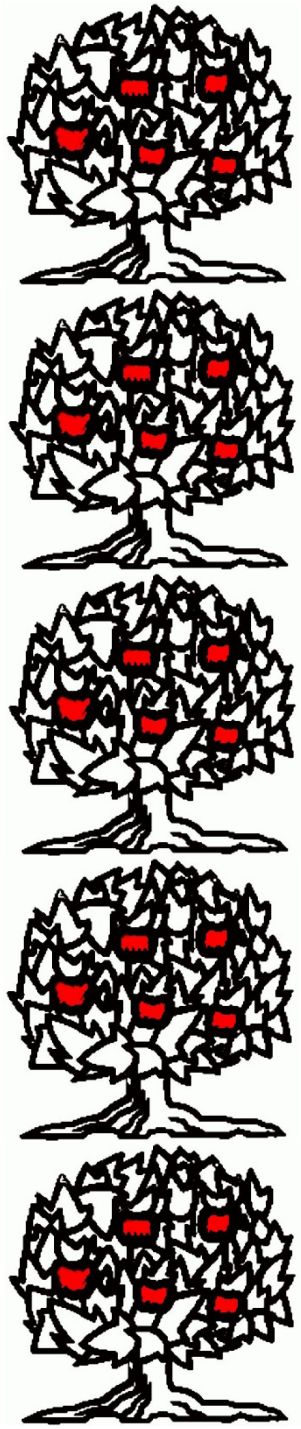

EDEN – European Dermato-Epidemiology Network

Survival Analysis

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Erasmus MC, Dermatology

Interactive questions

VOXVOTE

- Download app Voxvote and enter pin 23924

OR go to

- http://live.voxvote.com and enter pin 23924

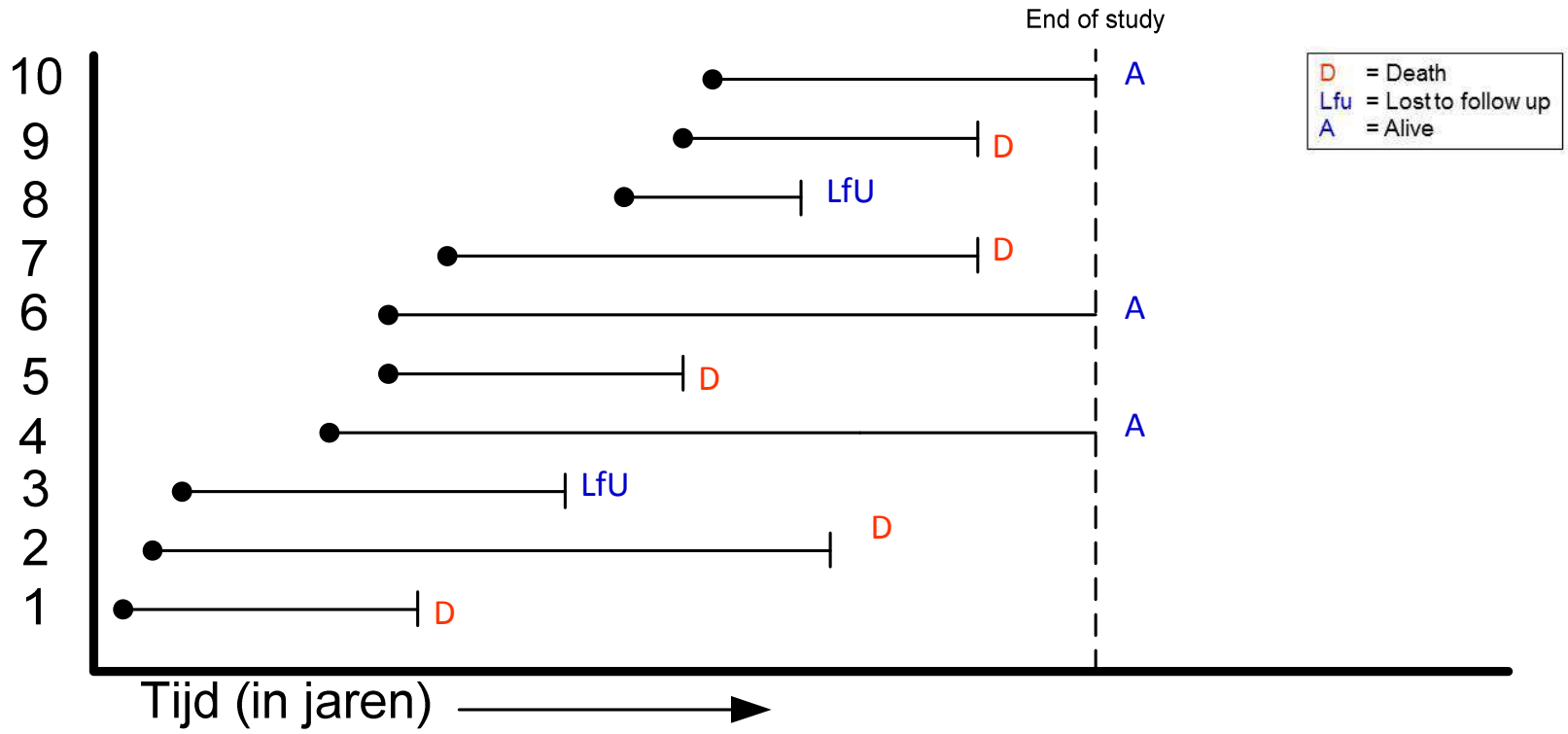
OR go to

- http://live.voxvote.com/?pin=23924

Objectives

- Kaplan Meier
  - Independent censoring
  - Logrank test
  - Competing risks
- Cox regression
  - Proportional hazards assumption
  - Multivariable regression
  - Time-varying analysis of covariates
  - Competing risks
- Recurrent Events
- Relative Survival

Time to event data



Independent Censoring

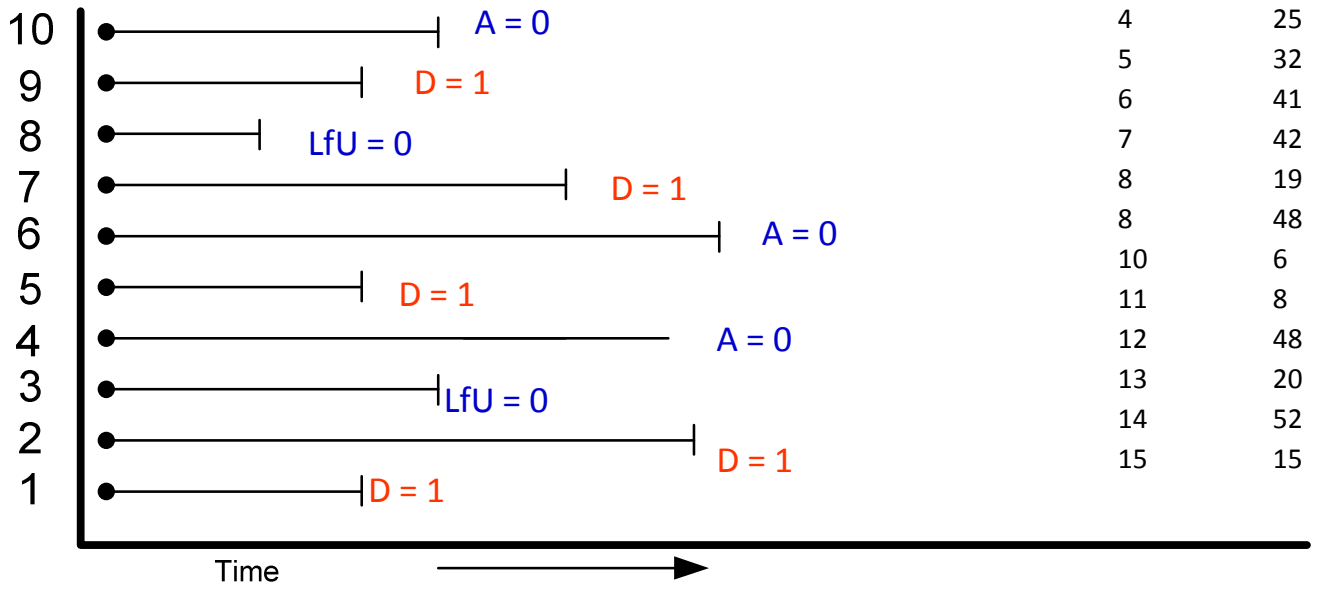
Censoring is independent/non-informative means:

A. Censored subjects have the same probability of survival of those who continue to be followed. This assumption can be tested

B. Censored subjects have the same probability of survival of those who continue to be followed. This assumption cannot be tested

C. No assumptions are made about the survival of censored subjects, as information of all subjects is used until censoring

Variables



Patient ID	Time	Status	Event
1	15	death	1
2	22	death	1
3	36	alive	0
4	25	death	1
5	32	LFU	0
6	41	LFU	0
7	42	alive	0
8	19	alive	0
8	48	LFU	0
10	6	alive	0
11	8	death	1
12	48	death	1
13	20	death	1
14	52	alive	0
15	15	death	1

Lifetable

1. Order all failure times

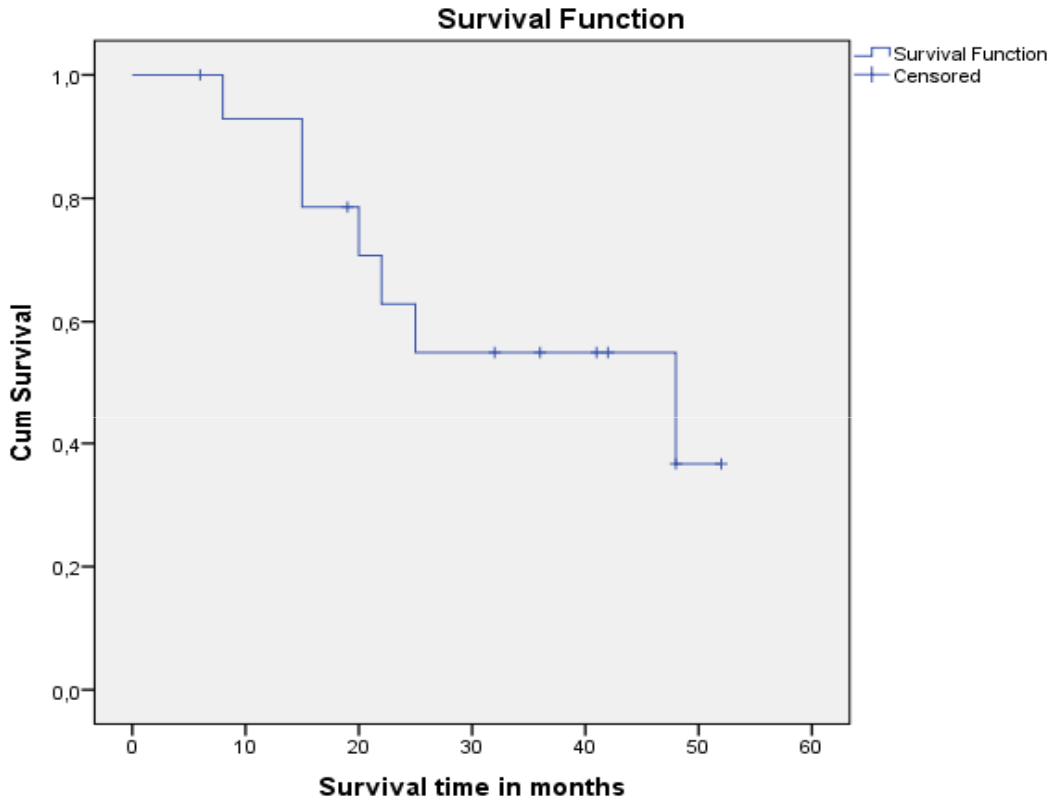
   6*,8,15,15,19*,20,22,25,32*,36*,41*,42*,48*,48,52*

   (*=censored)

2. Calculate the survival probability at each time point
3. Multiply the survival probability at time t with time t-1

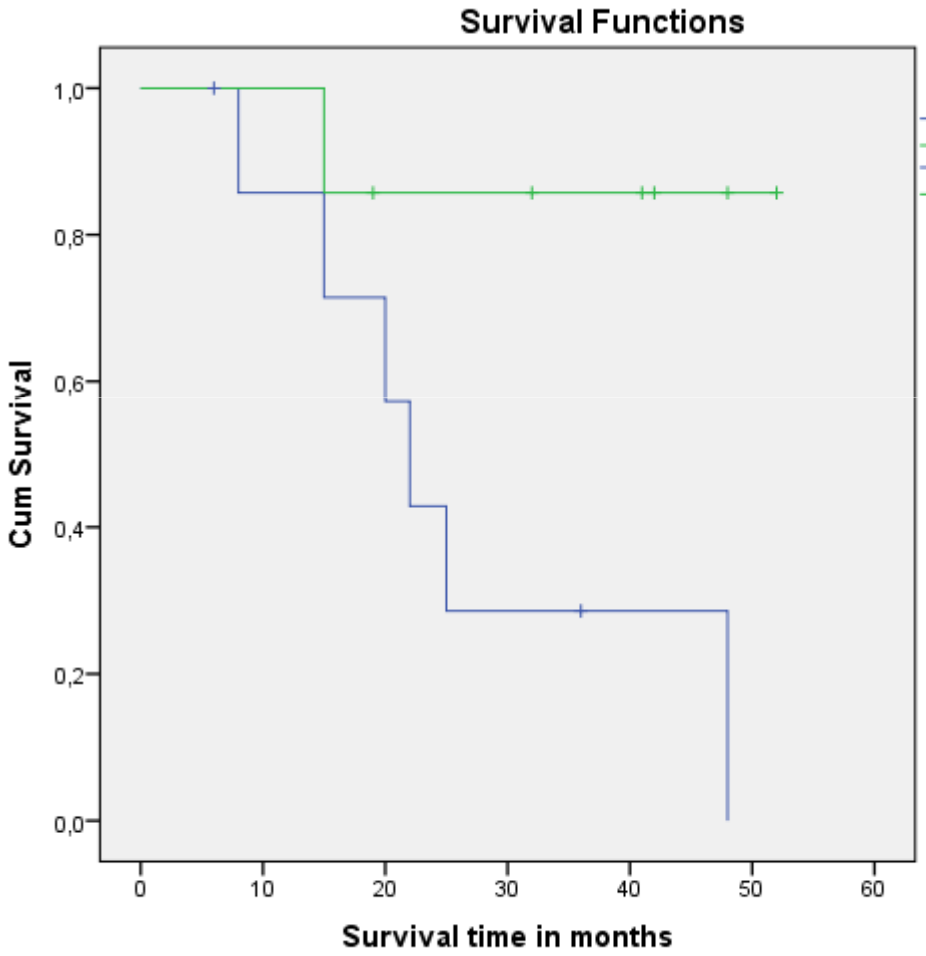
Time	N at risk	N failure	N survived	survival probability		KM survival probability	
8	14	1	13	(13/14)	0,93		0,93
15	13	2	11	(11/13)	0,85	(0,85*0,93)	0,79
20	10	1	9	(9/10)	0,90	(0,9*0,79)	0,71
22	9	1	8	(8/9)	0,89	(0,89*0,71)	0,63
25	8	1	7	(7/8)	0,88	(0,88*0,63)	0,55
48	3	1	2	(2/3)	0,67	(0,67*0,55)	0,37

Kaplan Meier curve



Time	8	15	20	22	25	48
N at risk	14	13	10	9	8	3

Logrank test

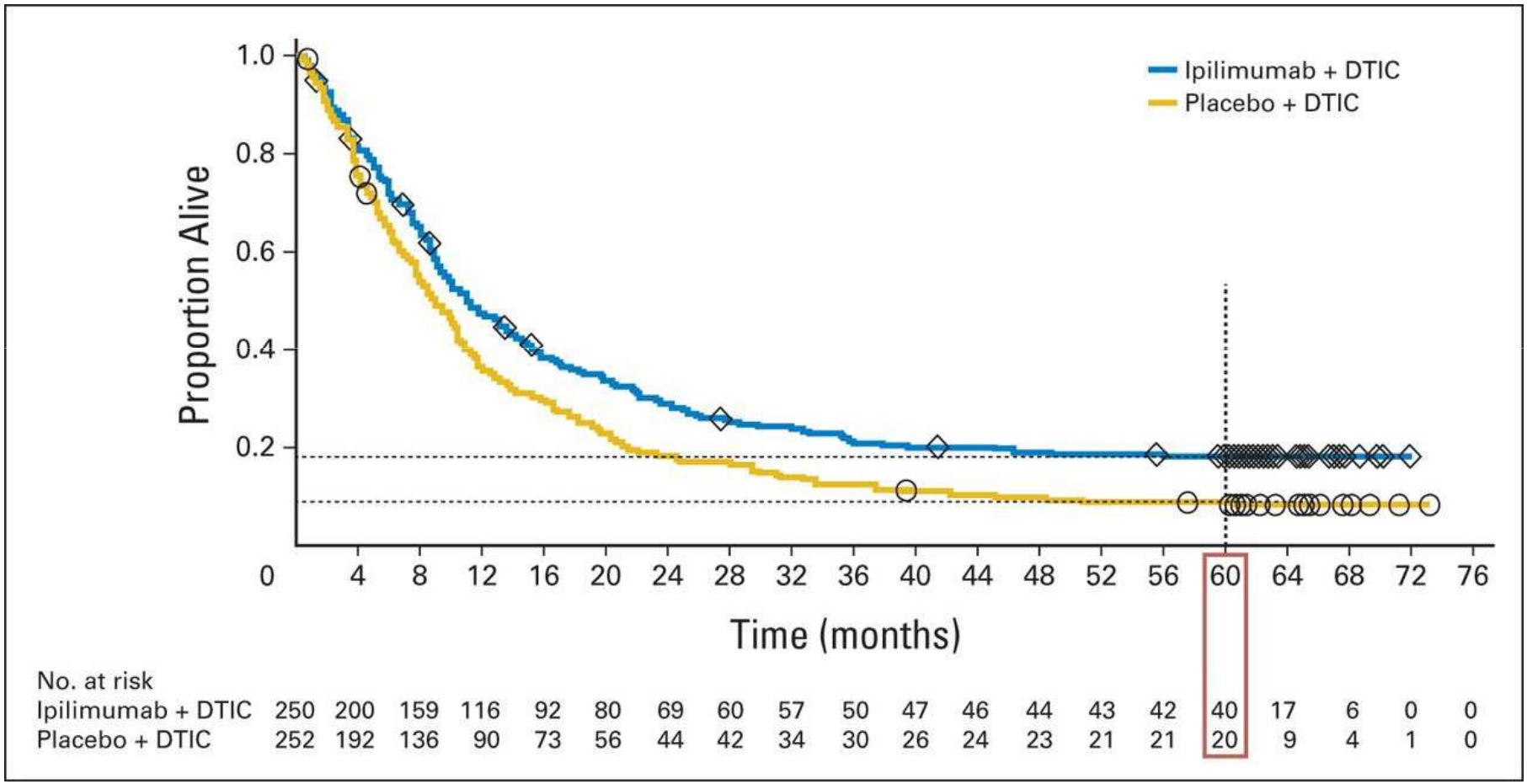


Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	5,154	1	,023

Test of equality of survival distributions for the different levels of Treatment.

Example



Maio et al, JCO 2015

Example: Survival table

Table 3. Updated Median OS and Milestone Survival Rates

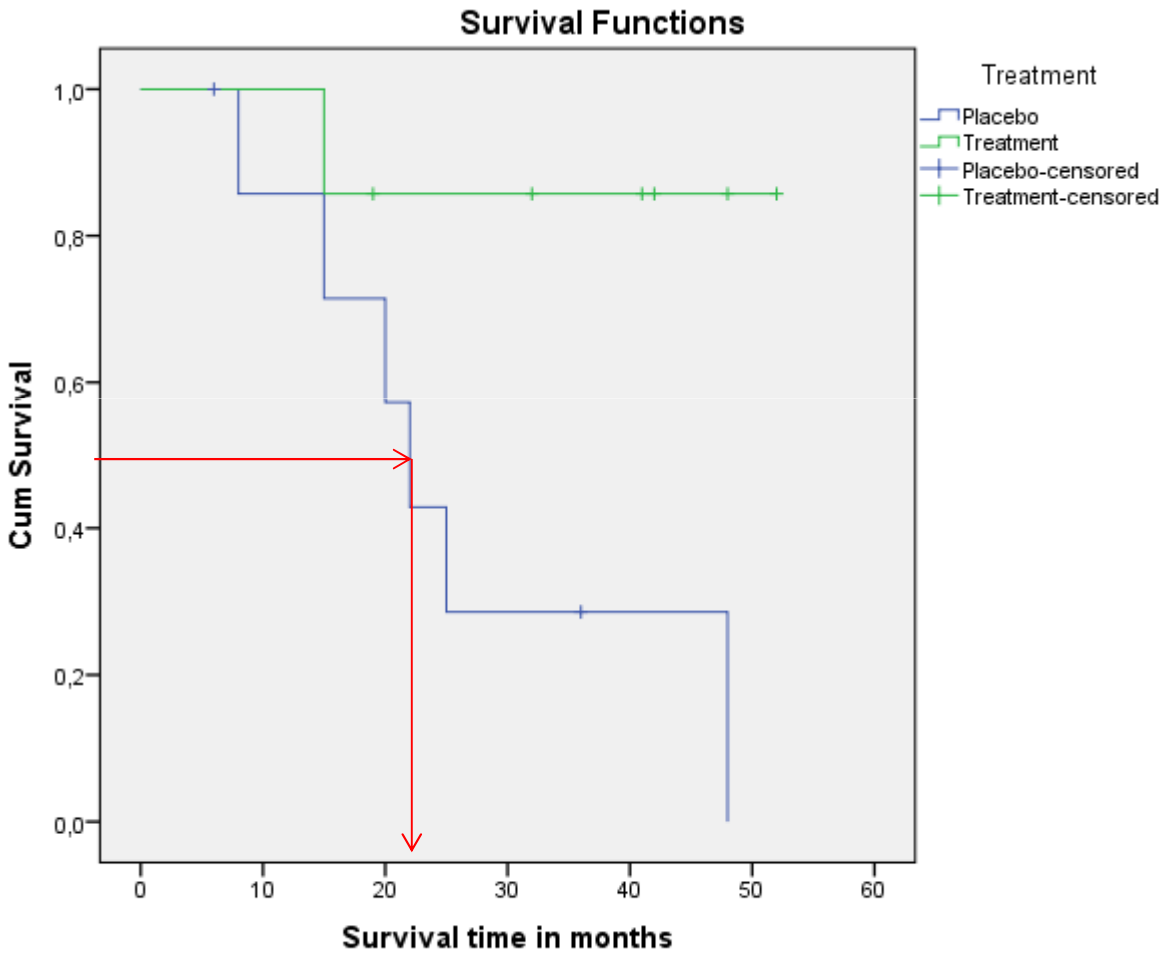
	OS (months)		OS Rate									
			1 Year		2 Years		3 Years		4 Years		5 Years	
Treatment Group	Median	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI
Ipilimumab + dacarbazine (n = 250)	11.2	9.5 to 13.8	47.6	41.2 to 53.7	28.9	23.3 to 34.7	21.3	16.3 to 26.6	19.1	14.4 to 24.3	18.2	13.6 to 23.4
Placebo + dacarbazine (n = 252)	9.1	7.8 to 10.5	36.4	30.4 to 42.4	17.8	13.3 to 22.8	12.1	8.4 to 16.5	9.7	6.4 to 13.7	8.8	5.7 to 12.8

Abbreviation: OS, overall survival.

Median survival represents:

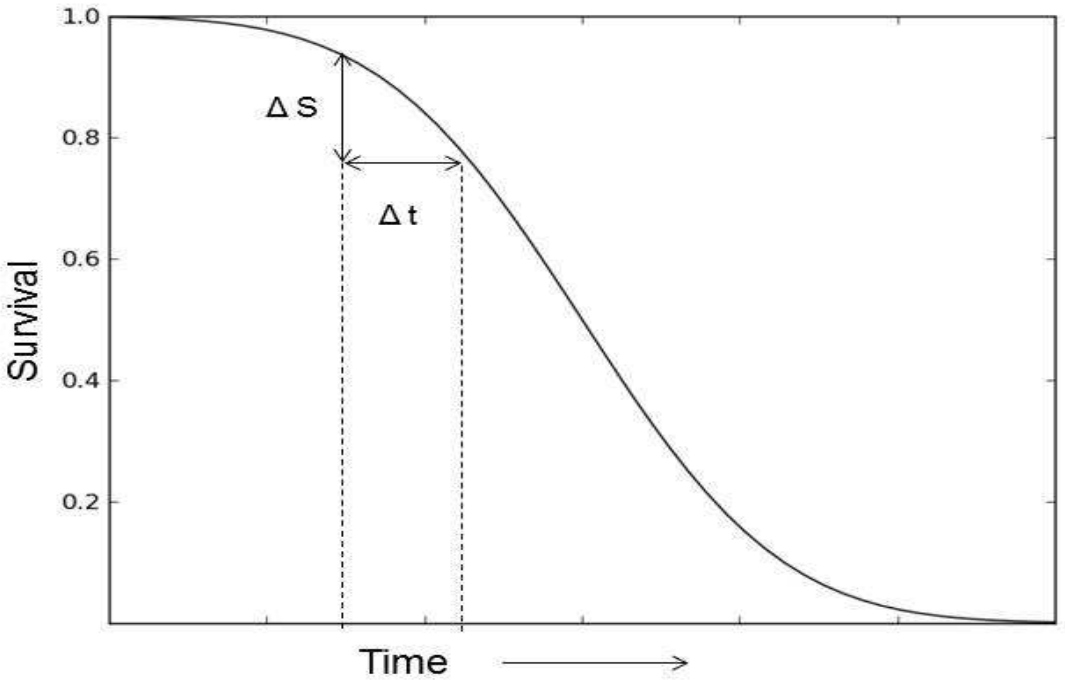
A. Time when survival probability is 50%
B. Time when 50% of the subjects have experienced the event
C. Median of all ordered survival times

Median survival time



Cox Regression

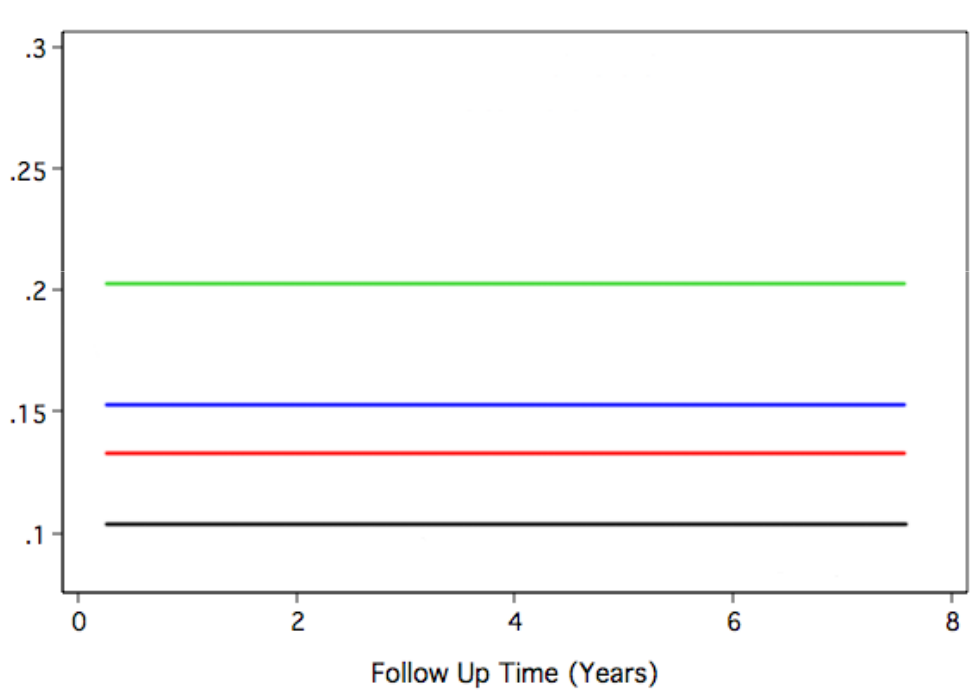
Hazard



Hazard is a conditional probability:
the hazard is the probability of experiencing the event at Δt,
given that the individual is alive at the beginning of Δt

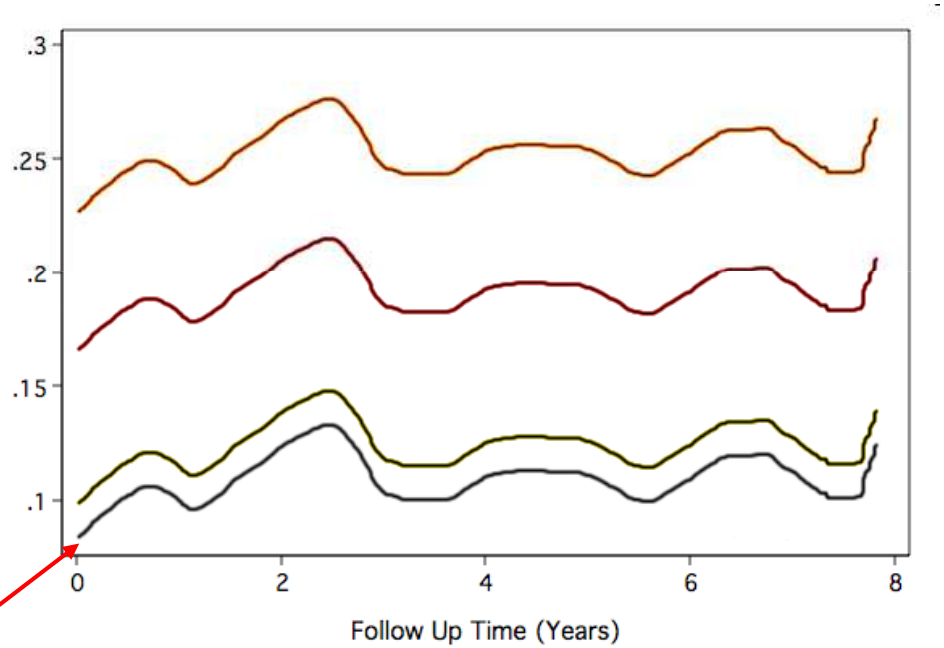
Hazard

Proportional Hazards assumption



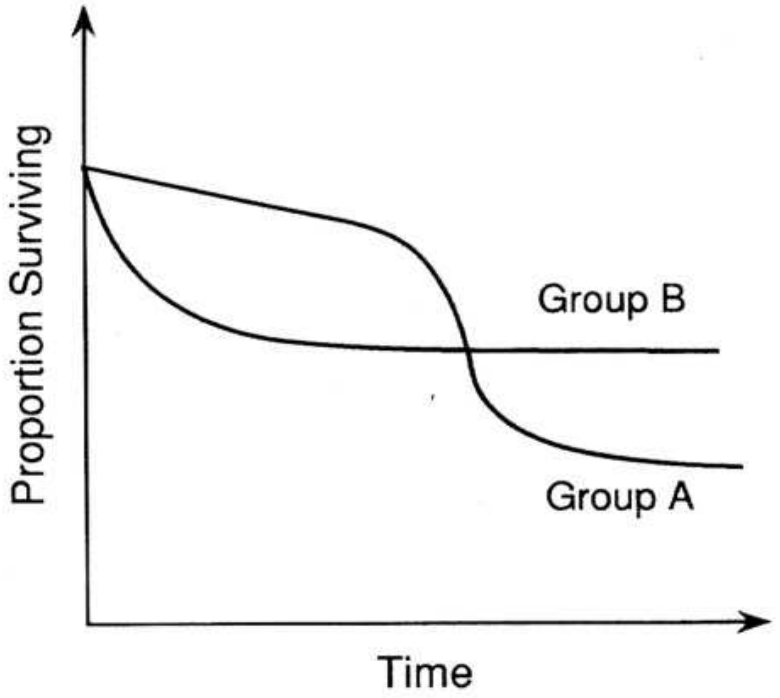
Hazards between groups are proportional over time

Cox regression is a semi-parametric model



Baseline hazard function can have any shape

Non-proportional hazards



Solution?

Concato et al, Ann.Intern. Med. 1993

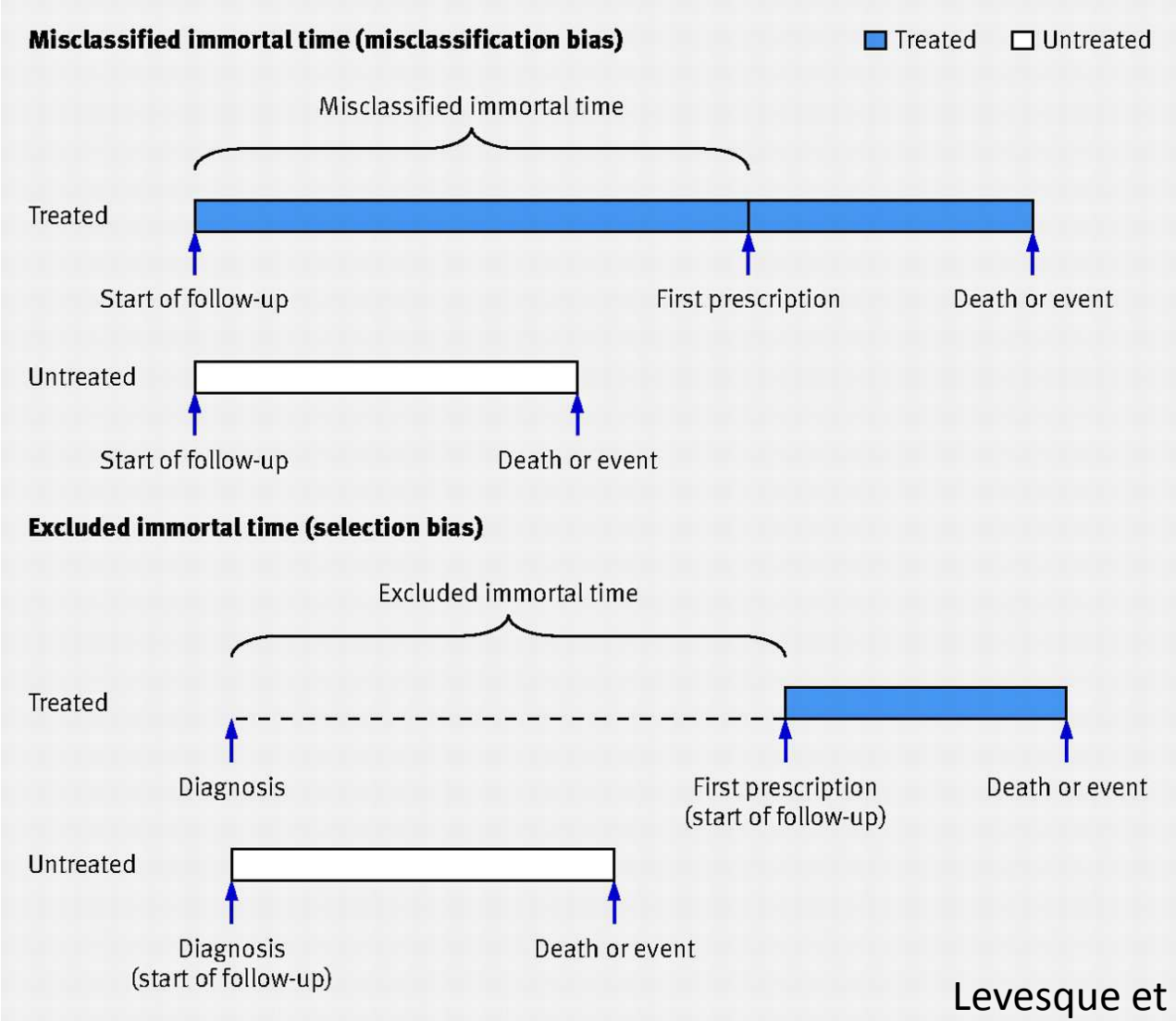
Multivariable Cox regression

Variables in the Equation

	B	SE	Wald	df	Sig.	Exp(B)	95,0% CI for Exp(B)	
							Lower	Upper
sex	-,466	,081	33,002	1	,000	,628	,535	,736
breslow_cats2_1			111,434	2	,000			
breslow_cats2_1(1)	,678	,154	19,455	1	,000	1,970	1,457	2,662
breslow_cats2_1(2)	1,329	,151	77,791	1	,000	3,776	2,811	5,074
age_rand	,011	,003	13,373	1	,000	1,011	1,005	1,017

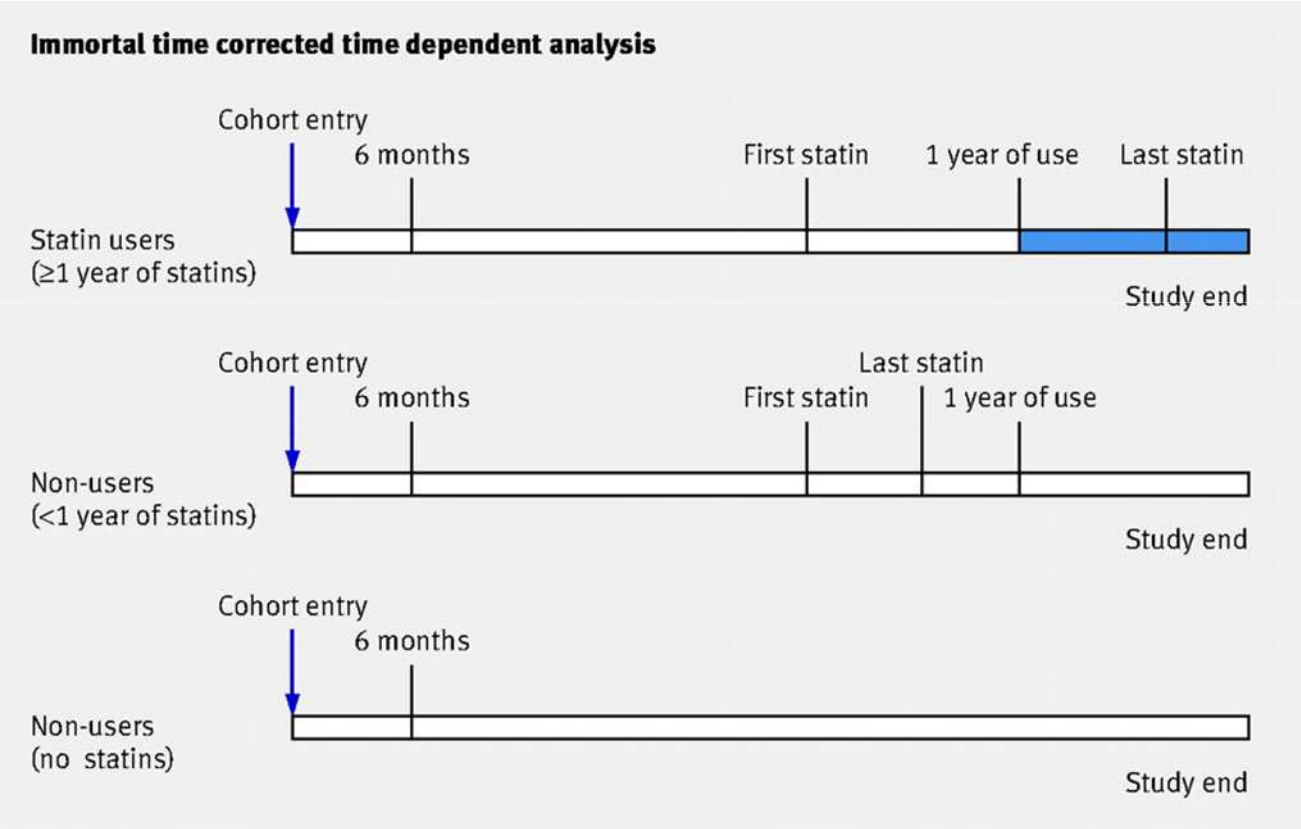
- Women have 37% survival advantage compared to men
- Hazard rate among thickest tumors is almost 4x higher compared to thinnest
- For each year 1% increase in hazard rate

Cox regression with time-varying variables



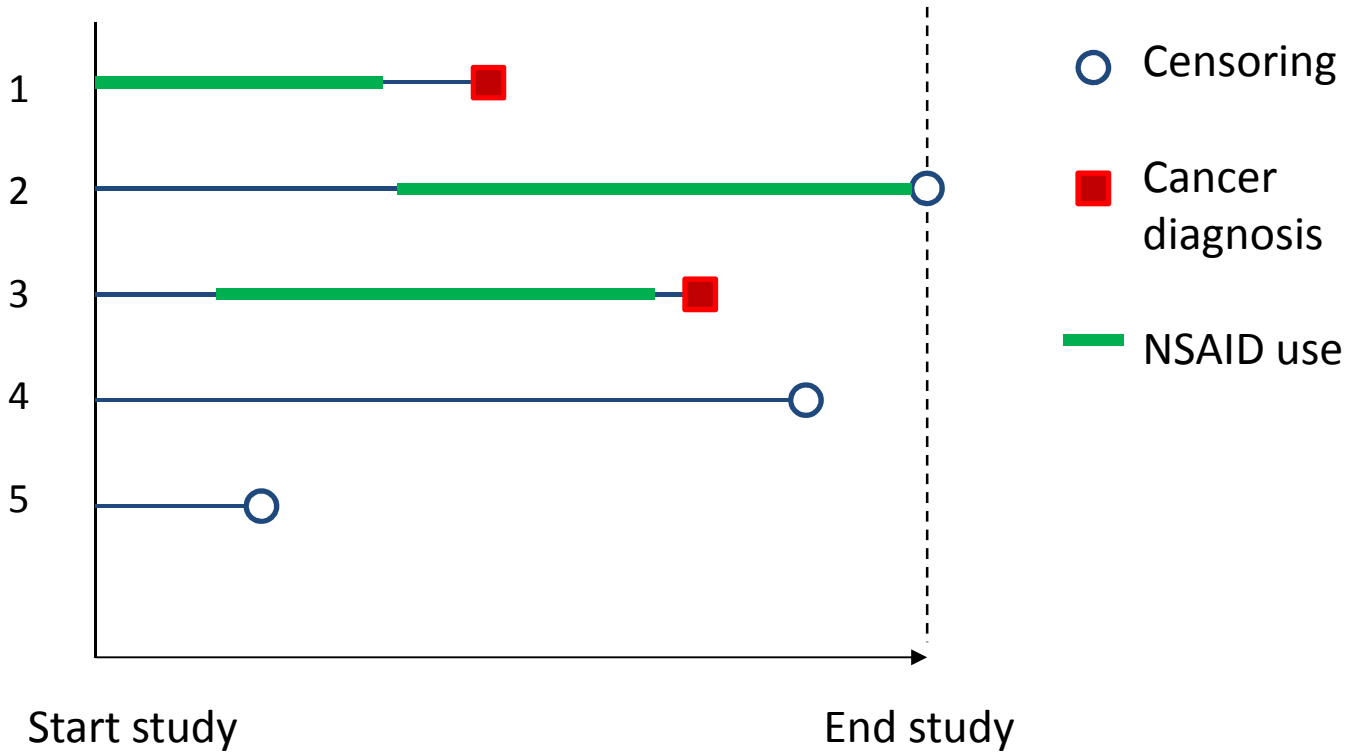
Levesque et al, BMJ, 2010

Cox regression with time-varying variables



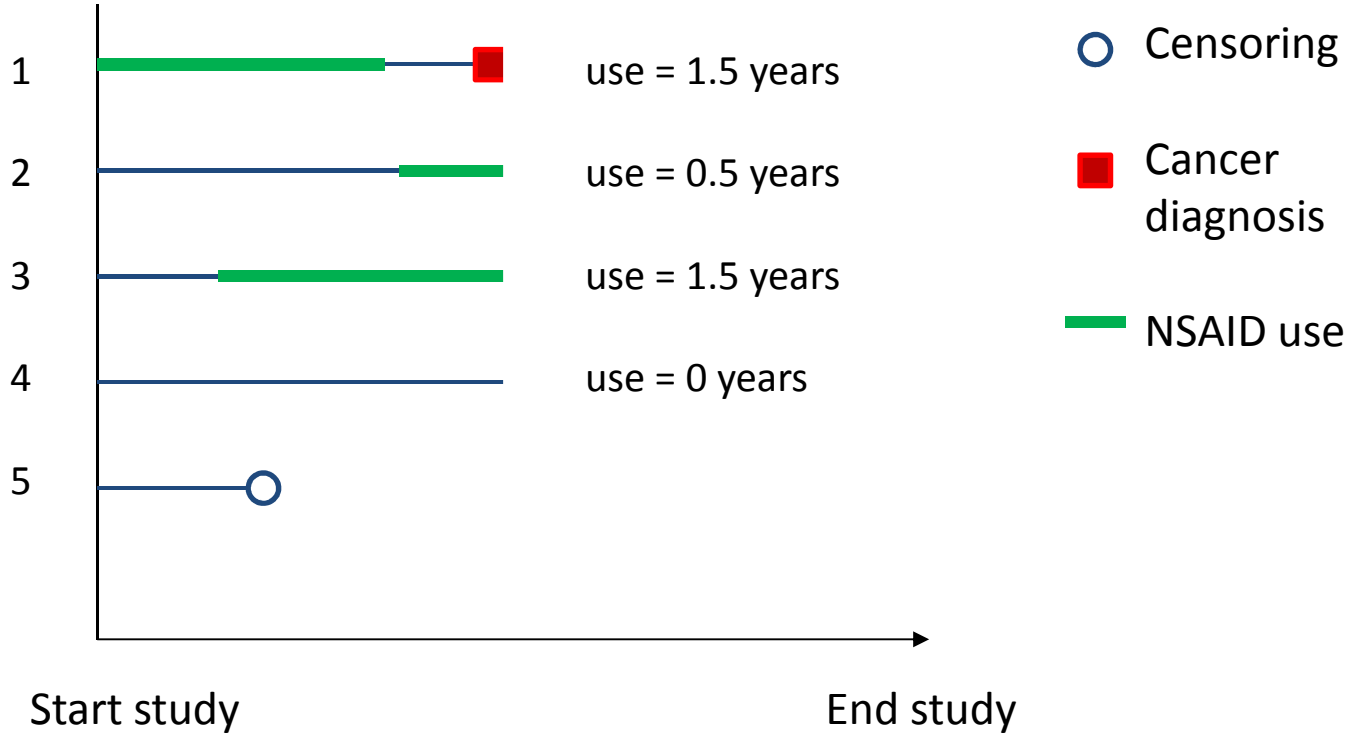
Levesque et al, BMJ, 2010

Cox regression with time-varying variables



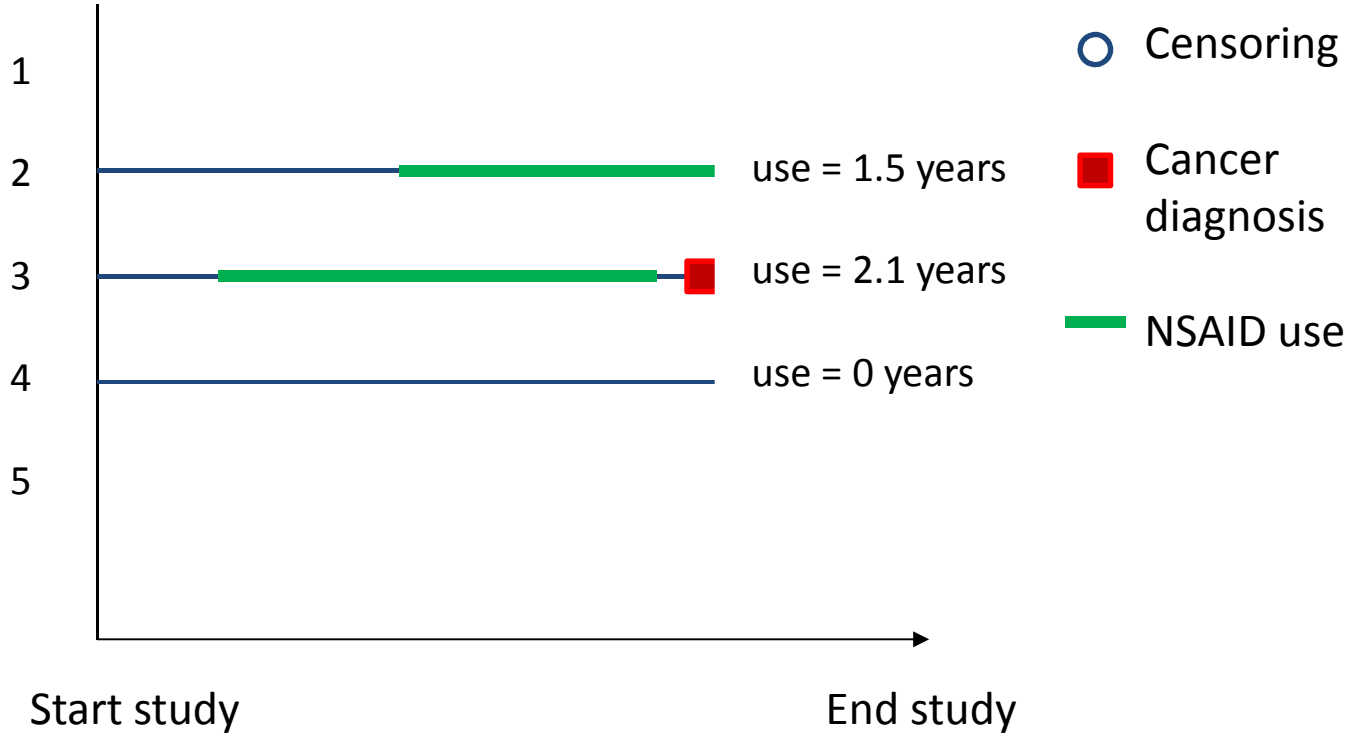
Cox regression with time-varying variables

Timepoint 1



Cox regression with time-varying variables

Timepoint 2



Competing risks

What are competing risks?

A. Conflicting hazard ratios of included predictors
B. Other investigators that could scoop your research
C. Certain outcomes that prevent your studied outcome from happening
D. Combination of risk increasing and risk decreasing independent variables in a model

Competing risks

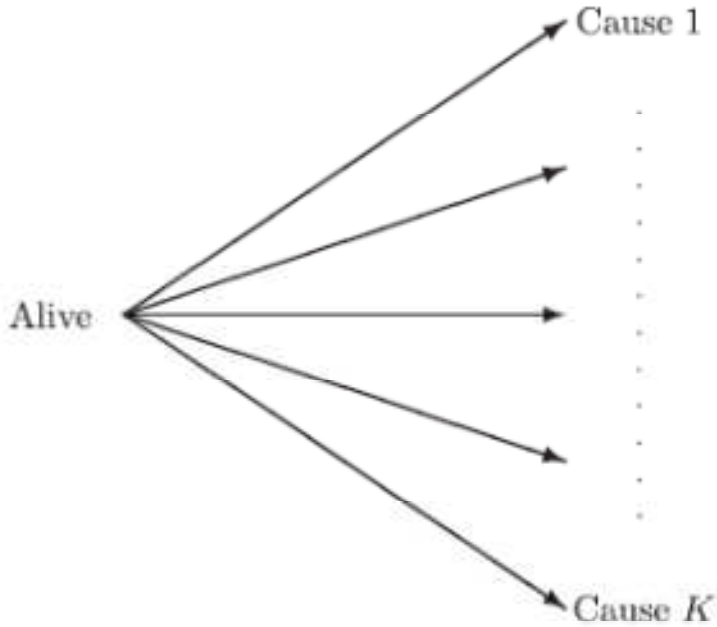


Figure 1. A competing risks situation with K causes of failure.

Putter et al., 2007, Stat Med.

Competing risks

What is the percentage of competing risk issues found in a review of 50 clinical studies performed in individuals susceptible to competing risks published in high-impact clinical journals?

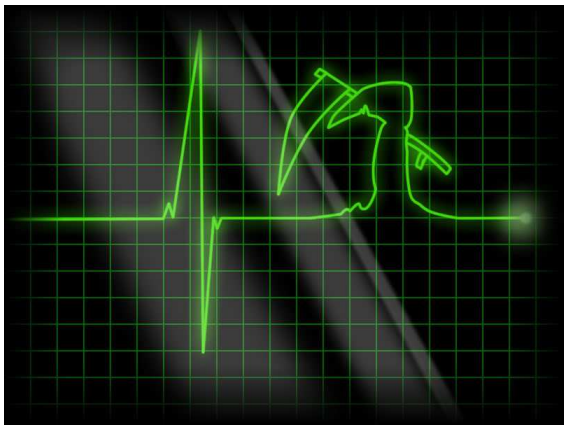
A. 10%
B. 25%
C. 50%
D. 70%

Koller et al., 2011, Stat Med.

Competing risks

Examples of competing risks in clinical research (observational and trials):

- Risk of a second basal cell carcinoma vs. death
- Risk of vascular death in diabetes patients vs. non-vascular deaths
- Risk of mortality on intensive care vs. translocation to other ward



Competing risks

For which study outcome could mortality never be a competing risk?

ALL-CAUSE MORTALITY

Competing risks

Which clinical studies and study populations are at risk?

- long follow-up
- elderly patients
- patients with multimorbidity
- critically-ill patients

Competing risks

Table I. Characteristics of two typical patient populations susceptible to competing risks.

The elderly/ multimorbid	The critically / severe ill
'(Slowly) progressive biology' Long-term risk exposure, e.g. smoking, diabetes, hypertension, HIV Period: late life Examples: Elderly patients, chronic kidney disease, long-term diabetes or hypertension, HIV/AIDS, cardiovascular risk patient, prostate cancer patients	'Destructing biology' Short term risk exposure, e.g. acute infection, cell depletion, mechanical ventilation Period: any Examples: Intensive care unit patients, transplant recipients, patients in aplasia, patients on chemotherapy

Koller et al., 2011, Stat Med.

Competing risks

What would be the right approach estimating survival/mortality probabilities in the presence of competing risks?

A. Kaplan-Meier curve
B. Cumulative incidence curve
C. Multiple imputation
D. Life table

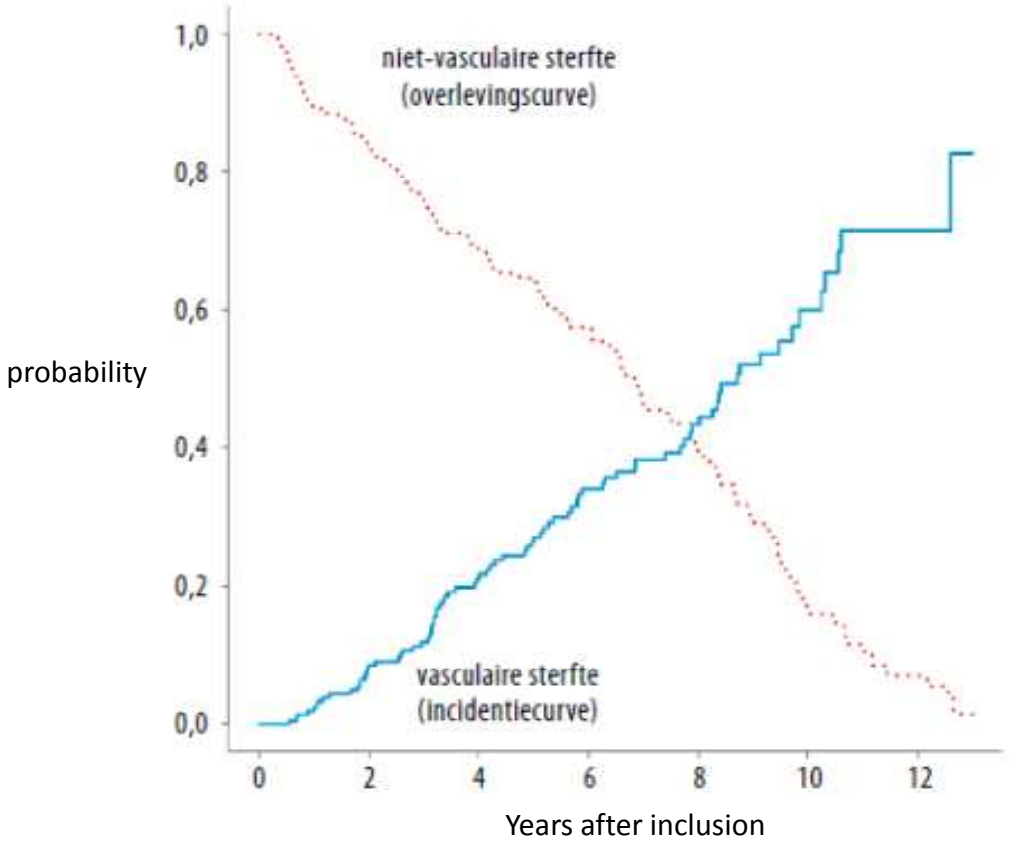
Competing risks

Why is using the Kaplan-Meier method wrong?

- patients get censored when a competing risk takes place (e.g. death)
- implicit independent censoring assumption: these patients have same chance of reaching primary endpoint as non-dead patients → IMPOSSIBLE
- which leads to overestimation of the probability of failure

Competing risks

Kaplan-Meier curve



Van Kruijsdijk et al., 2012, Ned Tijdschr Geneeskd.

Competing risks

Kaplan-Meier curve

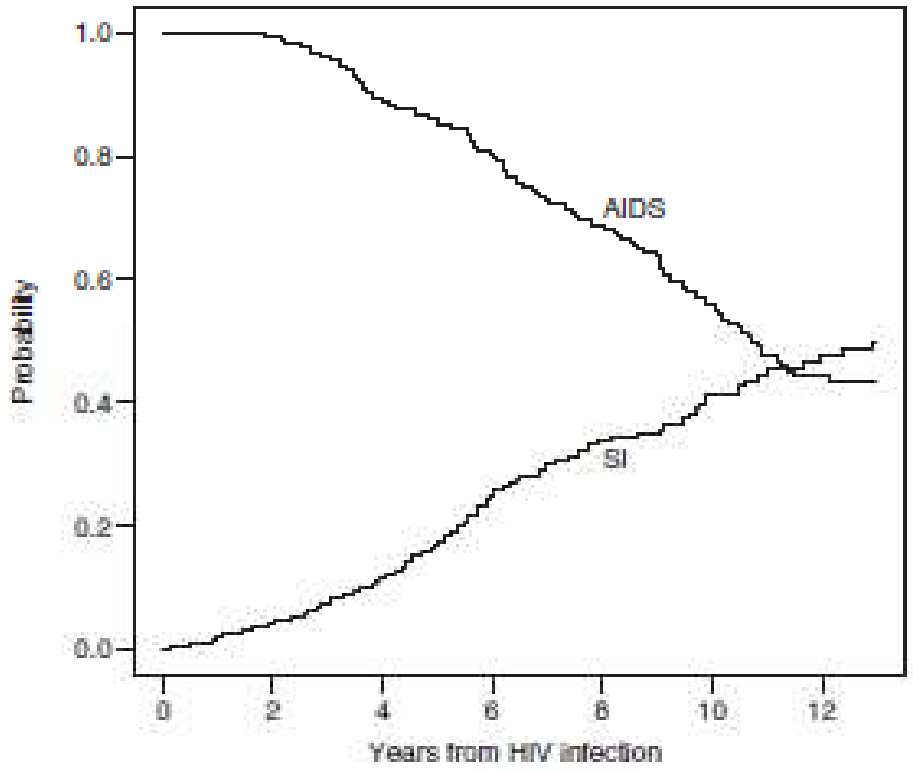


Figure 2. Estimated survival curve for AIDS and probability of SI appearance, based on the naive Kaplan–Meier estimator.

Putter et al., 2007, Stat Med.

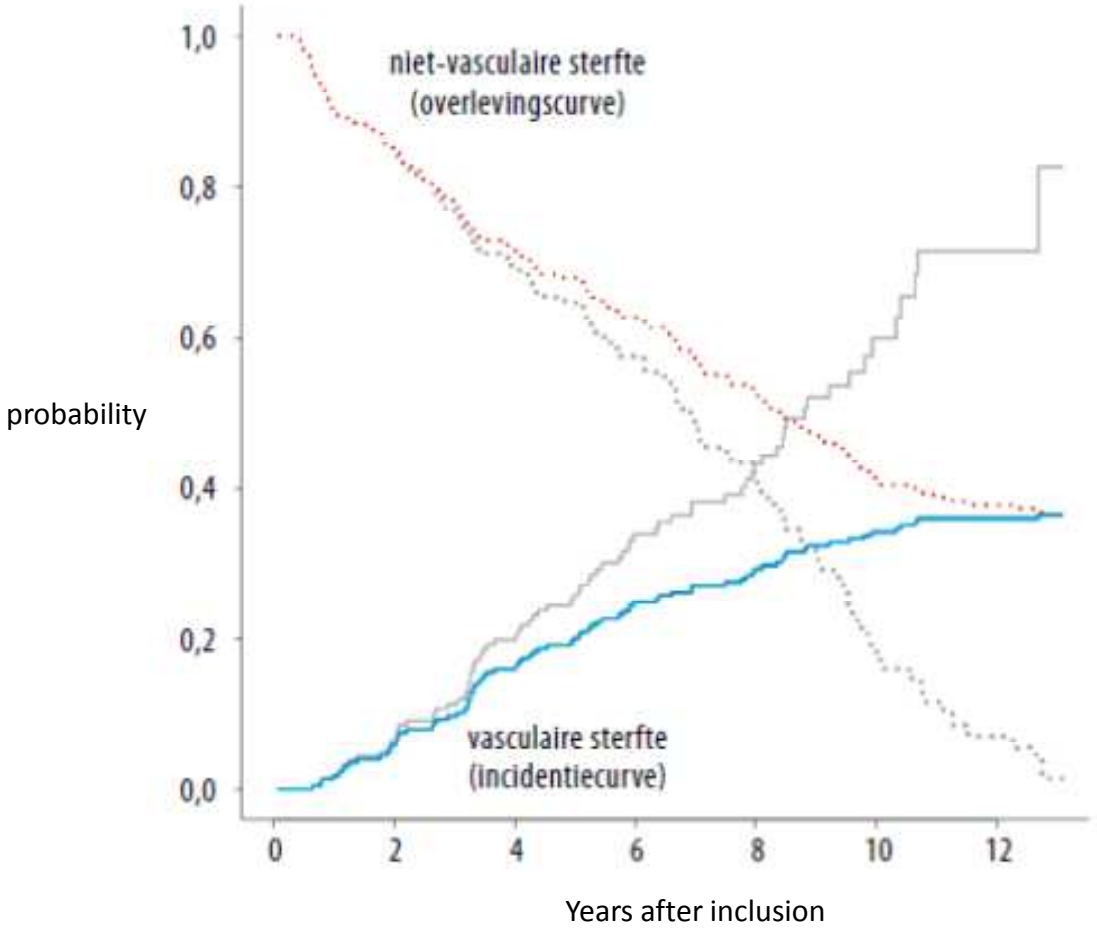
Competing risks

Cumulative incidence function

- patients who experience a competing risk don’t get censored
- takes into account that censored patients are not longer at risk of primary outcome

Competing risks

Cumulative incidence vs. Kaplan-Meier curve



Van Kruijsdijk et al., 2012, Ned Tijdschr Geneeskd.

Competing risks

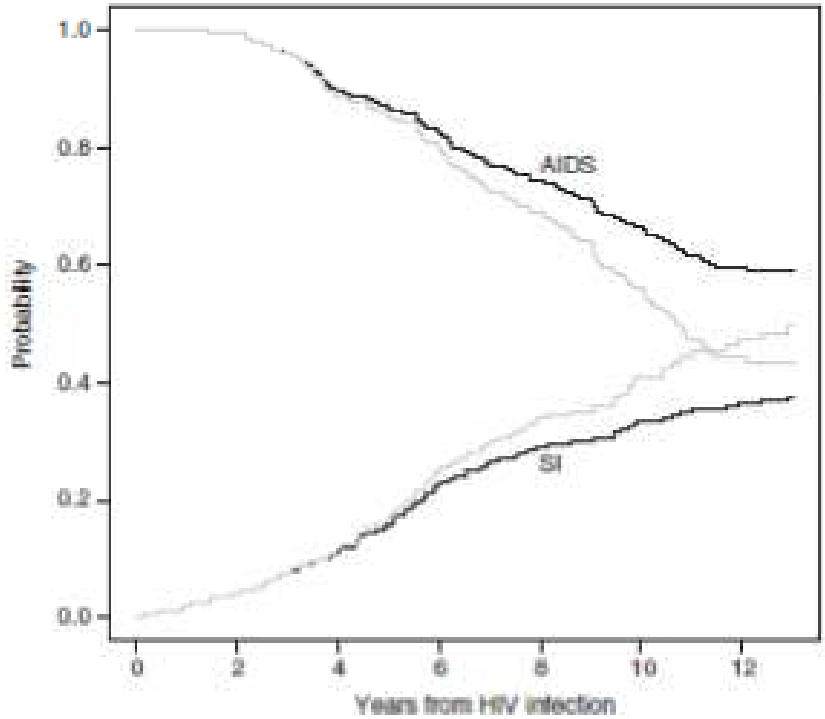
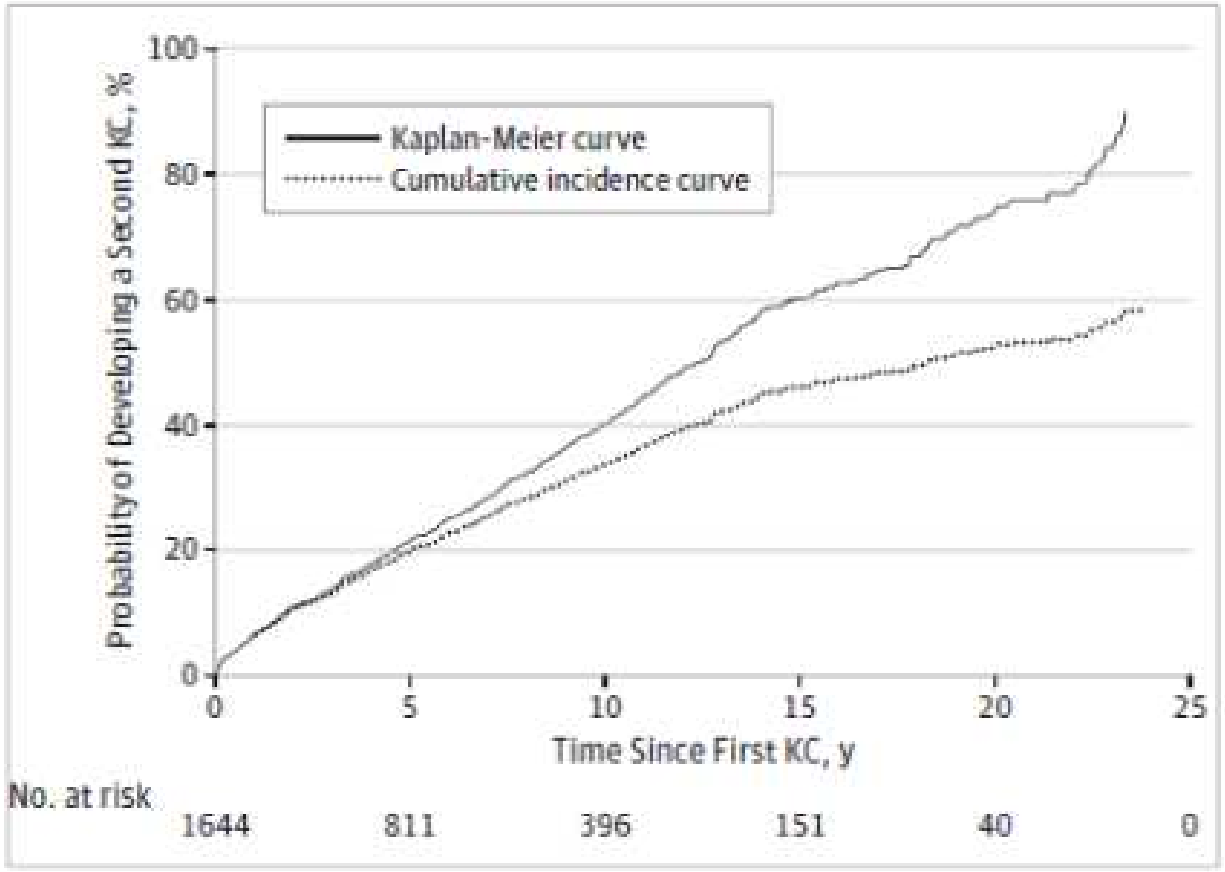


Figure 3. Estimates of probabilities of AIDS and SI appearance, based on the naive Kaplan–Meier (grey) and on cumulative incidence functions (black).

Putter et al., 2007, Stat Med.

Competing risks

Figure. Kaplan-Meier Curve vs Cumulative Incidence Curve of the Probability of Developing a Second Keratinocyte Cancer (KC)



Verkouteren et al., 2016, JAMA Dermatol.

Competing risks

What would be a right approach estimating hazard ratios for independent variables in the presence of competing risks?

A. Cox proportional hazards model
B. Binary multivariable regression analysis
C. Fine and Gray semiparametric proportional hazards model
D. Monte-Carlo model

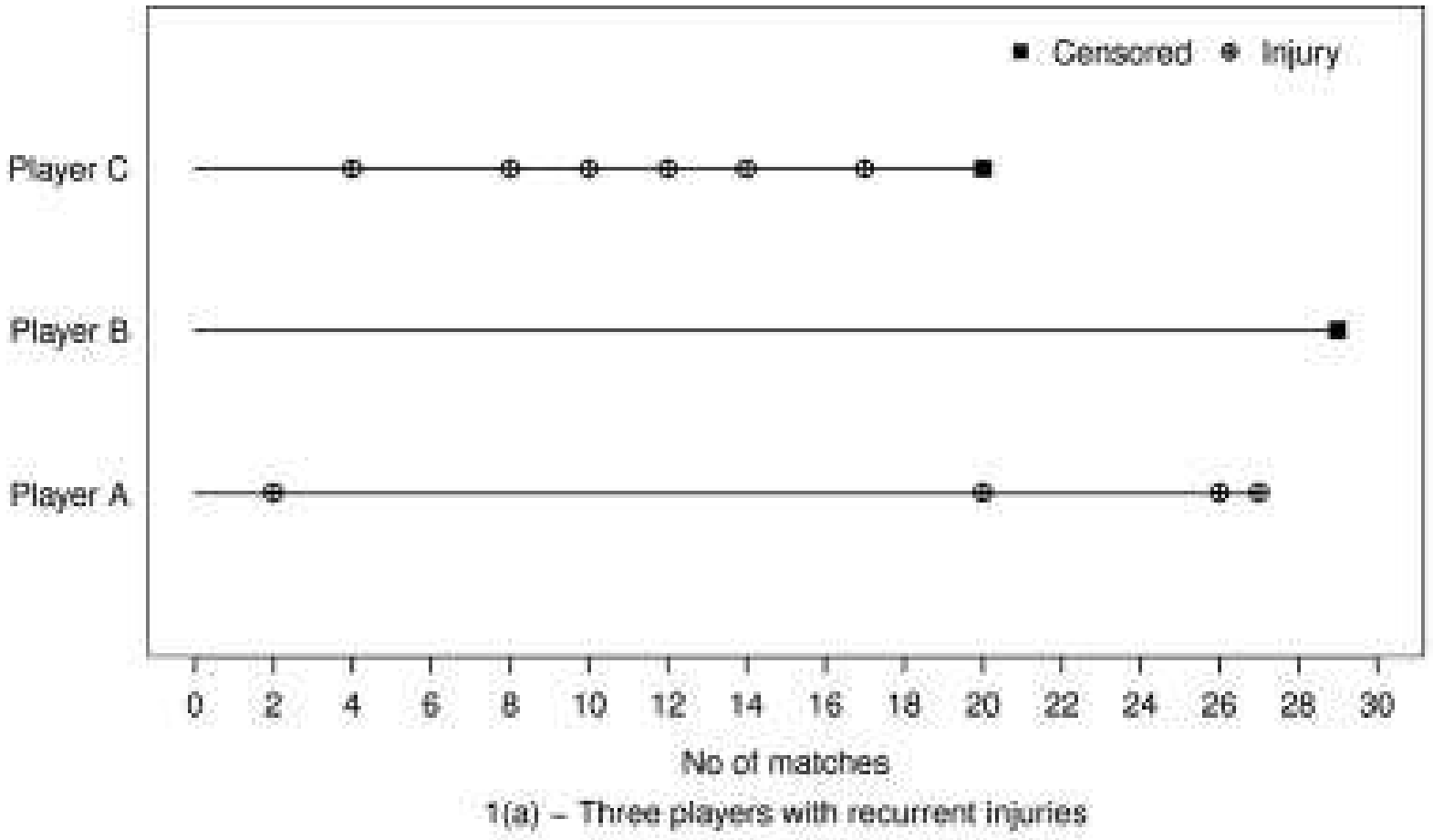
Competing risks

model†	uitkomst	HR nierfalen (95%-BI)	voorspeld 10-jaarsrisico
Cox	vasculaire dood	2,65 (1,88-3,71)	70% ‡
Fine en Gray	vasculaire dood	2,40 (1,70-3,40)	58% §
Cox	niet-vasculaire dood	2,46 (1,57-3,86)	37% ‡
Fine en Gray	niet-vasculaire dood	2,09 (1,34-3,27)	28% §

Van Kruijsdijk et al., 2012, Ned Tijdschr Geneeskd.

Dutch break

Recurrent events



1(a) – Three players with recurrent injuries

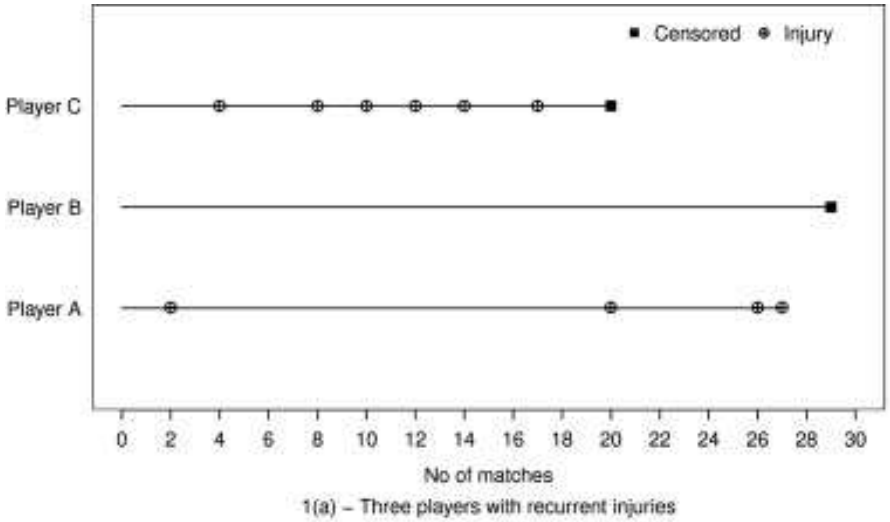
Ullah et al, 2012 BJSM

Recurrent events

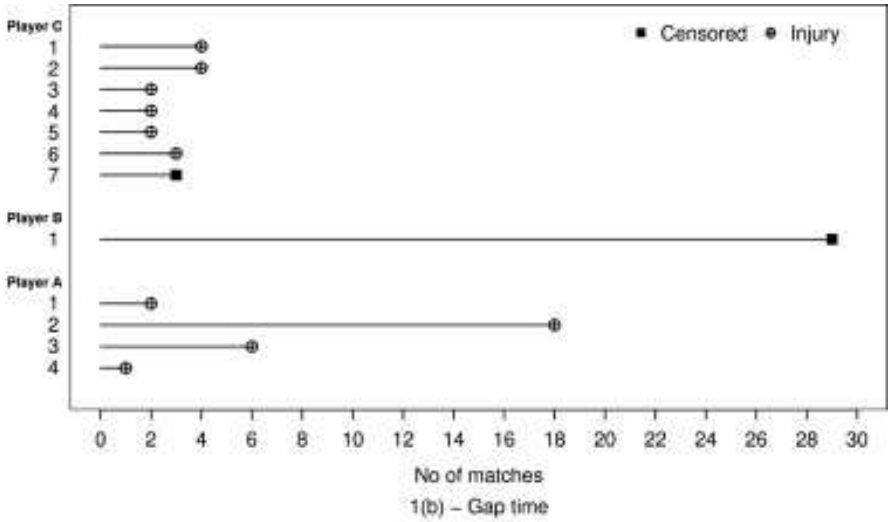
Properties and assumption of recurrent event models:

- Risk interval
- Risk set
- Baseline hazard
- Within-person correlation

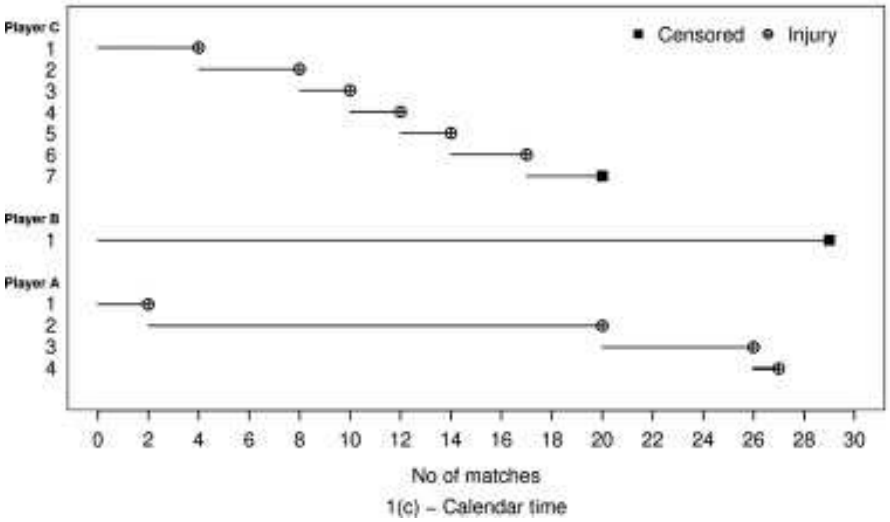
Recurrent events – Risk interval



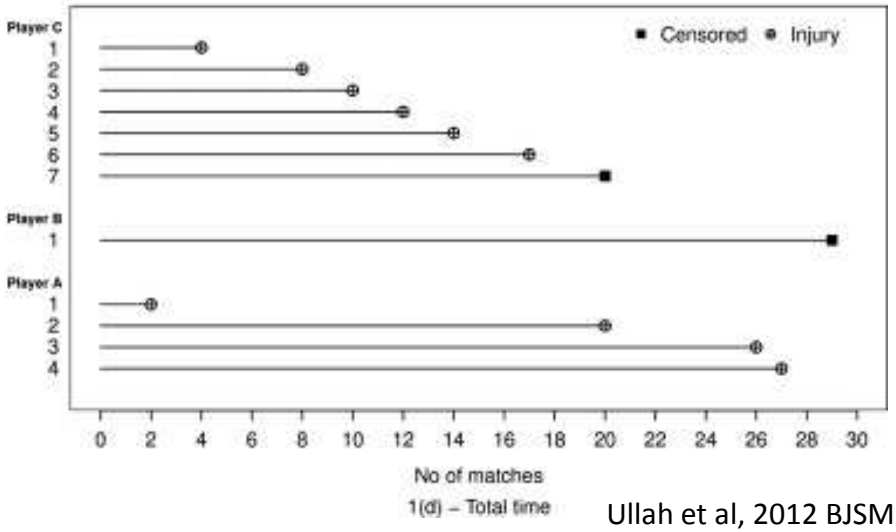
1(a) – Three players with recurrent injuries



1(b) – Gap time



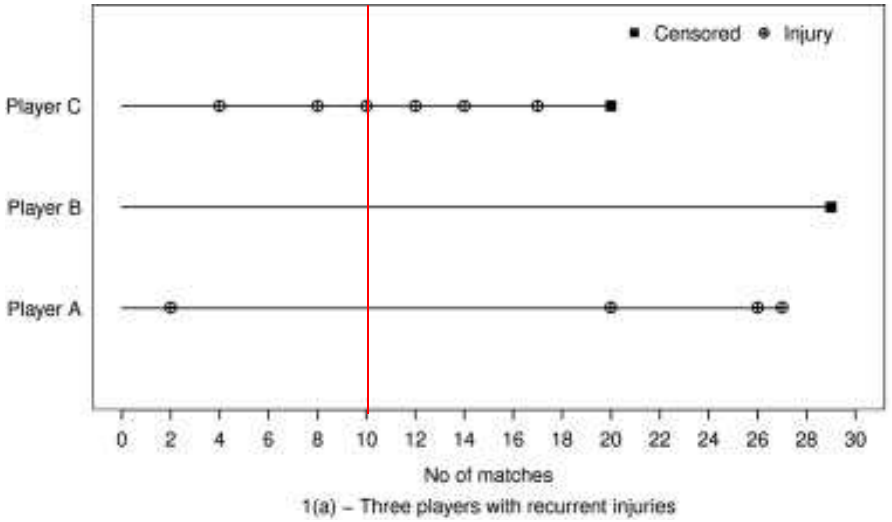
1(c) – Calendar time



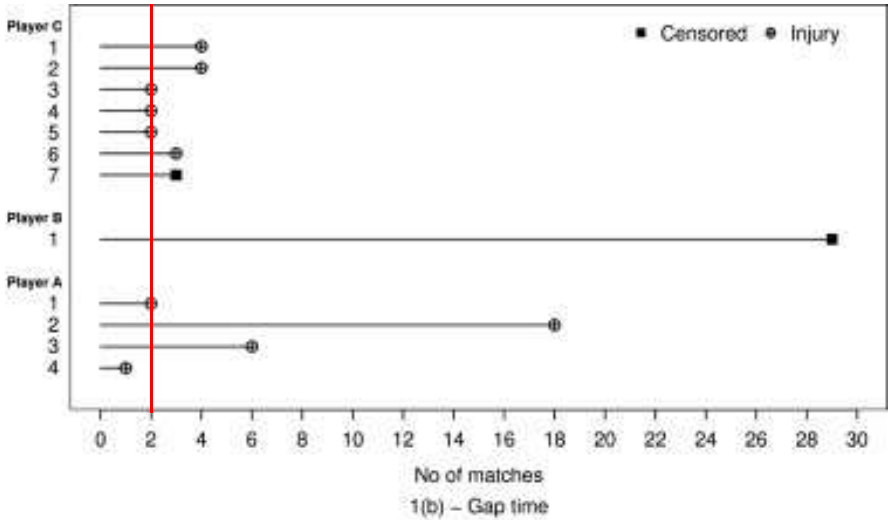
1(d) – Total time

Ullah et al, 2012 BJSM

Recurrent events – Risk set



1(a) – Three players with recurrent injuries



1(b) – Gap time

Risk set for the 3rd event of player C:

- Independent events: event 1-5 of C, event 1 of B, event 1-3 of A
- Persons who hasn't experienced the 3rd event yet: A, B and C
- Persons who haven't experienced the 3rd event yet, but have experienced the 1st and the 2nd event, only A

Ullah et al, 2012 BJSM

Recurrent events

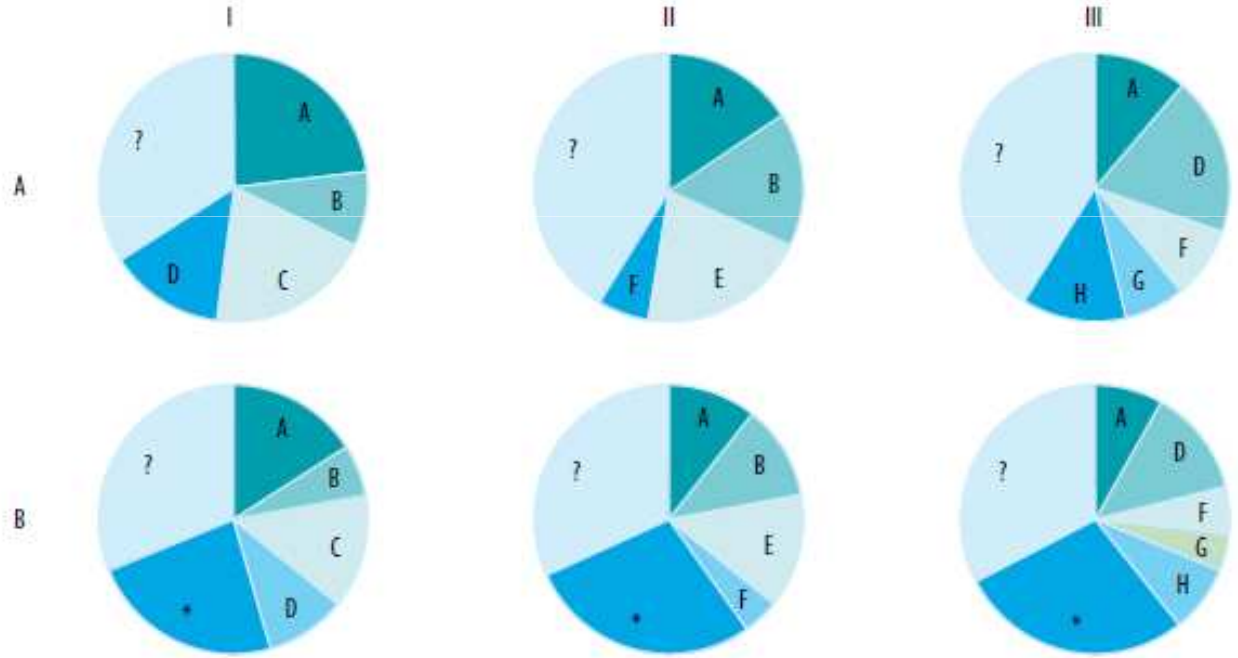
Stratify risk by event episode

TABLE 2. Hazards ratios comparing sunscreen interventions with noninterventions on repeated occurrence of basal cell carcinoma using the Wei-Lin-Weissfeld and the Prentice-Williams-Peterson gap-time multiple failure survival models, stratified by event episodes among 1,621 participants, Nambour Skin Cancer Prevention Trial, 1992–1996

	Wei-Lin-Weissfeld marginal proportional hazard model*			Prentice-Williams-Peterson gap-time model†		
	Hazard ratio	95% confidence interval	*p* value	Hazard ratio	95% confidence interval	*p* value
First occurrence	1.03	0.77, 1.38	0.83	1.03	0.77, 1.38	0.83
Second occurrence	0.70	0.43, 1.16	0.17	0.71	0.43, 1.17	0.18
Third occurrence	0.59	0.27, 1.28	0.18	0.67	0.31, 1.44	0.30

Pandeya et al, 2012 Am. J. Epidemiol

Index event bias



Smulders, 2011, NTvG

Index event bias

Table. Distribution of Selected Established Stroke Risk Factors in Individuals Screened for PFO During Heart Surgery and Individuals Who Have Had an Index Stroke Event, Stratified by PFO Status[a]

	Population Screened for PFO (N = 13 815)		Population Selected for Index Stroke (N = 1126)	
Risk Factors	PFO (n = 2277)	No PFO (n = 10 815)	PFO (n = 404)	No PFO (n = 722)
Age, mean, y	63.5	62.9	53.6	60.6
Hypertension, %	65	67	43	62
Diabetes mellitus, %	23	24	13	19
Smoking, %	58	58	27	35

Abbreviation: PFO, patent foramen ovale.

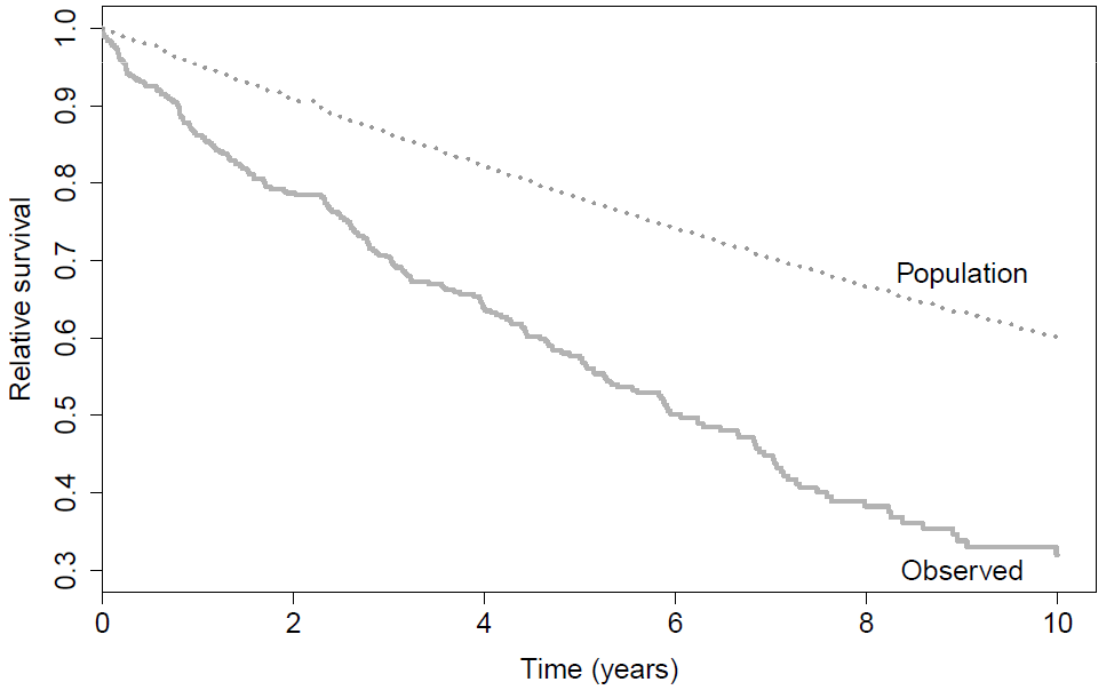
Dahabreh et al., 2011, JAMA

Relative Survival

Relative Survival

- Proxy for disease-specific survival

- $$Relative\ survival = \frac{observed\ survival}{population\ survival}$$



Relative Survival Melanoma Netherlands

Tabel

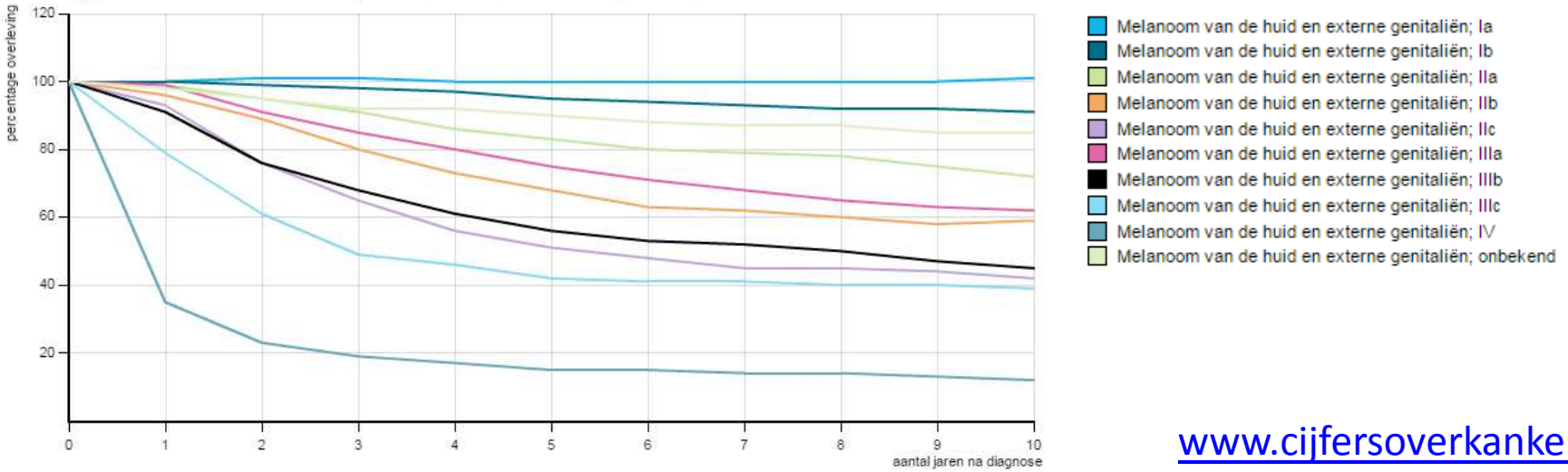
Overleving | Melanoom van de huid en externe genitaliën; Stadium

	Aantal tumoren	Aantal jaren na diagnose										
		0	1	2	3	4	5	6	7	8	9	10
TNM 6e editie (2003-2009)												
Ia	11376	100%	100%	101%	101%	100%	100%	100%	100%	100%	100%	101%
Ib	5788	100%	100%	99%	98%	97%	95%	94%	93%	92%	92%	91%
IIa	2577	100%	99%	95%	91%	86%	83%	80%	79%	78%	75%	72%
IIb	1618	100%	96%	89%	80%	73%	68%	63%	62%	60%	58%	59%
IIc	825	100%	93%	76%	65%	56%	51%	48%	45%	45%	44%	42%
IIIa	644	100%	99%	91%	85%	80%	75%	71%	68%	65%	63%	62%
IIIb	824	100%	91%	76%	68%	61%	56%	53%	52%	50%	47%	45%
IIIc	566	100%	79%	61%	49%	46%	42%	41%	41%	40%	40%	39%
IV	858	100%	35%	23%	19%	17%	15%	15%	14%	14%	13%	12%
onbekend	697	100%	98%	95%	92%	92%	90%	88%	87%	87%	85%	85%

Grafiek

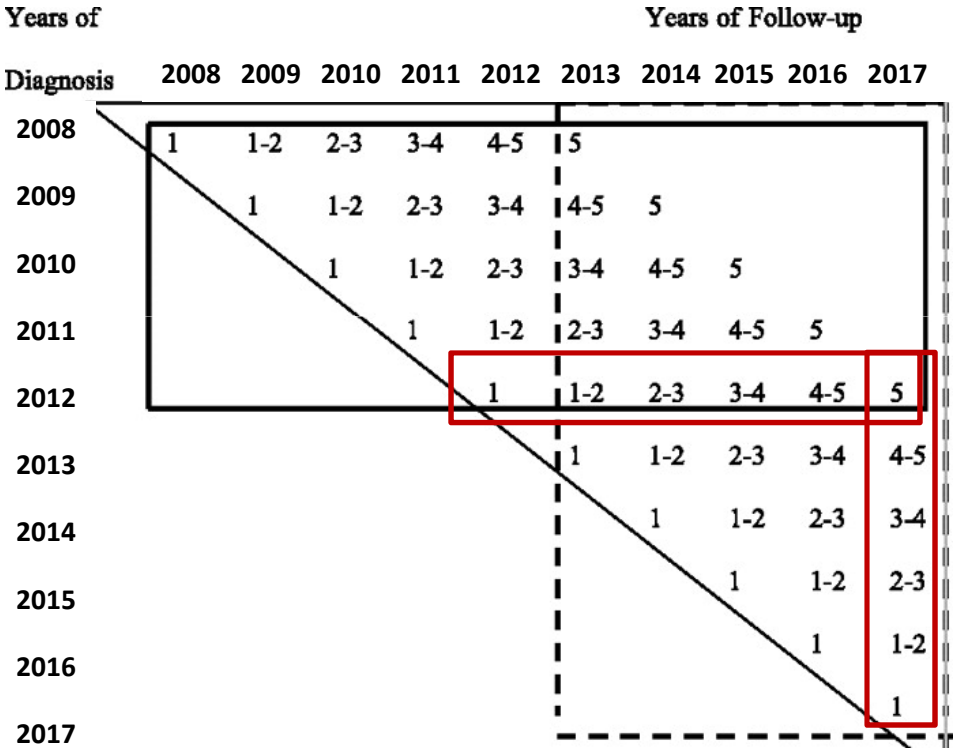
lijn | staaf

Overleving | Melanoom van de huid en externe genitaliën; Stadium; TNM 6e editie (2003-2009)



www.cijfersoverkanker.nl

Cohort vs Period based relative survival

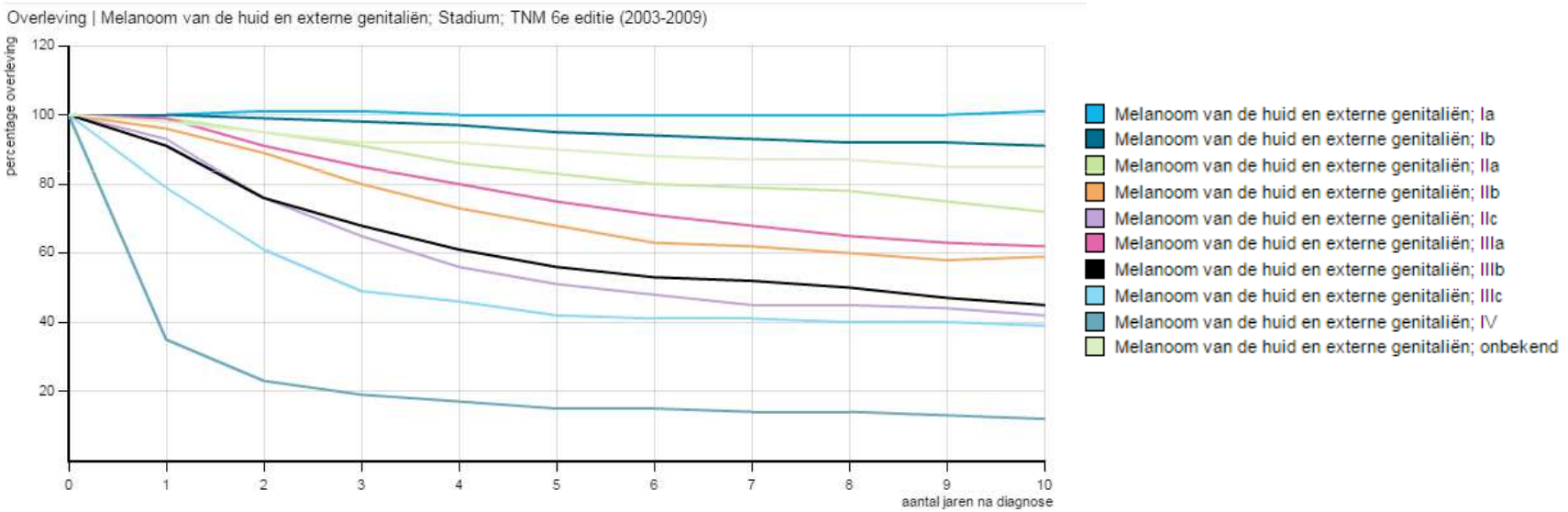


Cohort based analysis

Period based analysis
(up-to date survival estimates)

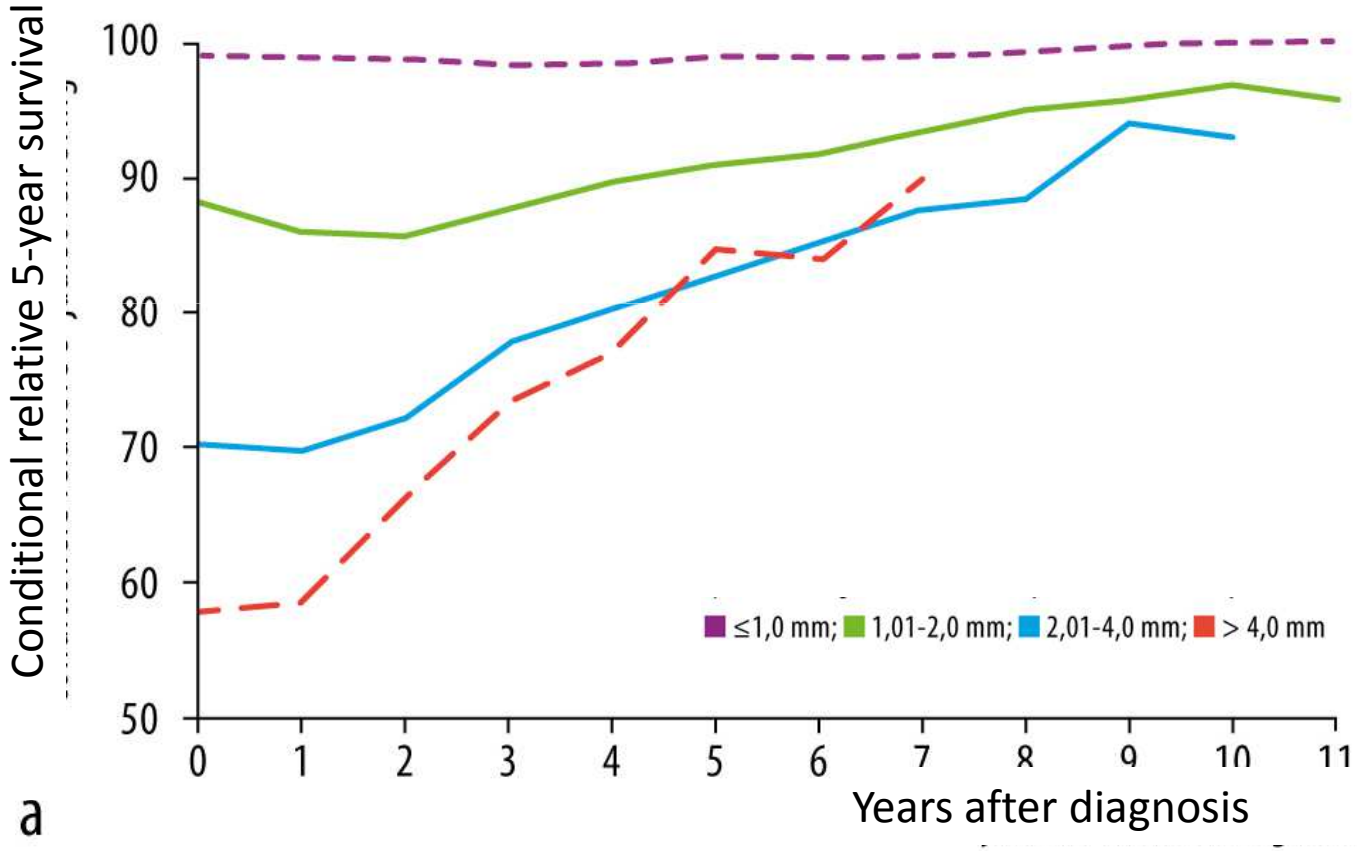
Brenner and Hakulinen, 2006

Relative Survival



Conditional relative survival

Prognosis at different timepoints after diagnosis



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