Conceptual basis for active surveillance

1. Screening results in overdiagnosis
2. Clinically insignificant disease can be identified
3. All treatments have significant side effects and cost.
4. Delayed radical treatment is still curative.
5. The psychological burden is acceptable (less than the effects of overtreatment).

The Screening Problem: U.S. Example

Welch JNCI 2005:97:1132-7

- Biopsy of all men with PSA > 2.5:
  - Result in 775,000 diagnosed cases, 3 x higher than current incidence
  - This is 25 times the 30,350 Prostate Cancer deaths per year in the US!

PSA testing in US men

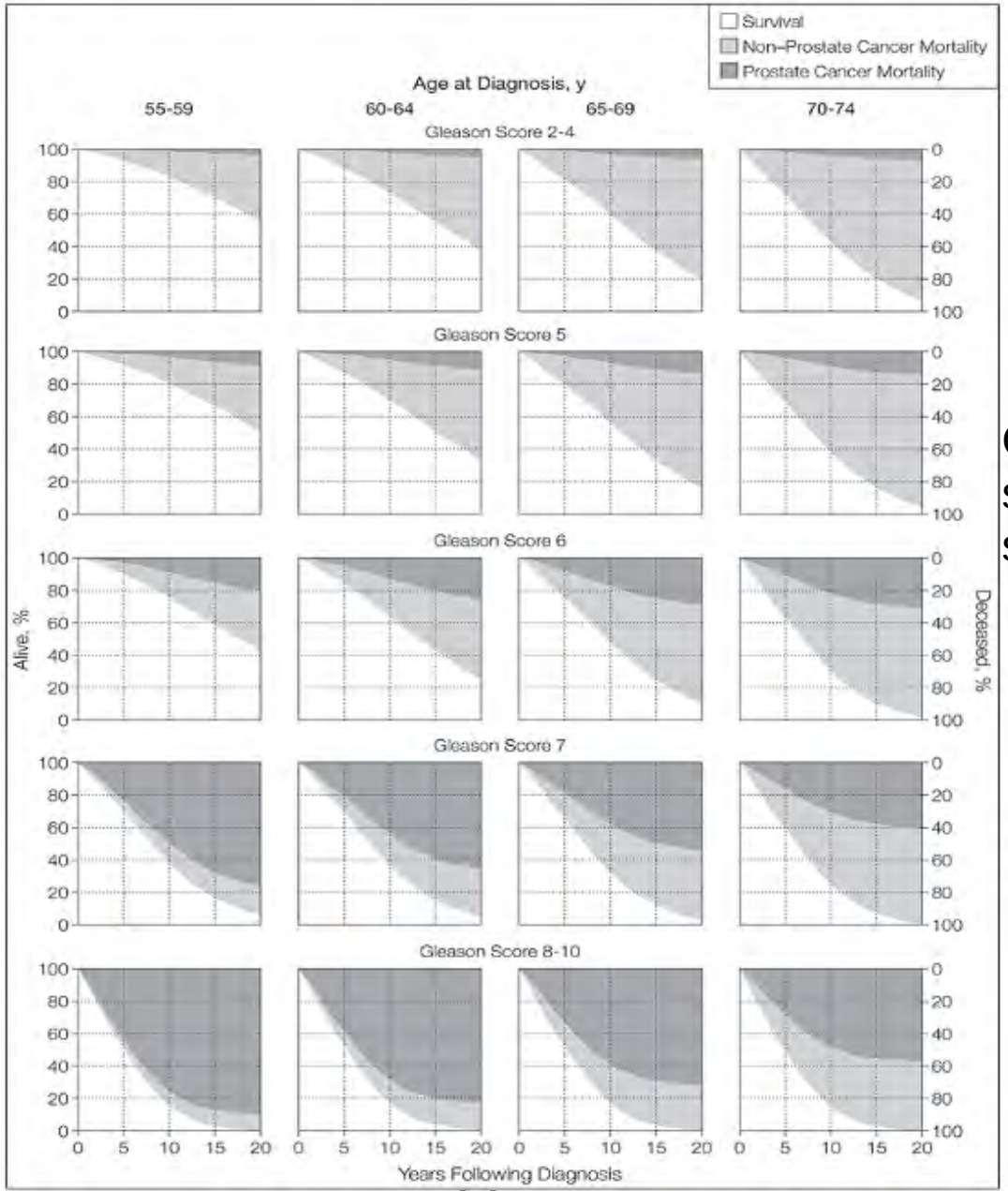
- 75% of men and 87% of male MDs have had a PSA
- 50% tested regularly
- Lifetime risk of diagnosis 19% (from 10% in pre PSA era)
- >90% treated radically

Overtreatment is common

- Studies of non-screen detected men
  - Albertsen
  - Johannson
  - SPCGS-4
- PSA era studies
  - Cancer registries
  - PCPT
  - ESRPC

20-Year Outcomes Following Conservative Management of Clinically Localized Prostate Cancer

Albertsen P et al,
JAMA. 2005;293:2095-2101



Gleason score shift
10
20
30

Lead Time effect 0 10 20 30

Years 0 10 20 25

ESRPC: % of indolent cancer at surgery

PSA	1st screen	2nd screen
<3	67	56
3-4	45	31
4-10	27	46
>10	13	36
Total	33	43

Estimates of overdiagnosis: Draisma 2007

T1	69%
T2	38%
T3	30%
Gleason < 7	62%
7	40%
>7	8%

Candidates for active surveillance

- 60% of new cases are Gleason 5-6 (CapSure)
- 80% PSA ≤ 10
- 65% T1c, 25% T2a
- Thus 45-50% of newly diagnosed cases are favorable risk
- About 50% of these fulfill criteria for insignificant prostate cancer
- One third of patients (85,000/year in US and Canada)

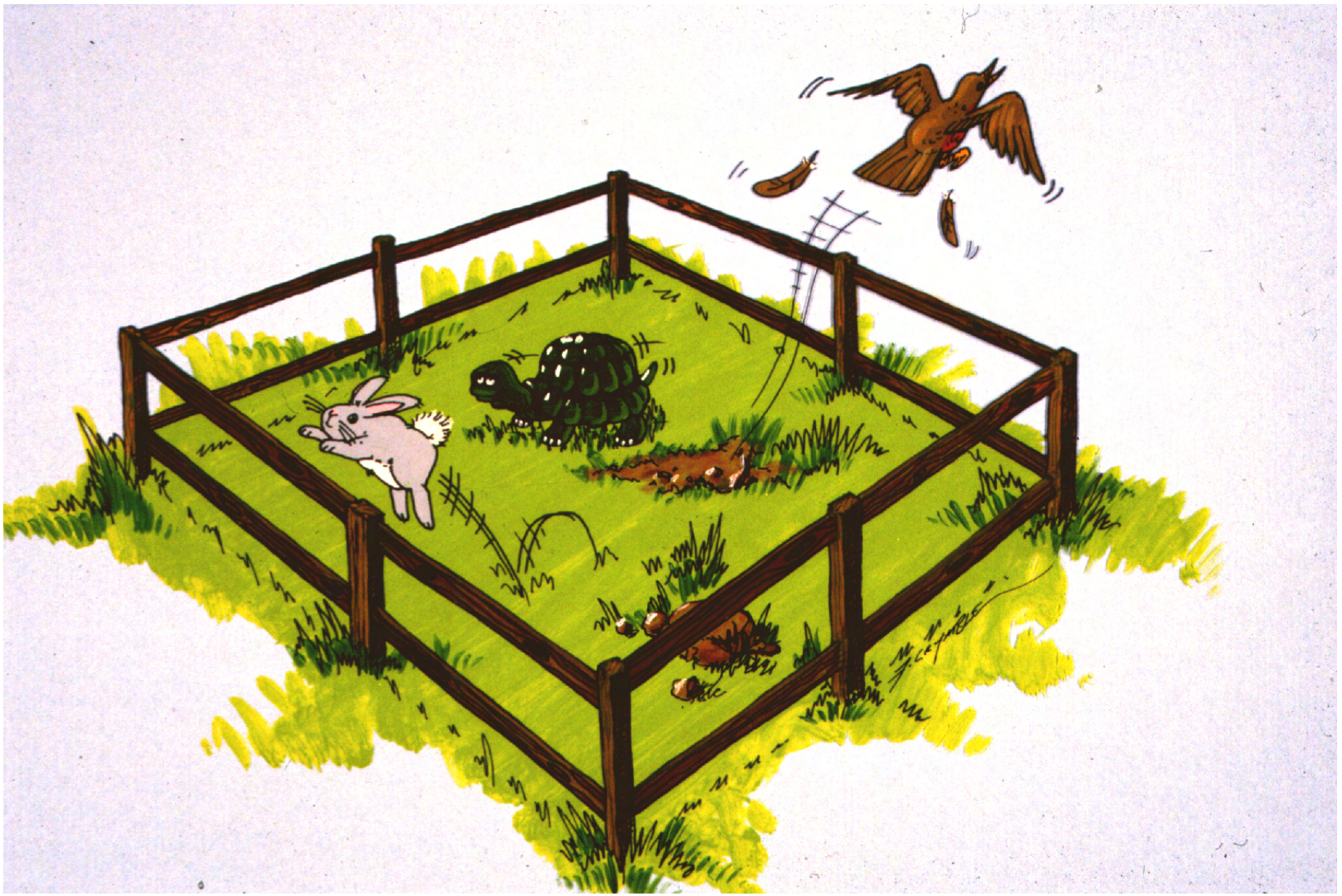
The three challenges of surveillance

- Identifying the right patient
- Communicating safety (‘cancer hysteria’)
- Trigger for intervention
  - Timely treatment for patients reclassified as high risk
  - Avoid jumping the gun

Surveillance therapy with selective delayed intervention

- Favorable risk (D'Amico):
  - Gleason ≤ 6
  - PSA ≤ 10
  - T1c/T2a
- In younger patients
  - ≤ 1/3 cores positive
  - < 50% involvement of all cores
- If available, PSA DT > 3 years or PSA velocity < 2.0 ng/ml/year
- Hypothesis:
  - Most can be observed
  - Delayed treatment effective in those whose disease appears to be higher risk over time

‘Animals in the barnyard’ and cancer natural history



Only the rabbits benefit from early diagnosis and treatment.

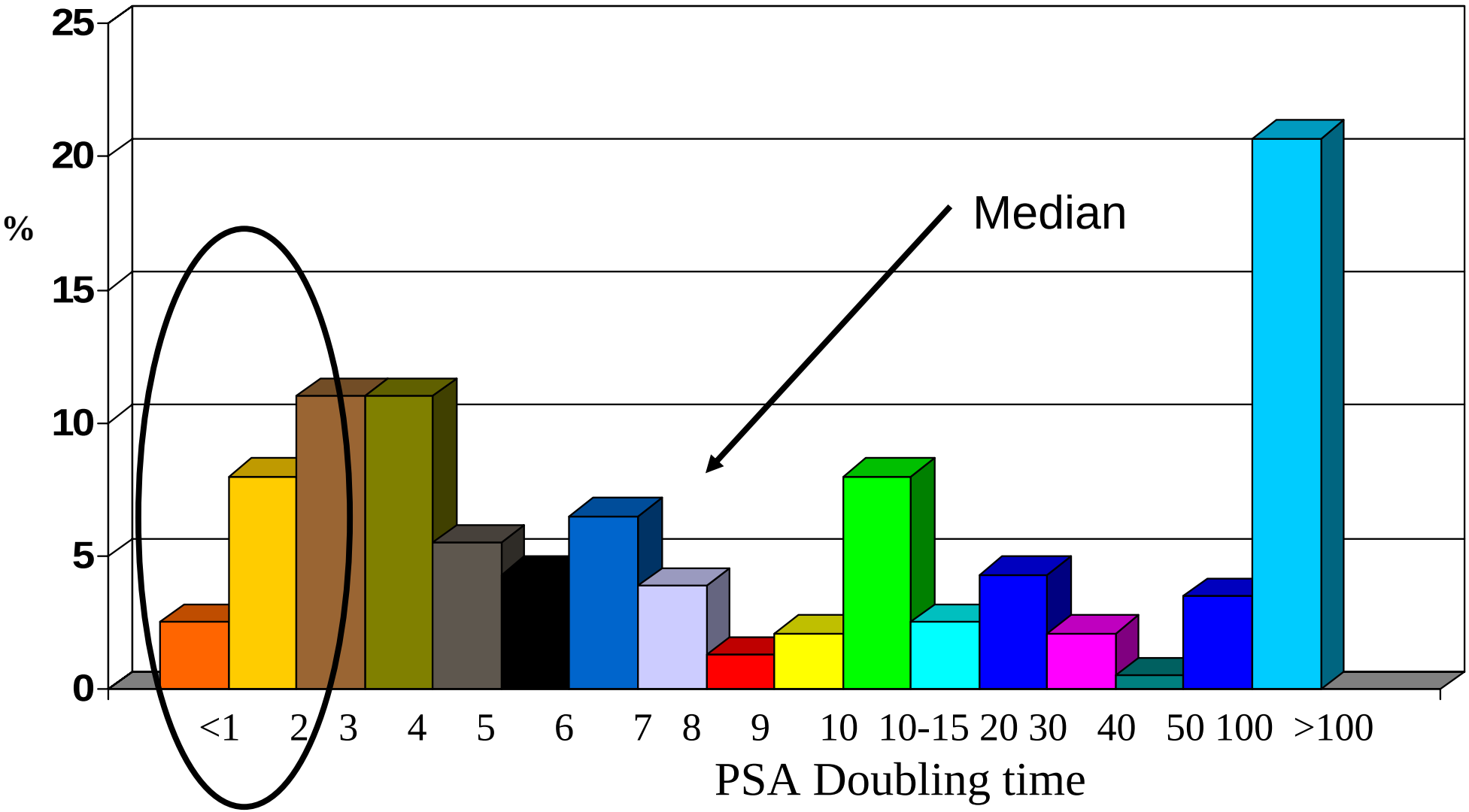
Identifying the rabbits: the controversies

- PSA kinetics
  - Reliability (? too late)
  - Interpretation (Velocity vs doubling time)
  - How to calculate
- Biopsy
  - How often, how many cores
  - Trigger for intervention: extent/volume/grade shift

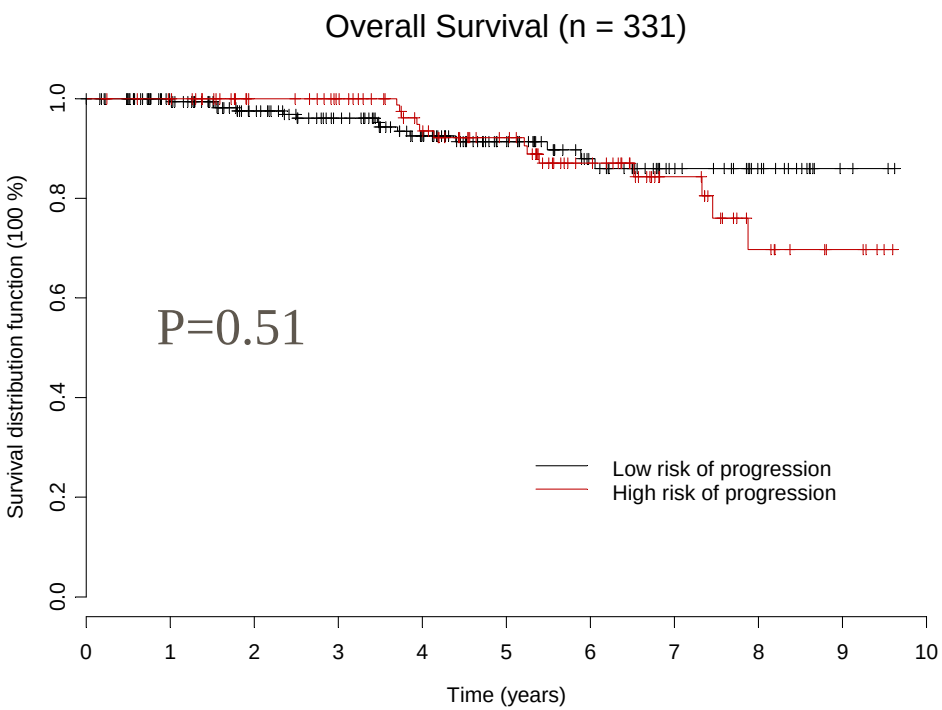
Identifying the rabbits: Toronto approach

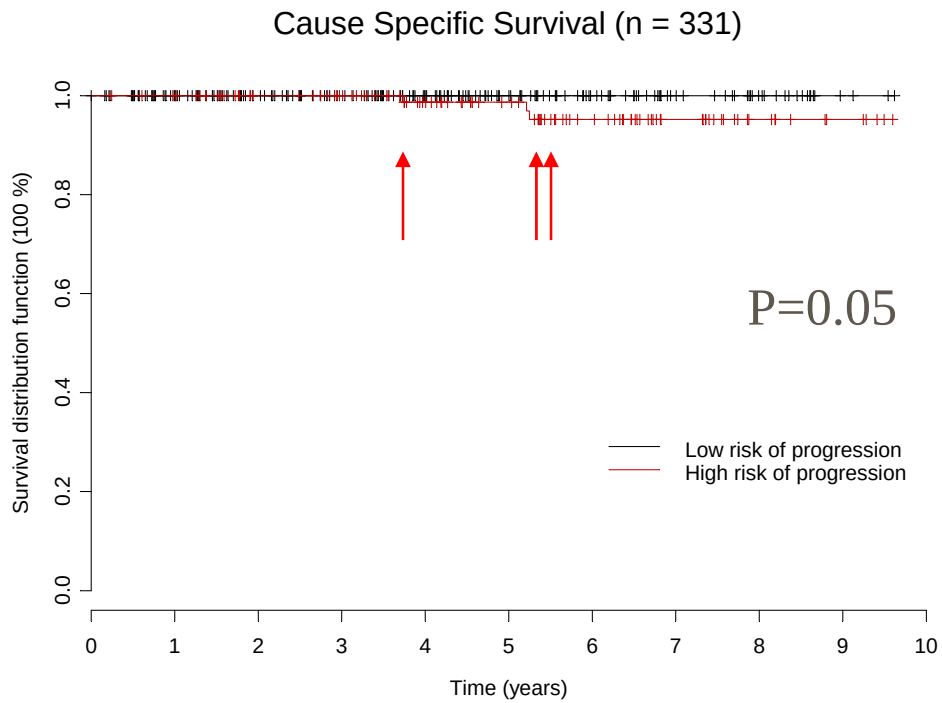
- Rapid PSA doubling time
  - PSA every 3 months x 2 years then every 6 months
  - Usually decision to intervene at 2 years, 8-9 PSAs
  - PSA DT < 3 years (20% of patients)
- Gleason grade progression
  - Biopsy at 1 year (confirmatory)
  - Then every 4 years (progression)
  - Treat if Gleason 4+3 or worse (5% of patients)
- Unequivocal clinical progression to T3 (3%)
- Guidelines, not rules

Distribution of PSA doubling times in 331 patients on surveillance. Choo, Klotz J Urol 2002



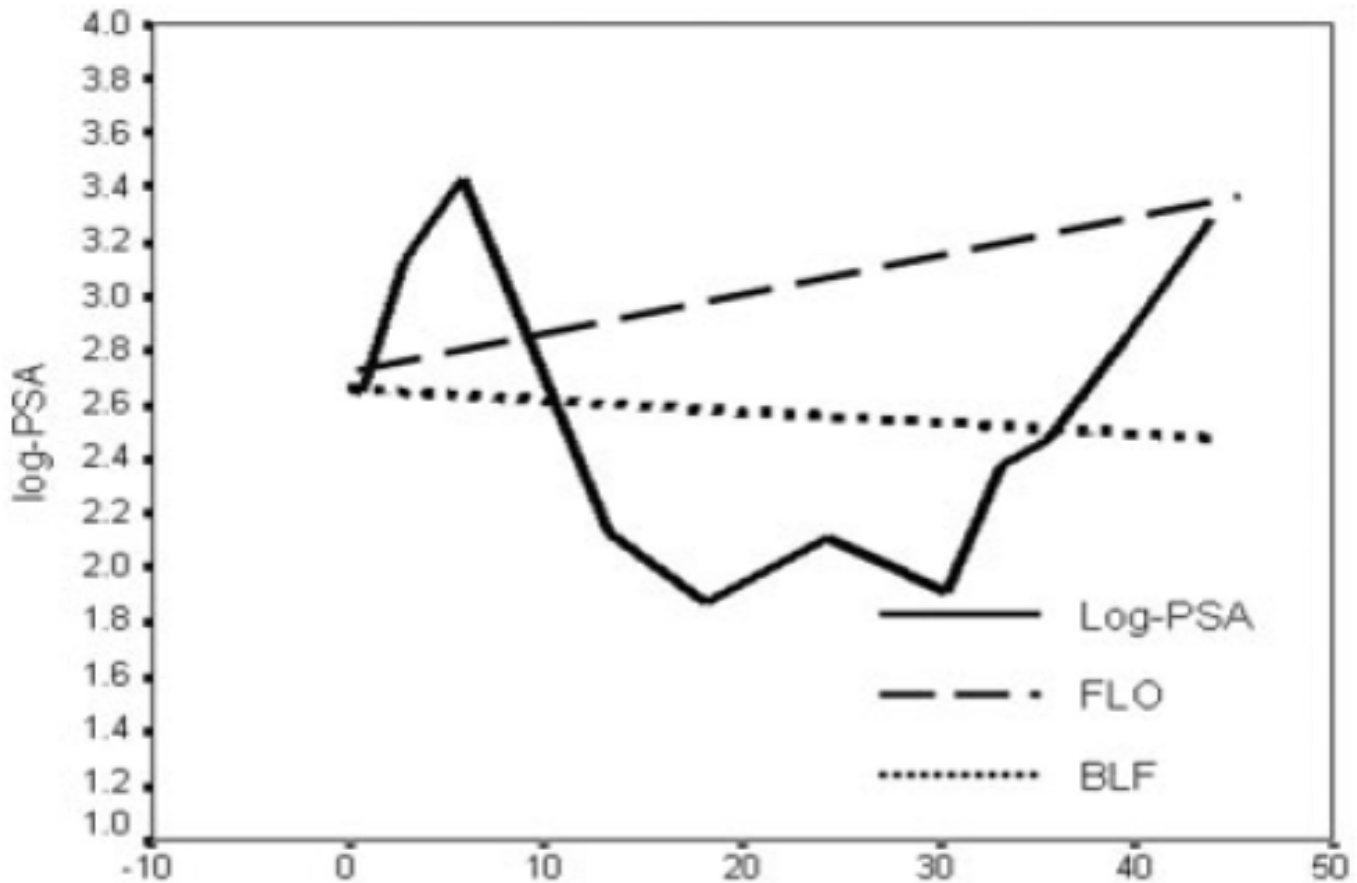
Overall and disease specific survival in Toronto surveillance cohort (adapted from Klotz L, J Clin Oncol. 2005 Nov 10;23(32):8165-9)





The problem of calculating PSA DT

FLO: First and last months observation
BLF: Best line fit

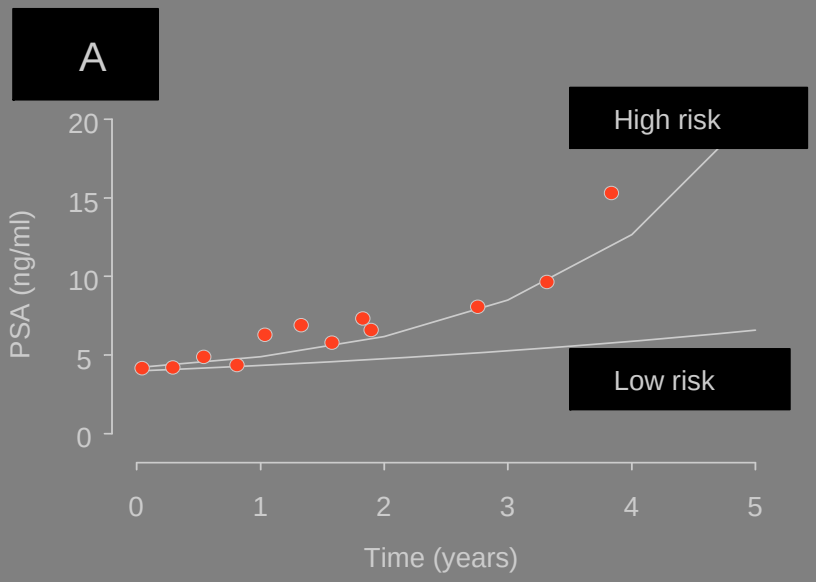


General Linear Mixed Modeling

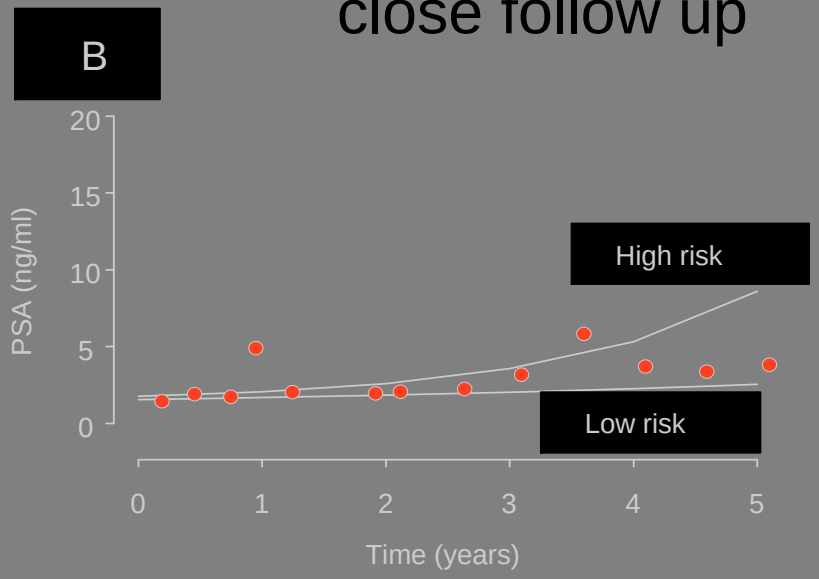
- Allows for individual predictors of intercept and slope to be integrated into model
- Aggregate estimate of variation used to reduce effect of individual PSA variation on PSA DT calculation
- For high risk line:
  $\ln(PSA) = 1.003 \times \ln(\textit{baseline PSA}) + 0.112 \times \text{time} + 0.041 \times \textit{time2}$
- For low risk line:
  $\ln(PSA) = 1.03 \times \ln(\textit{baseline PSA}) - 0.0056 \times \textit{Age} + 0.046 \times \textit{Gleason} + 0.081 \times \textit{time} + 0.0038 \times \textit{time2}$

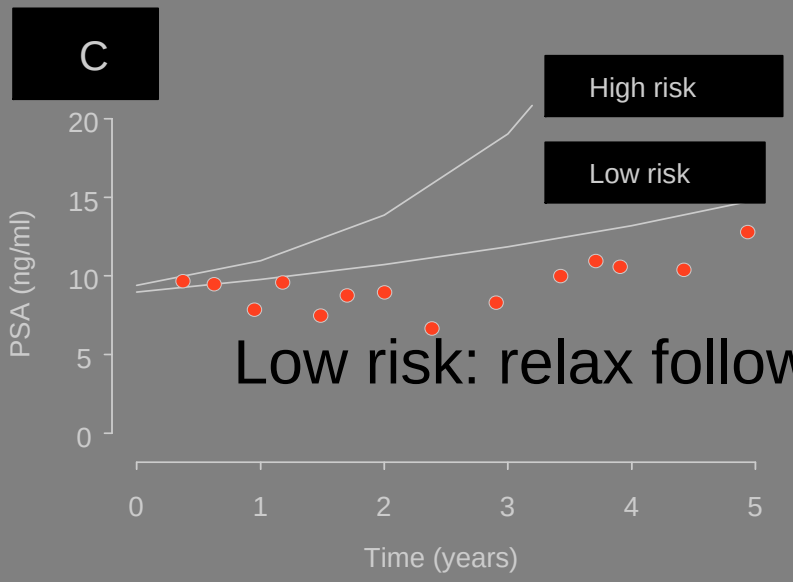
Zhang L, Loblaw DA, Klotz L. J Urol 2006

High risk—Intervene



Intermediate: continue close follow up





Low risk: relax follow up

GLMM approach to PSA DT during active surveillance

www.psakinetics/sunnybrook.ca

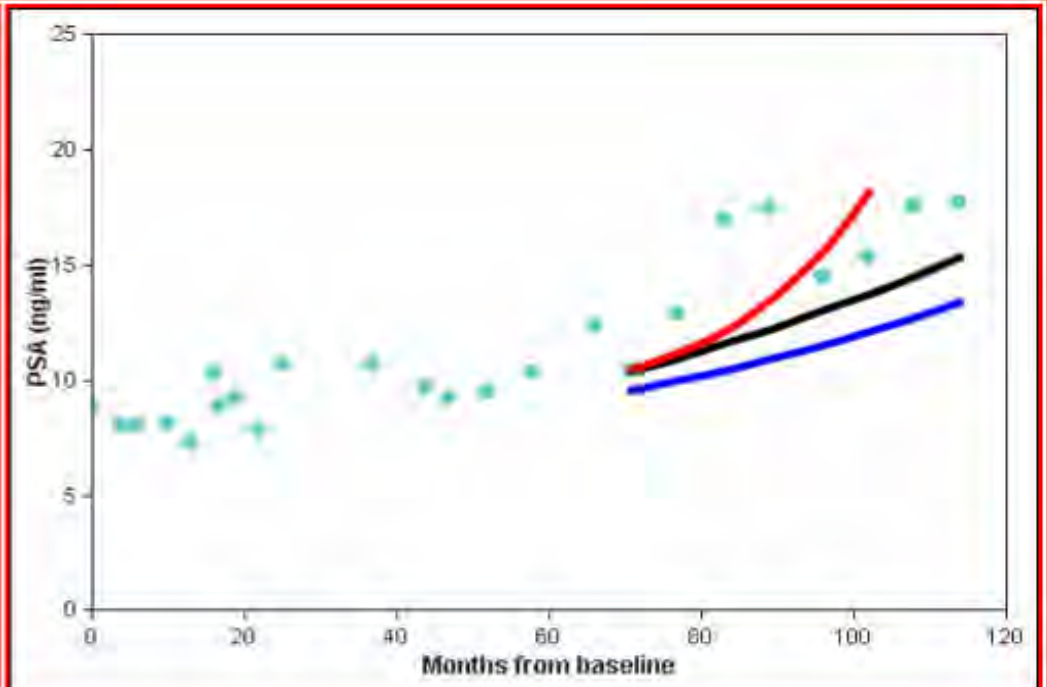
http://psakinetics.sunnybrook.ca

Baseline data for patient 3. Institution: TSRCC
Age: 79.0 years; Gleason: 6 (mean value used)

Start	End	YYYY-MM-DD	PSA
○	○	1995-10-20	8.70
○	○	1996-02-23	8.00
○	○	1996-05-16	8.00
○	○	1996-09-19	8.10
○	○	1996-11-28	7.30
○	○	1997-02-27	10.30
○	○	1997-03-27	8.90
○	○	1997-05-22	9.20
○	○	1997-09-04	7.90
○	○	1997-11-20	10.70

Set Start/End dates to process a subset of the data

More info



Select PSA metric:

○ Velocity (lin.model) ◉ Doubl.Time (exp.model)

Select patient: 3

then click: Process

Summary: PSA doubling time = 6.4 years.

For the 3.5-year period PSA level was fluctuating between progression and non-progression lines therefore the patient should have ongoing close monitoring.

Effect of PSA triggers on stable patient cohort

General linear mixed model of ln(PSA)	0%
PSA threshold > 10	15%
Linear regression of ln(PSA) vs time < 2yr	39%
Ln(PSA) vs time < 2 years using first and last PSA	29%
Actual PSA velocity > 2.0	49%
Calculated PSA velocity > 2.0	49%

PSA DT and surveillance:

Khatam A, Hugusson Int J Cancer 120, 170-174 (2006)

- 270 active surveillance (from Swedish arm of ESRCP)
  - 39% treated
  - 70 RPs
    - 9 (12%) PSA relapse
    - 80% of these had PSA DT < 2 years
    - 0/37 with PSA DT > 4 years relapsed
  - 14 deaths (5%); 0 from PCa
    - No metastatic progression

Williams SK, Soloway M AUA 2007 Ab 1410

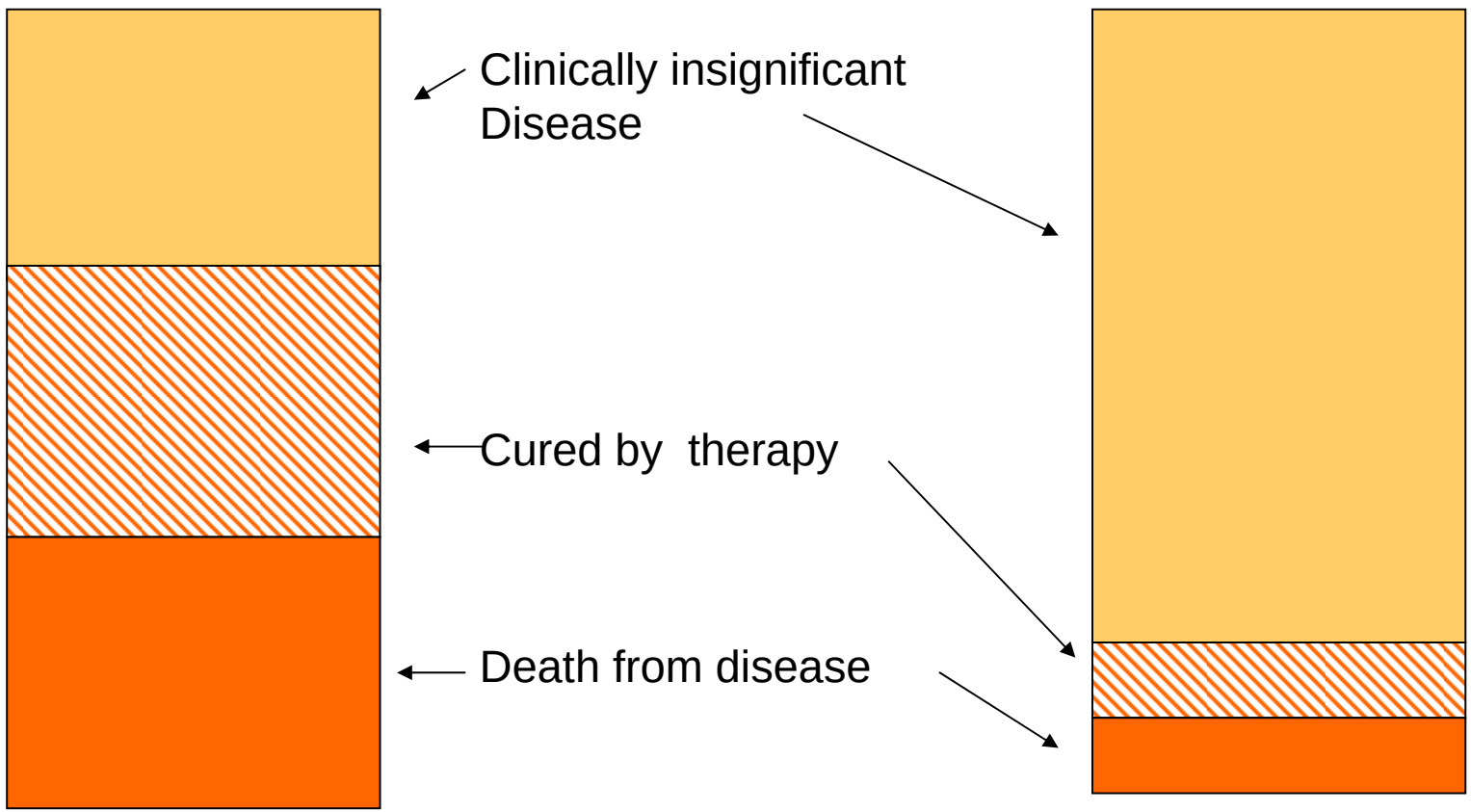
- 175 favorable risk patients managed with ‘Toronto’ approach
- 99 with > 1 yr f/u, median 4 yrs
- Mean age 66
- Mean PSA 5.7
- Intervention 8%: 2 RP, 3 XRT, 3 ADT
- Mean PSA DT
  - Untreated 13.1 yrs
  - Treated 3.6 yrs
- 5 year PFS 85%
- PCa survival 100%

Modelling the risk: A number needed to treat analysis

The Scandinavian trial

		Mortality reduction at 10 years	NNT
Bill-Axelson 2005	All	5%	20
Holmberg 2006	<65	11%	9
	➢65	0.3%	>300

A 50% risk reduction may yield little clinical benefit



Swedish cohort differed from patients diagnosed in 2006

Swedish trial

- Mean age 64.7
- Mean PSA 12.8
- 5% screen detected
- 75% T2
- 40% Gleason 7 or higher

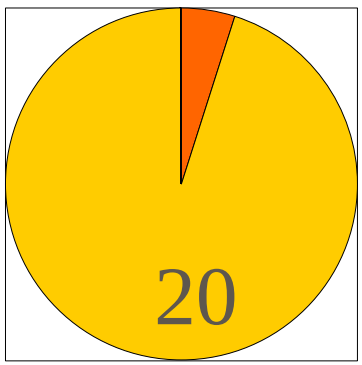
Typical screen diagnosed patient

- Mean age 62
- Mean PSA 6
- 95% screen detected
- 70% T1c
- 60% Gleason ≤ 6
- Volume migration

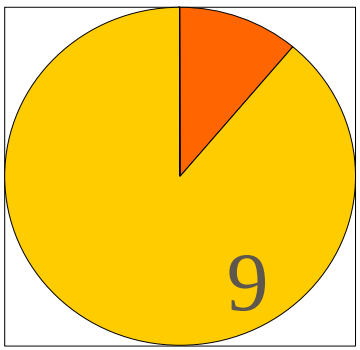
Unanswered question:

- NNT for
  - Low grade
  - Small volume
  - Screen detected
  - Option of selective delayed therapy

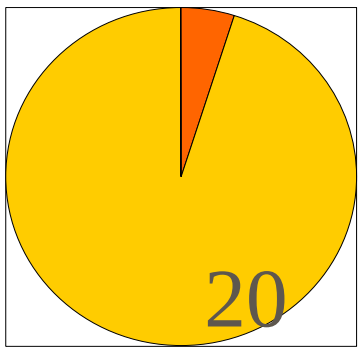
NNT for each cancer death avoided at 20 years for favorable risk prostate cancer: RP vs surveillance



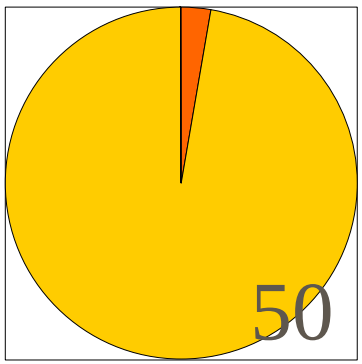
Swedish trial
10 years



Swedish trial
20 years (estimate)

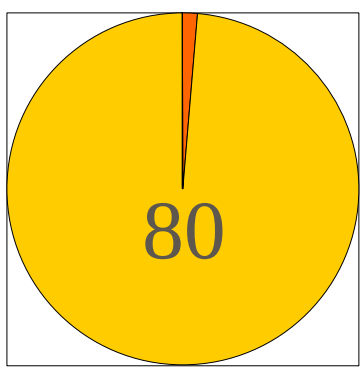


Lead time in screened population 20 years

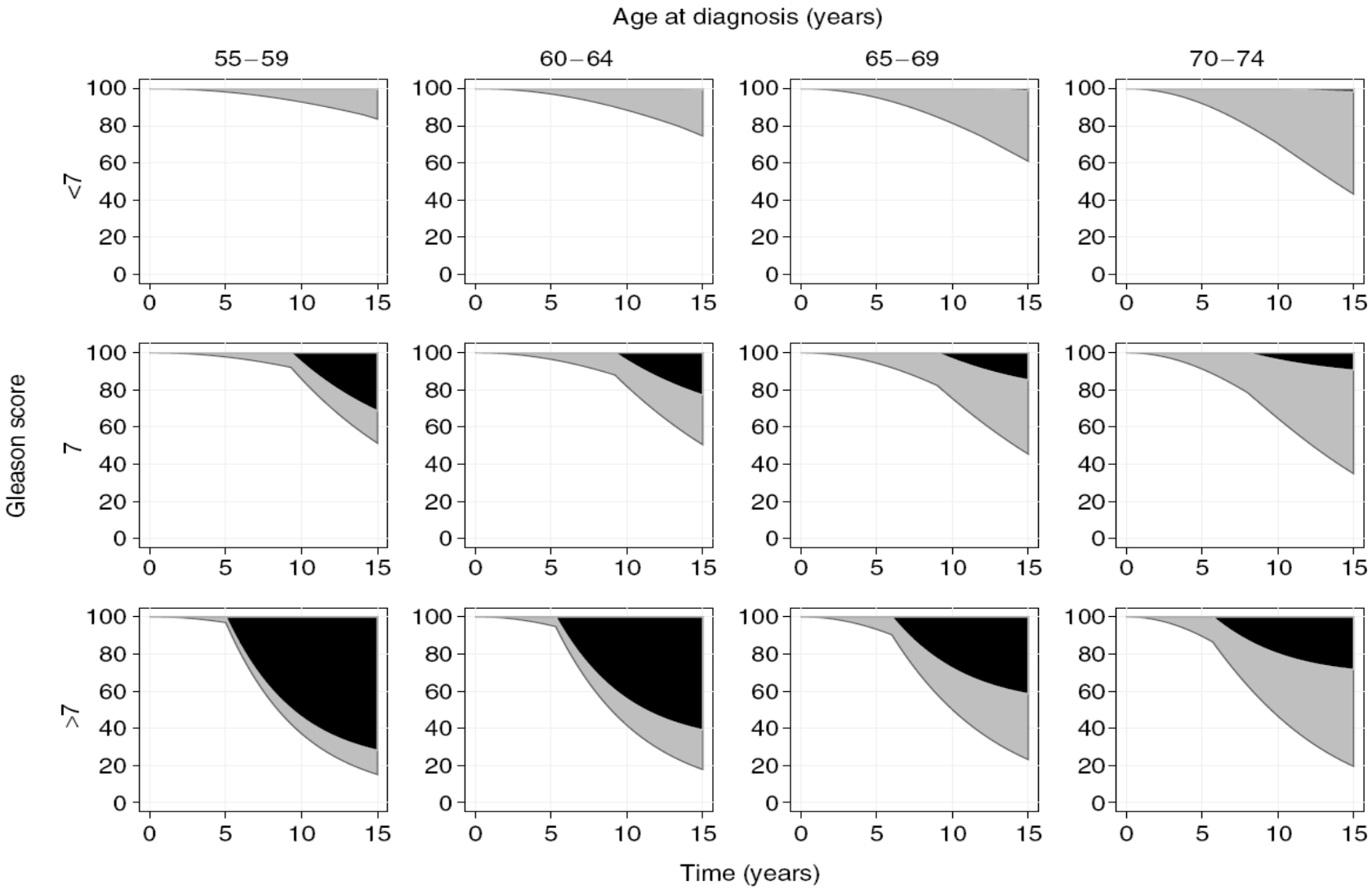


Corrected for grade difference

Include salvage opportunity

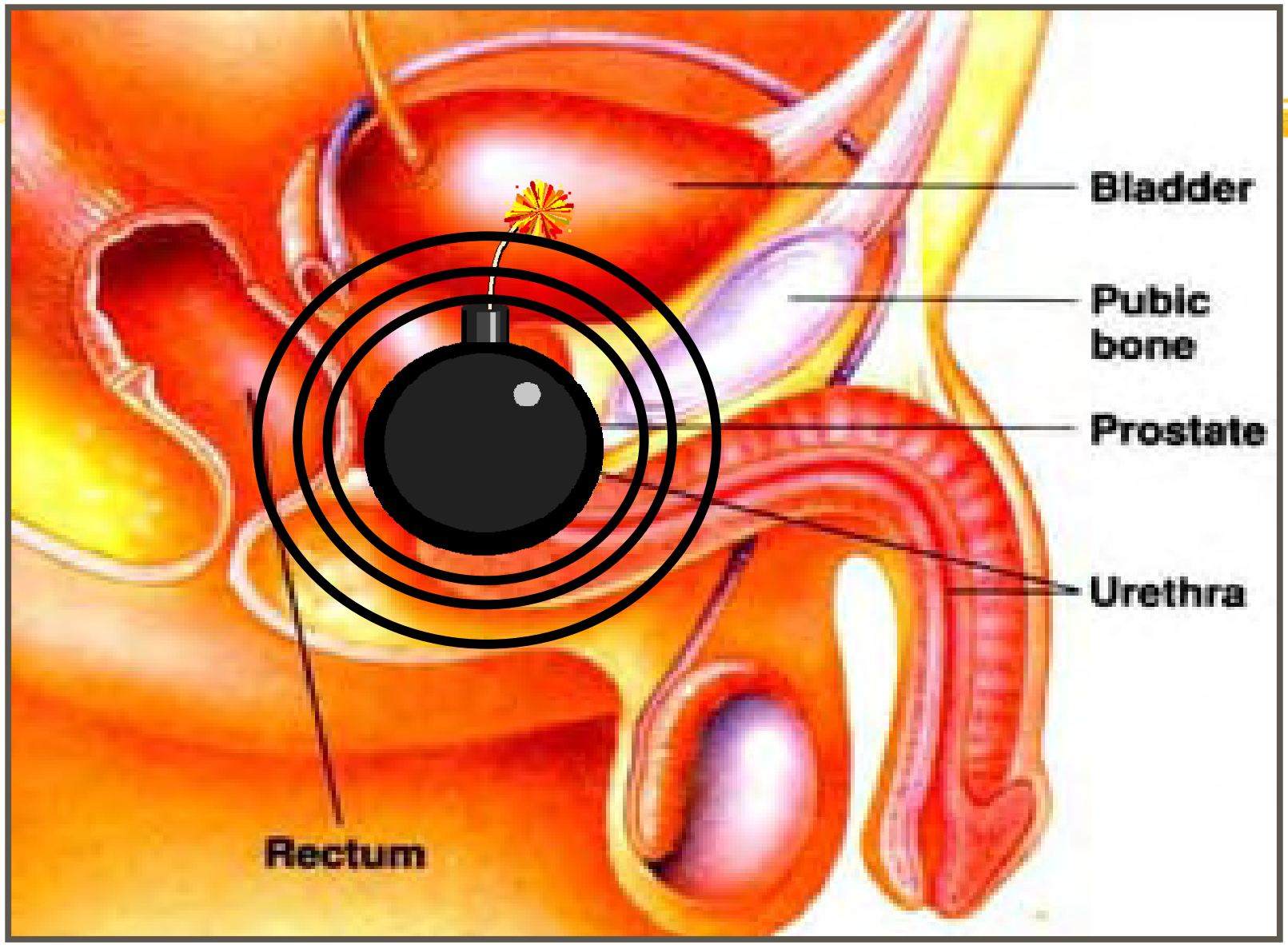


Predicted survival - conservative management of screen-detected prostate cancer



Parker et al. BJC (2006) 1361-8

Why Men Don’t Want to Wait



Cancer Hysteria: Who benefits?

- Fundraising Cancer Societies
- Cancer Research organizations
- Physicians
- Researchers
- Other health care workers in the cancer field
- Media
- Environmental activists

Who is Disadvantaged by Cancer Hysteria?

The patient

Fear is a Danger to Your Health

- ‘Cancer’ and sense of doom
  - “The dread expands and solidifies into such a major obstacle that I simply can’t get past it.”
- Patients may feel so hopeless that they can’t absorb the medical facts

Communicating Risk

"The first step in positive thinking is to be able to understand what's actually going on. Positive thinking begins with clear thinking."

- a Patient

Our challenge

- “I will remember that there is an art to medicine as well as science in that warmth, sympathy and understanding may outweigh the surgeon’s knife or the chemist’s drug”.

-Louis Lasagna, Academic Dean of the School of Medicine at Tufts University, 1964

The Crucial Question:

“What do you want from the rest of your life?”

Our Responsibility

- Reassure and offer hope
- Put the risk in perspective
- De-mystify the word ‘Cancer’
- Provide accurate data (use facts)
- Help the patient think clearly about the risks and benefits
- Avoid exploiting the patient’s fears
- Primum non nocere

Risk Assessment

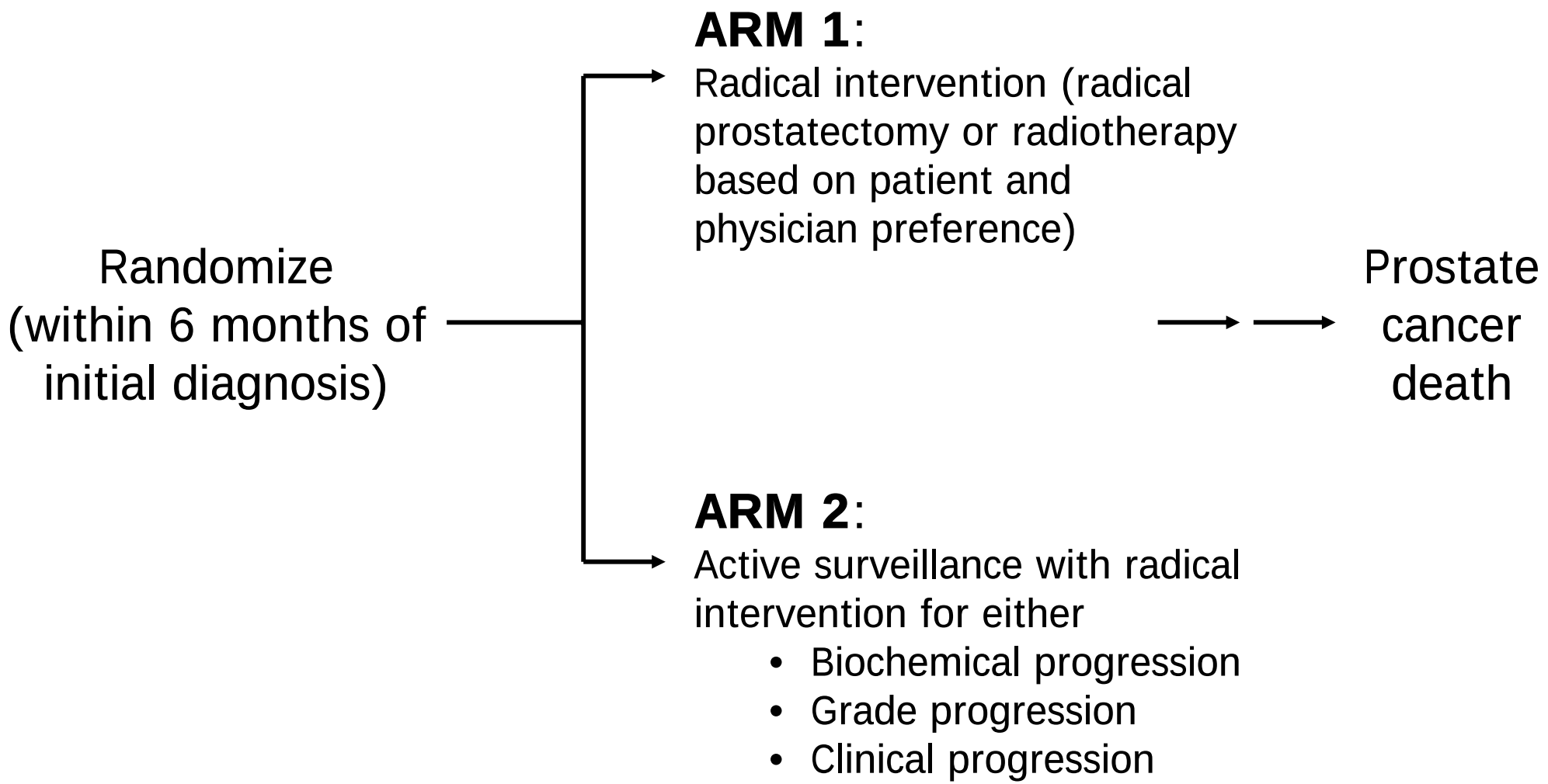
A Phase III Study of Surveillance Therapy Against Radical Treatment (START) in patients Diagnosed with Favourable Risk Prostate Cancer

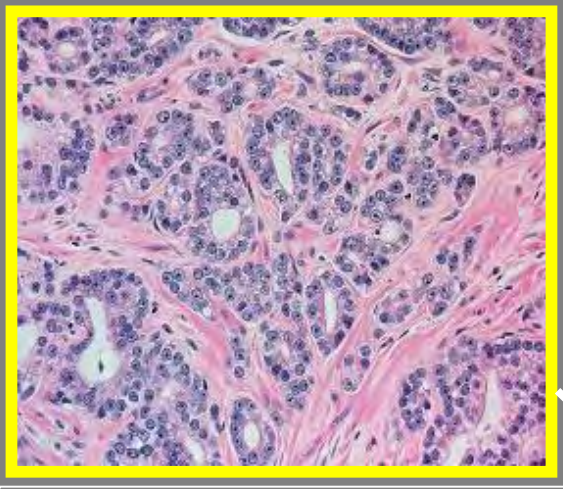
NCIC CTG Protocol Number: PR.11

SWOG/ECOG/CALGB/RTOG/UKCCR

Study to open 2Q 2007 (any day now!)

START Trial Schema

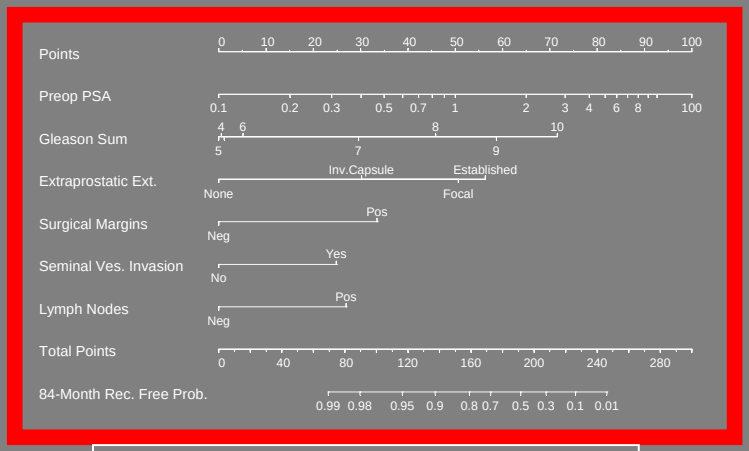




Serial Biopsy Bank

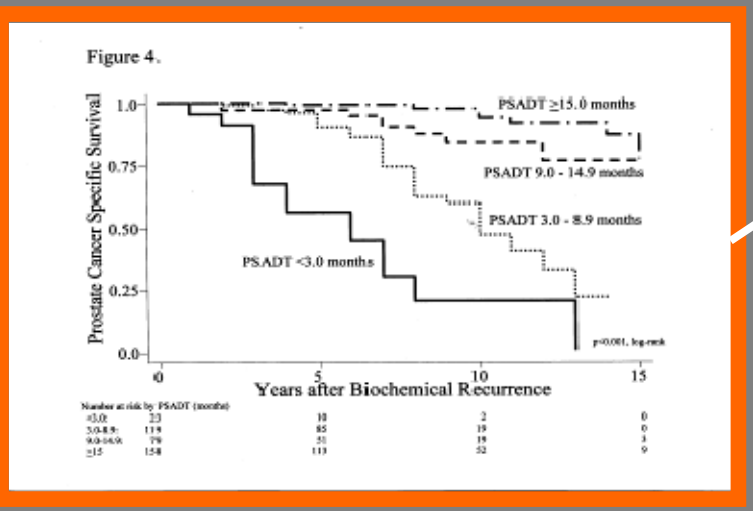
Biomarker Discovery

Serum Bank



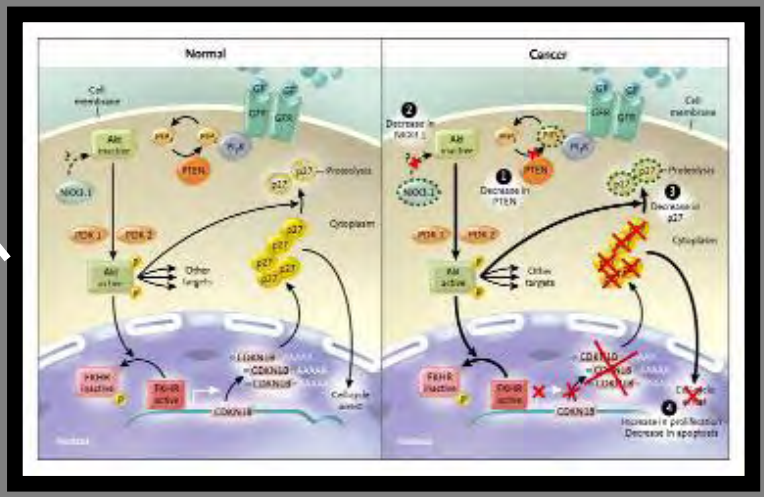
Validation of Nomograms

START Trial



Natural History Data Base

Global Study 2100 pts



Correlative Sciences

Thank You