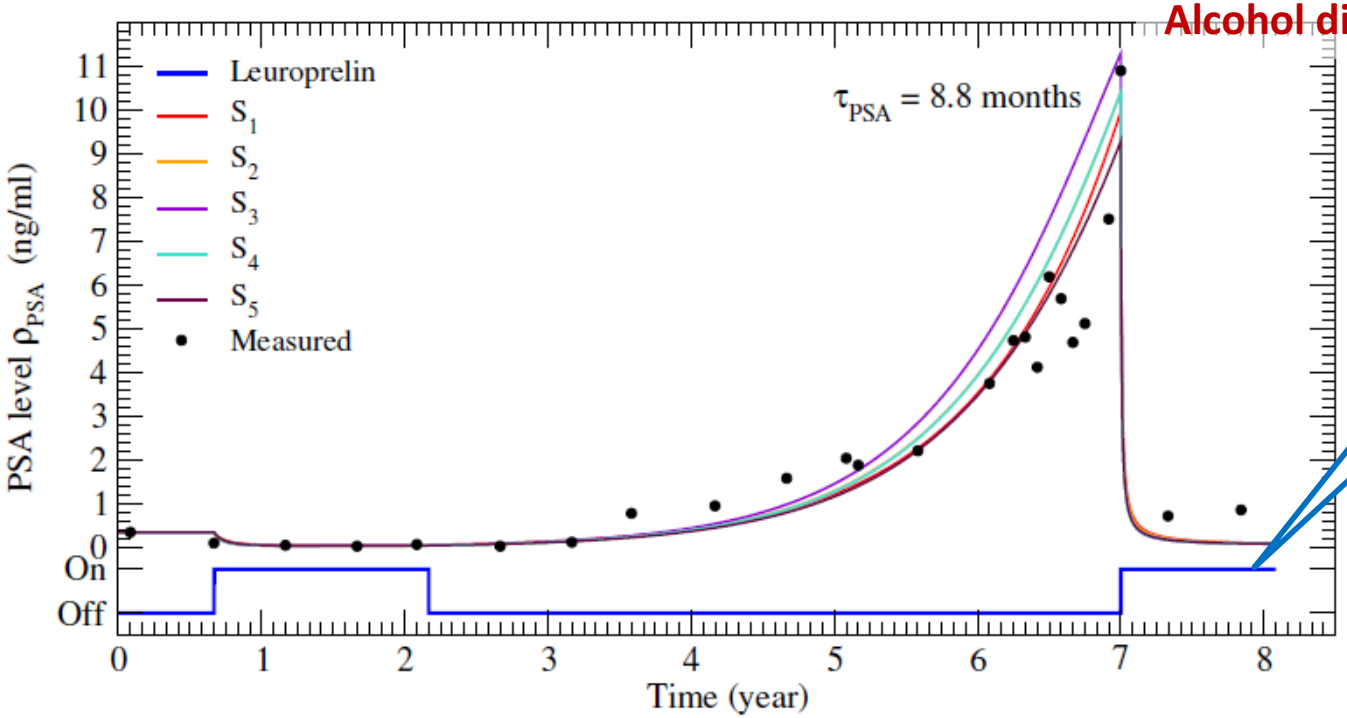
- **LHRH analogs** are **very efficient but must be initiated quickly (first year)**
- **Recommended intermittent treatment**

  1 injection per 2 year should be sufficient

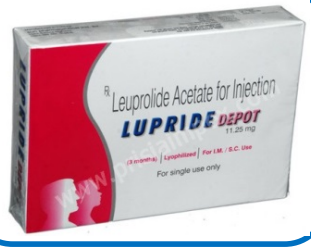


✓ Another easy case

75 years old
Gleason score = **6**
Alcohol disorders & arterial hypertension



LHRH analogs



➢ Model parameter values

	ρ_p	α_{pa}	ρ_a	ρ_d	δ_{da}	α_{dp}	ρ_i	α_{ip}	ϵ
Patient P_3 (61 years, $G = 6$): $\delta_{aL} = 300$, Er = 11%									
1	6	46	89	9	132	85	0	0	0
2	8	46	93	10	148	97	0	0	0
3	12	59	96	10	173	96	0	0	0
4	9	49	89	10	171	94	0	0	0
5	6	37	81	10	168	72	0	0	0

No hormone-hypersensitive tumor cells

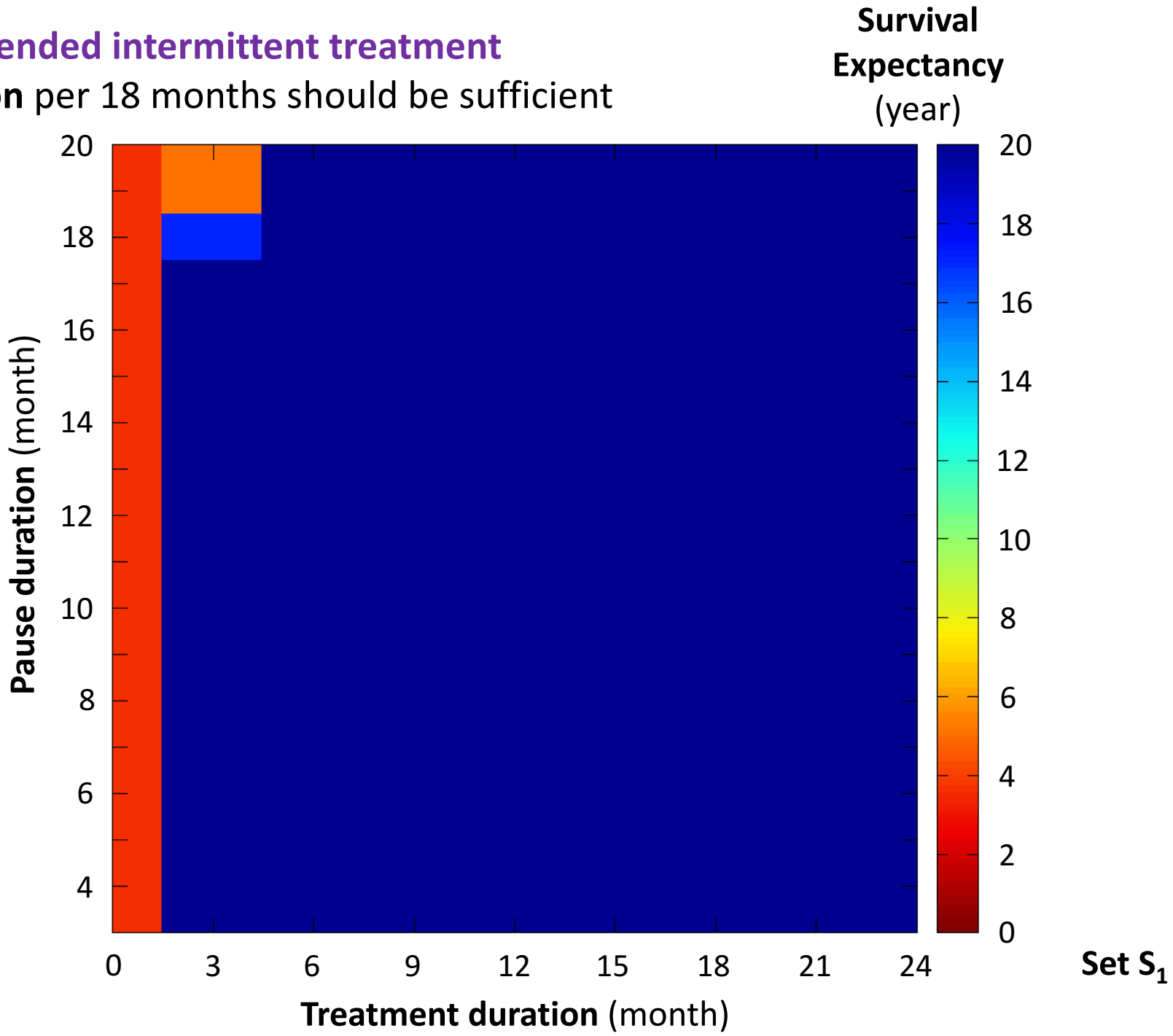
➢ Weak cancer

➢ Weak environment

(Small ρ_d and ρ_a)

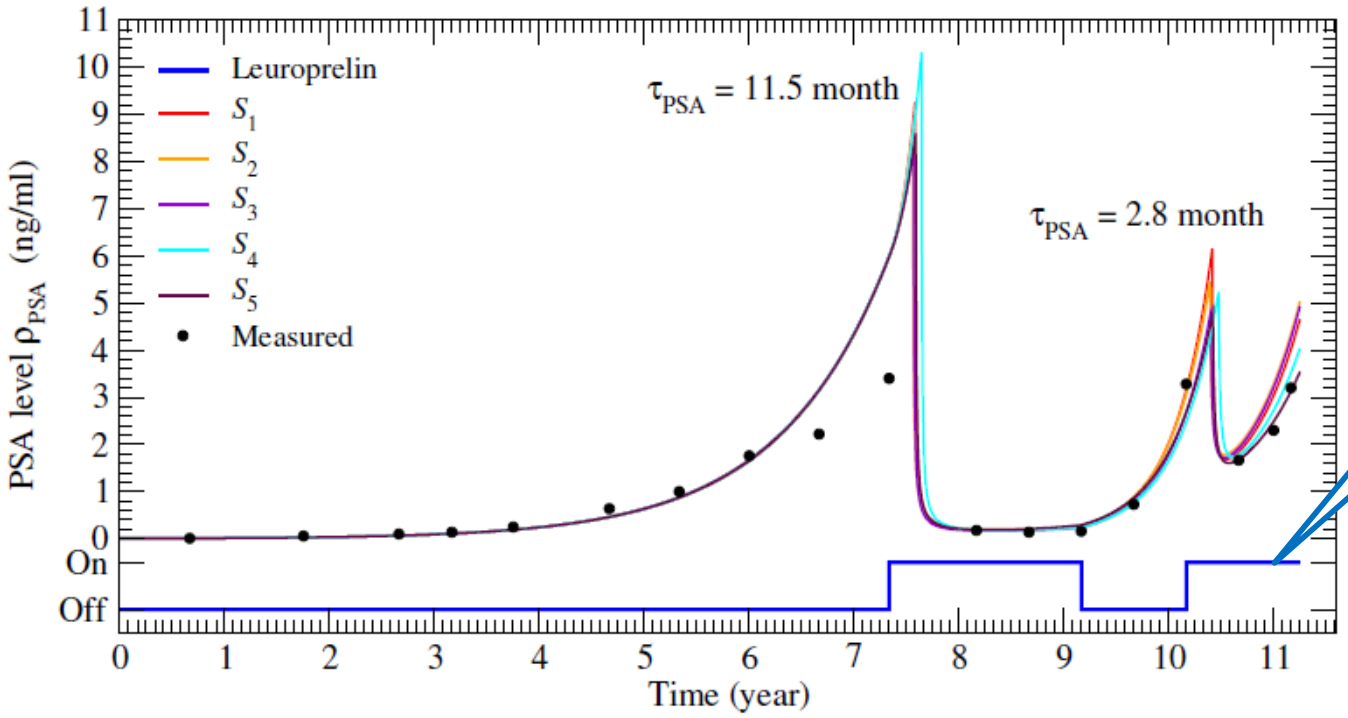
- **LHRH analogs** are **very efficient but must be initiated quickly (first year)**
- **Recommended intermittent treatment**

  1 injection per 18 months should be sufficient

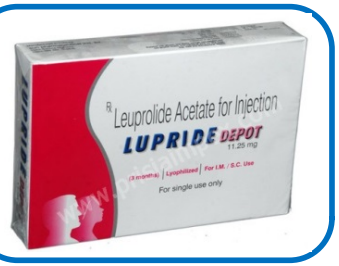


✓ An evolutive case

77 years old
Gleason score = **6**
No particular medical history



LHRH analogs



➢ Model parameter values

	ρ_p	α_{pa}	ρ_a	ρ_d	δ_{da}	α_{dp}	ρ_i	α_{ip}	ϵ
Patient P_7 (77 years, $G = 6$): $\delta_{aL} = 300$, Er = 18%									
1	45	90	115	24	170	16	15	47	0.160
2	52	90	103	23	153	15	15	8	0.154
3	19	39	86	23	176	15	15	2	0.145
4	27	78	142	22	169	14	14	38	0.140
5	27	43	91	23	169	15	13	18	0.104

Hormone evasion initiated

➢ **"Normal" cancer**

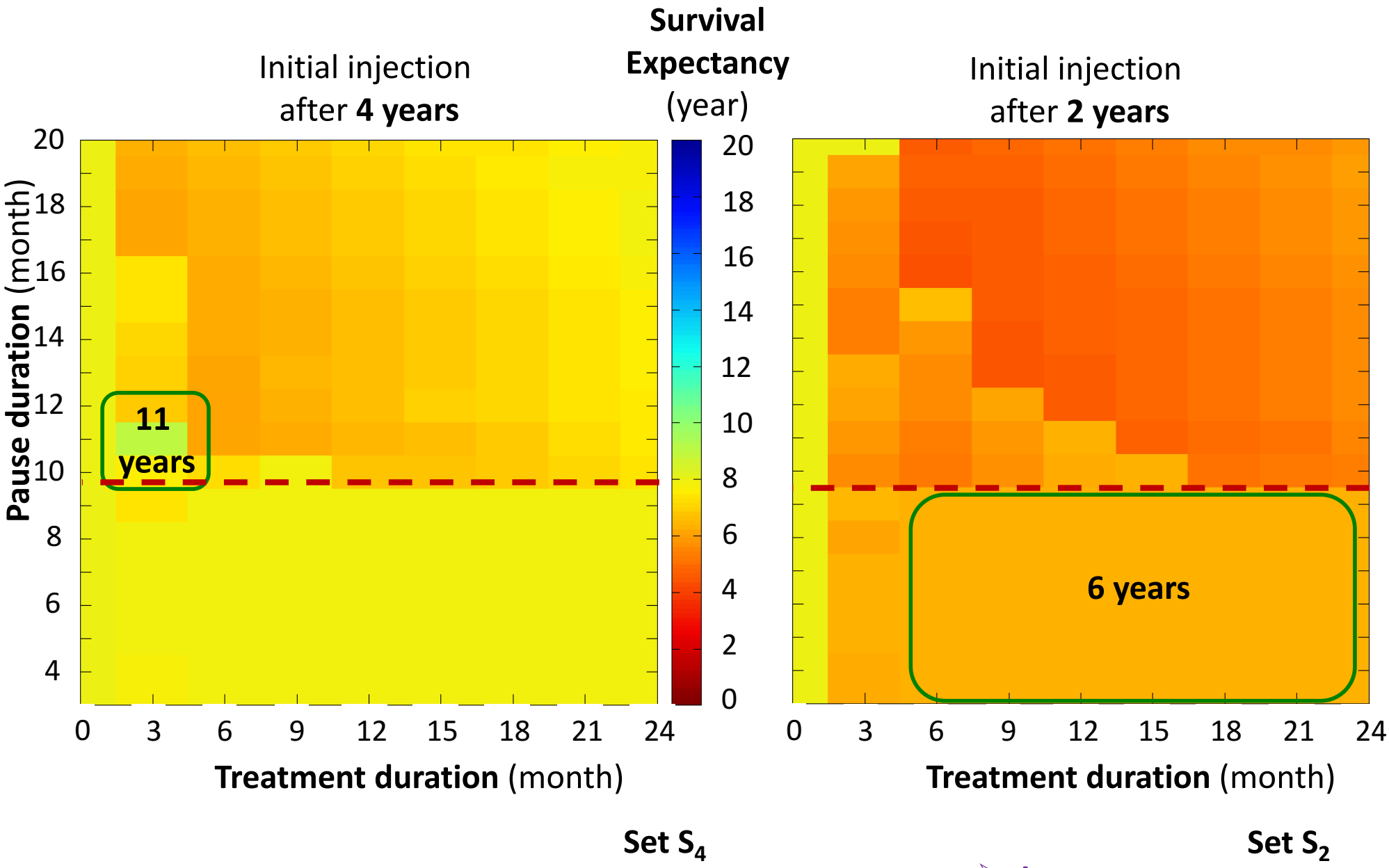
➢ **Slightly weak environment**

➢ **Recommended intermittent treatment**

1 injection per 14 month

➢ **Optimal intermittent treatment**

1 injection per year



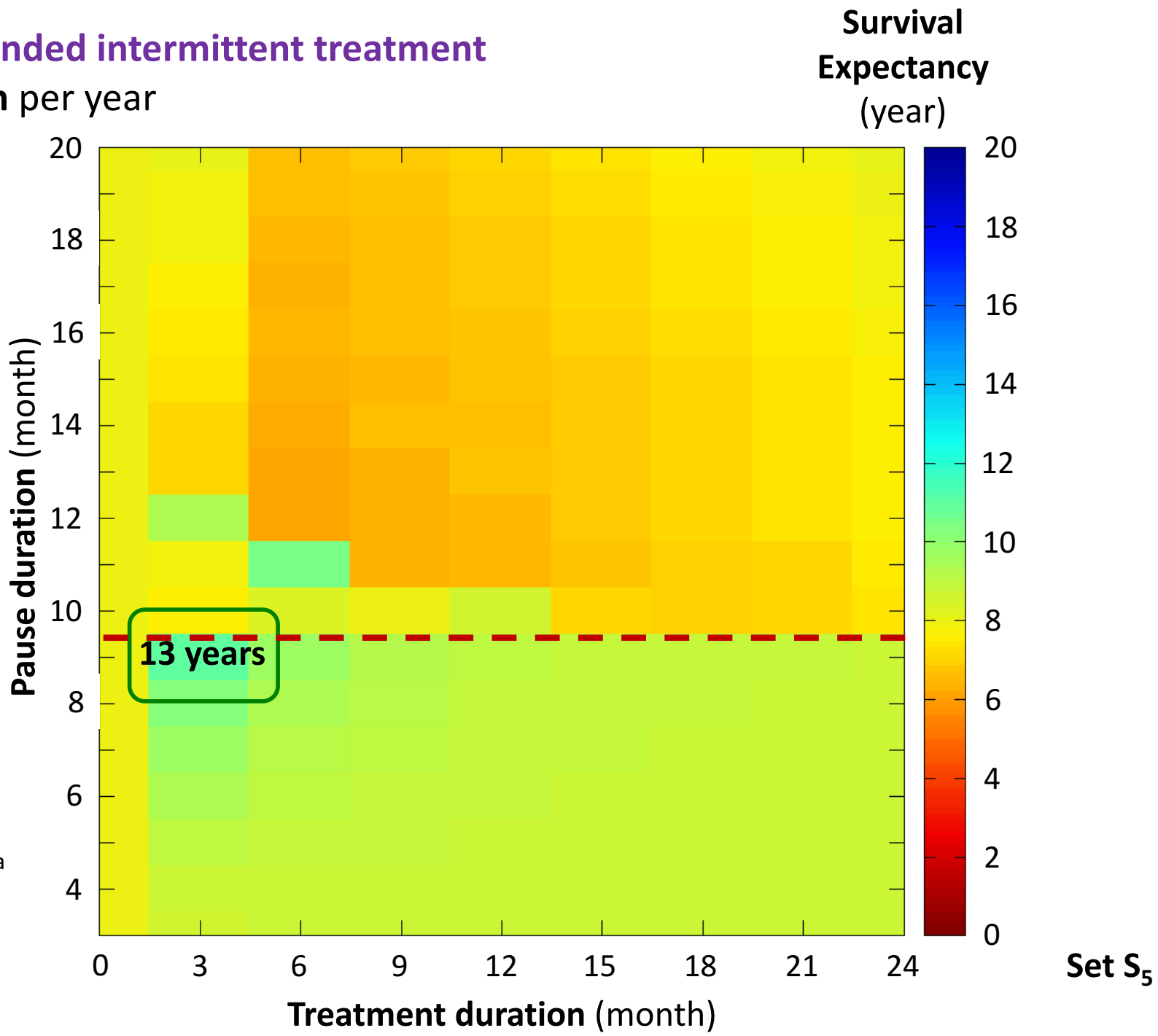
Set S_4

Set S_2

➢ **Larger** ρ_a

- **LHRH analogs** are **efficient!**
- **Recommended intermittent treatment**

  1 injection per year



- **Smaller** ρ_a

✓ A complicated case

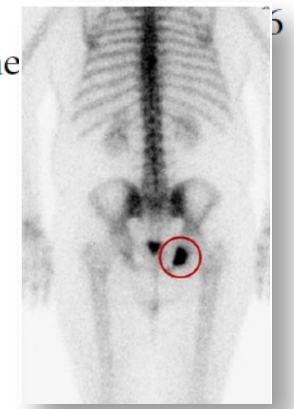
66 years old
Gleason score = **7**
Smoker

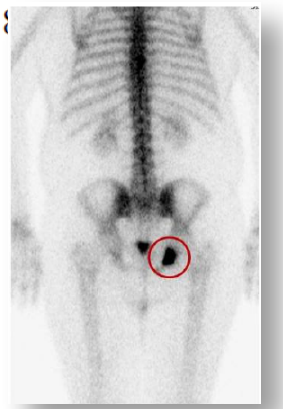
Bone Metastatsis

LHRH analogs

LHRH analogs

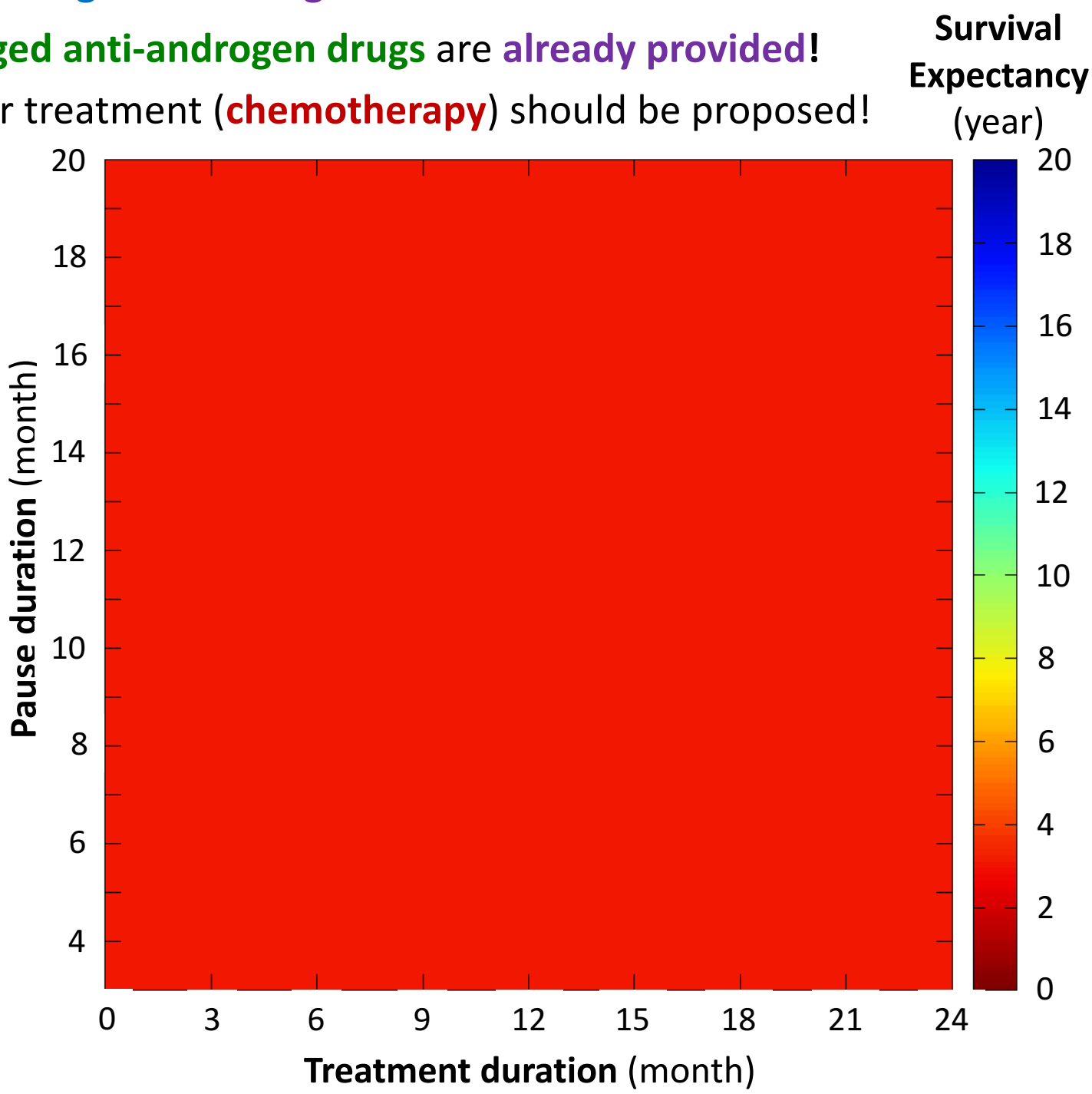
Anti-androgen





➢ **Radiotherapy** is not described by the model

- **LHRH analogs** are **no longer efficient!**
- **Prolonged anti-androgen drugs** are **already provided!**
- Another treatment (**chemotherapy**) should be proposed!



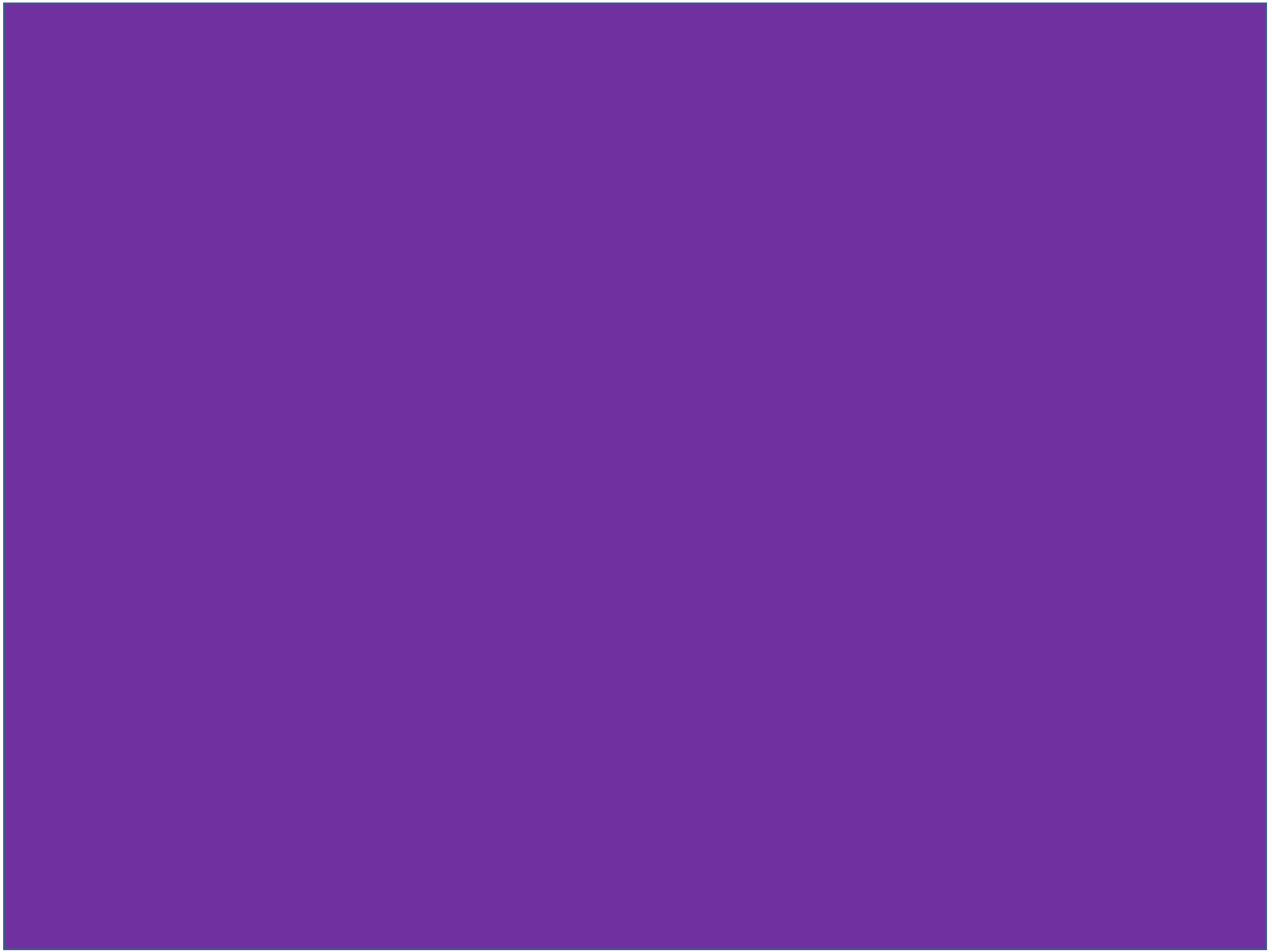
Conclusion

❖ Clinically

- ➢ **Gleason score** and **doubling duration** are **prognosis factors**
  - ✓ For metastasis free survival
  - ✓ For survival

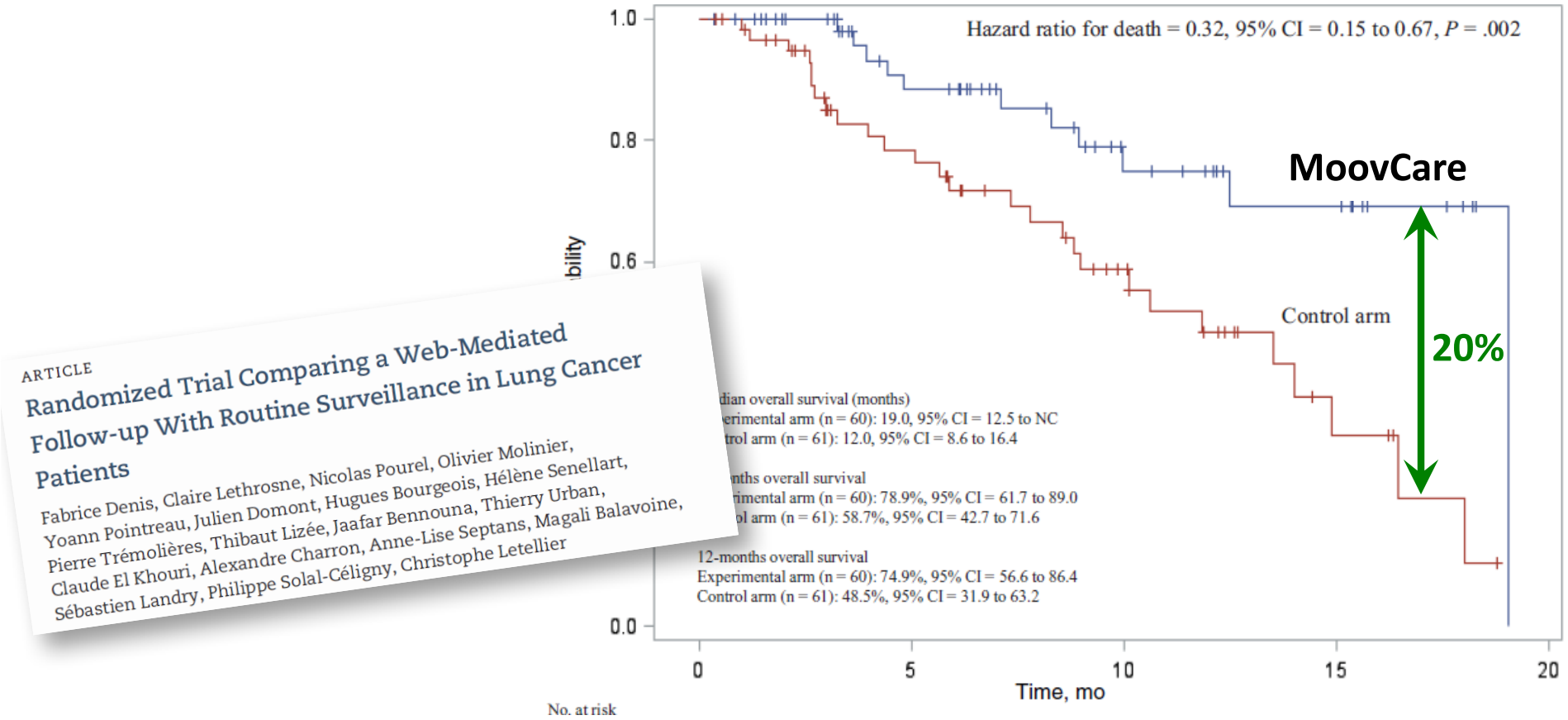
- ▪ But do not allow to optimize treatment
  - ➢ **Biologically motivated mathematical models** for better understanding the dynamics underlying tumor growth
  - ➢ Numerical simulations could allow to **optimize intermittent treatment**

- ➢ Individualized modelling could become a **predictive factor**



➢ Weekly self-reported symptoms

➢ Phase III (randomized) clinical trial: survival curve

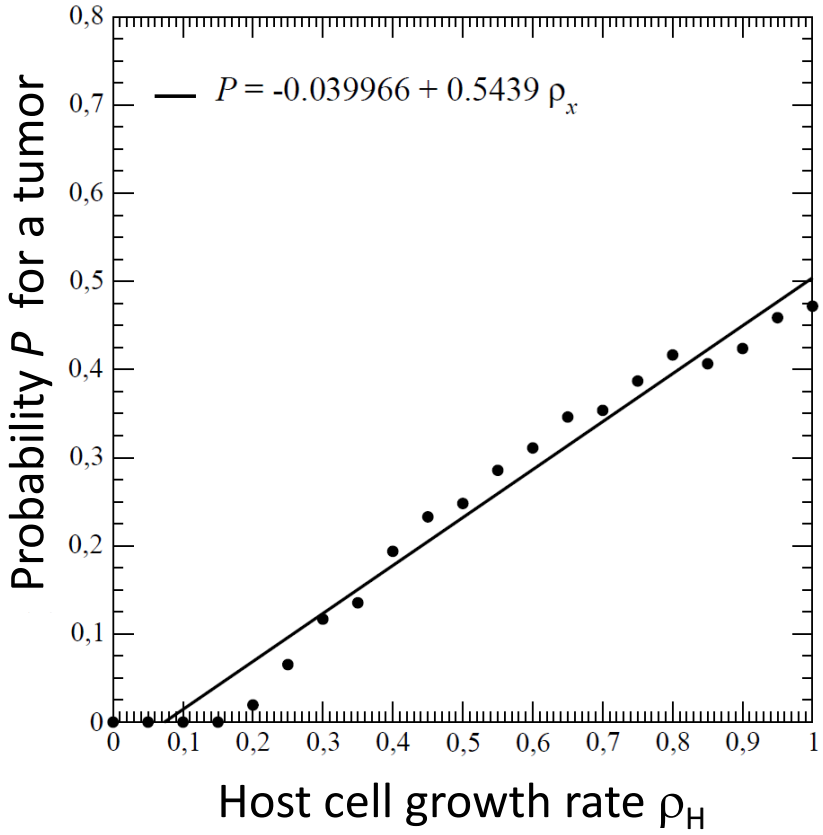


➢ More than **20%** at 18 month

➢ **Cancer relapses** are **treated earlier** (5 weeks), leading to a more **efficient treatment** and a **better quality of life** (less stress, less pain, …)

➢ How can cancer risk depend on normal cells?

➢ The **probability to detect a tumor** depends on the growth rate of host cells, that is, on how **competitive** are the normal cells



CHAOS 27, 093101 (2017)

How the growth rate of host cells affects cancer risk in a deterministic way

Clément Draghi,[1] Louise Viger,[1] Fabrice Denis,[1,2] and Christophe Letellier[1]

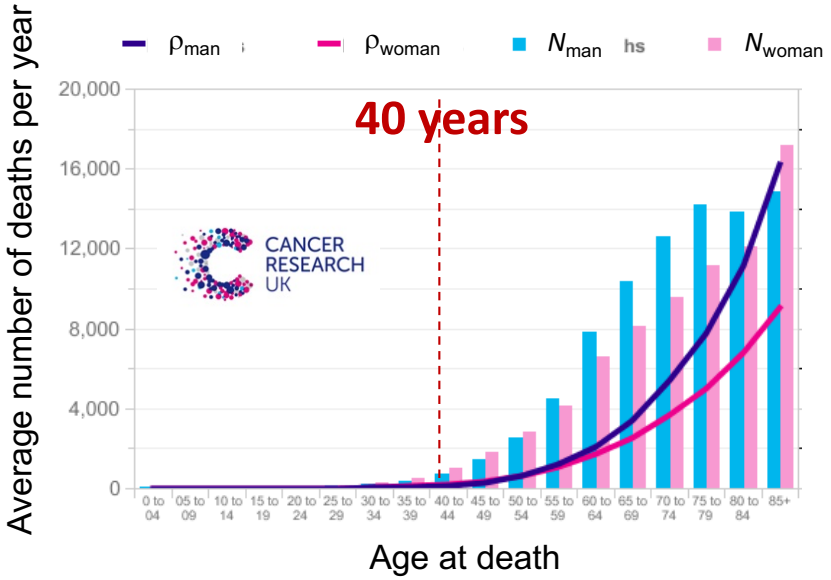
➢ Cancer incidence versus age

Hypothesis: the probability to present tumor cells depends on the number of cell divisions during life

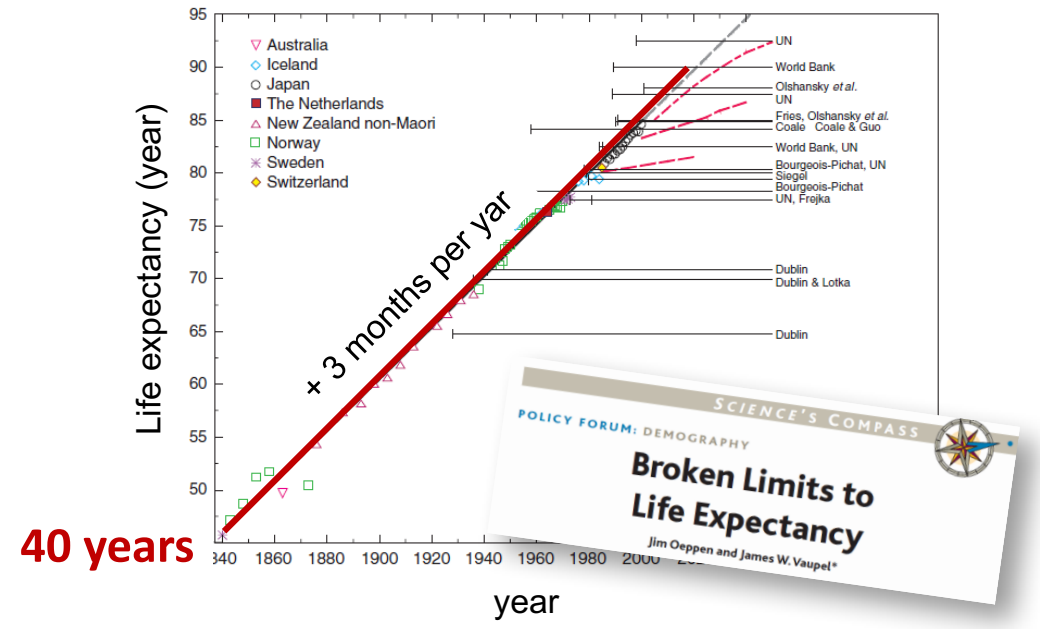
Corollary: The longer the life, the larger the cancer risk

True but…

In the United-Kingdom
(all types of cancer included)



Evolution of life expectancy

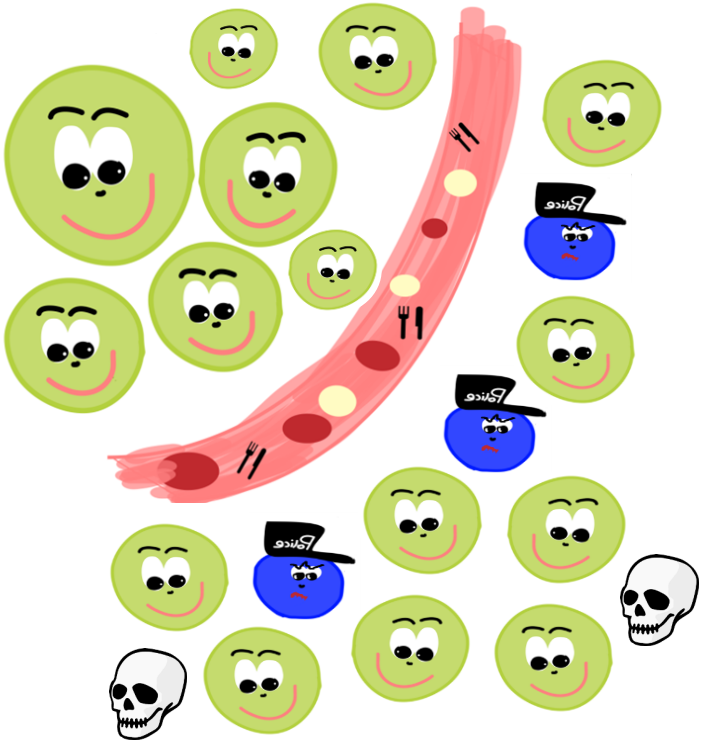


40 years

➢ The probability does not increase linearly with age…

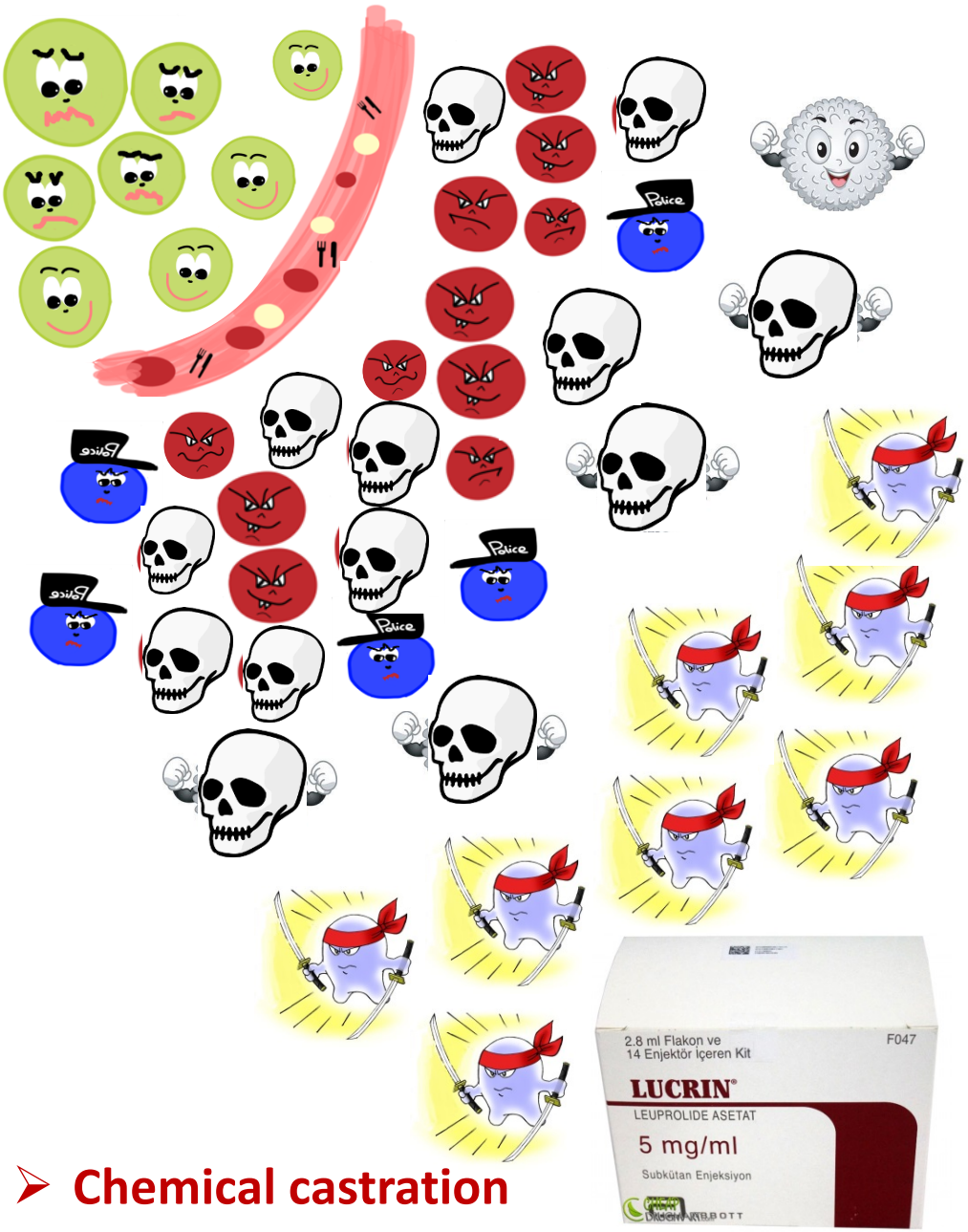
➢ Biology of cancer in 2 min…

➢ Strongly competitive host tissue



BUT…

➢ Weakly competitive host tissue



➢ Chemical castration