Survival analysis

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Survival analysis

- Time to **event data**.
- **Censoring**.

- **Survivor function – Kaplan-Meier plot**.

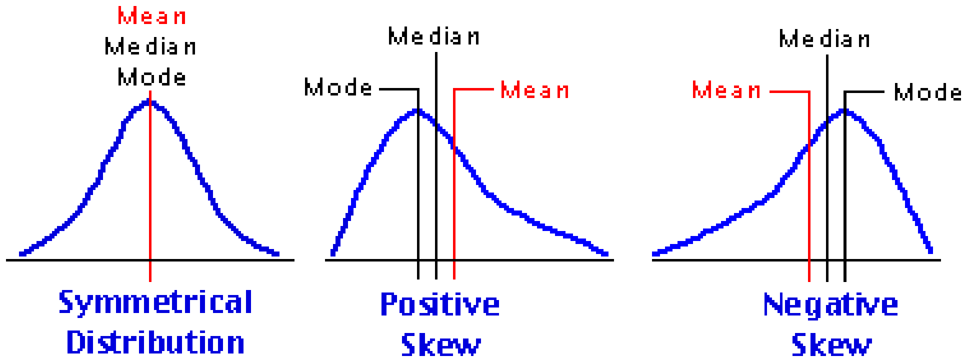
- **Log-rank test**.

- **Hazard function and Hazard ratio** .

Time to event data: examples

- Time to death.
- Time to progression of cancer.
- Time to development of diabetes.
- Time to recovery from diarrhea.
- Time to event data typically collected in
  - cohort studies (time between study baseline and event of interest).
  - clinical trials (time between randomisation and event of interest).
- Also known as **survival data**.

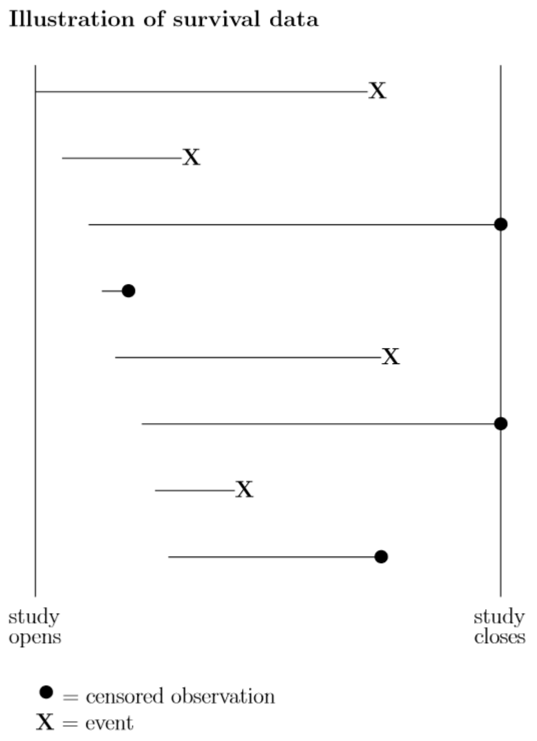
Features of time to event data



- Non-negative values.
- Not normally distributed (usually positively skewed).
- Event not usually observed for all individuals during the study.
- An observation is **censored** if individual does not experience event during the study.
- **Censoring time**: time from baseline/randomisation until latest date at which individual is known to be still alive and event-free.

Censoring

- Definition: Event of interest not observed for all individuals.
- **Fixed censoring:** event has not occurred when study has ended or data analysis is performed.
- **Loss to follow-up:** individual has been lost to follow-up (e.g. he/she no longer wishes to take part in study).



- Survival analysis methods make use of information from censored observations.
- Assume censoring is **non-informative**, i.e. if an individual is censored, his/her subsequent risk of the event of interest is unaffected.

Example of time to event data

Weeks to death or censoring (*) in 20 adults with recurrent astrocytoma:

6	13	21	30	31*	37	38	47*	49	50
63	79	80*	82*	82*	86	98	149	202	219

ID	death	weeks
1	1	6
2	1	13
3	1	21
4	1	30
5	0	31
6	1	37
7	1	38
8	0	47
9	1	49
10	1	50
11	1	63
12	1	79
13	0	80
14	0	82
15	0	82
16	1	86
17	1	98
18	0	149
19	1	202
20	1	219

Data reproduced from BMJ 2004; 328:1073.

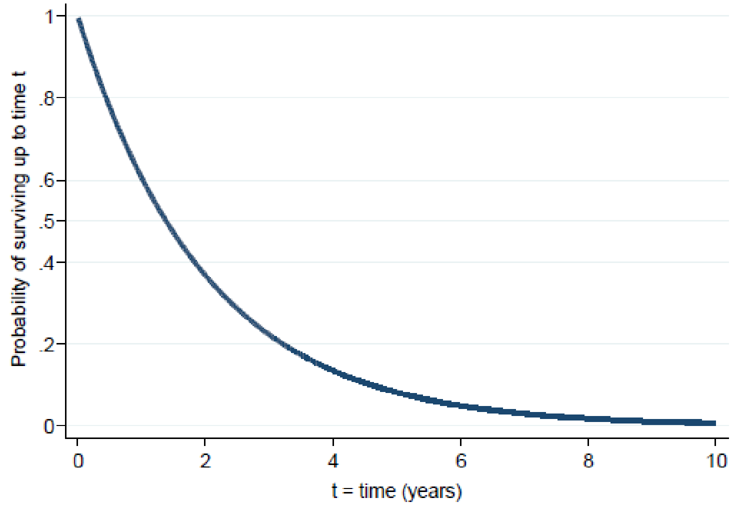
Aims of survival analysis

- To estimate probability of not experiencing event of interest (not dying = “surviving”) over any given time period (e.g. 5 year survival rate).

- To compare overall survival experience between different groups of individuals (e.g. between groups in a randomised clinical trial).

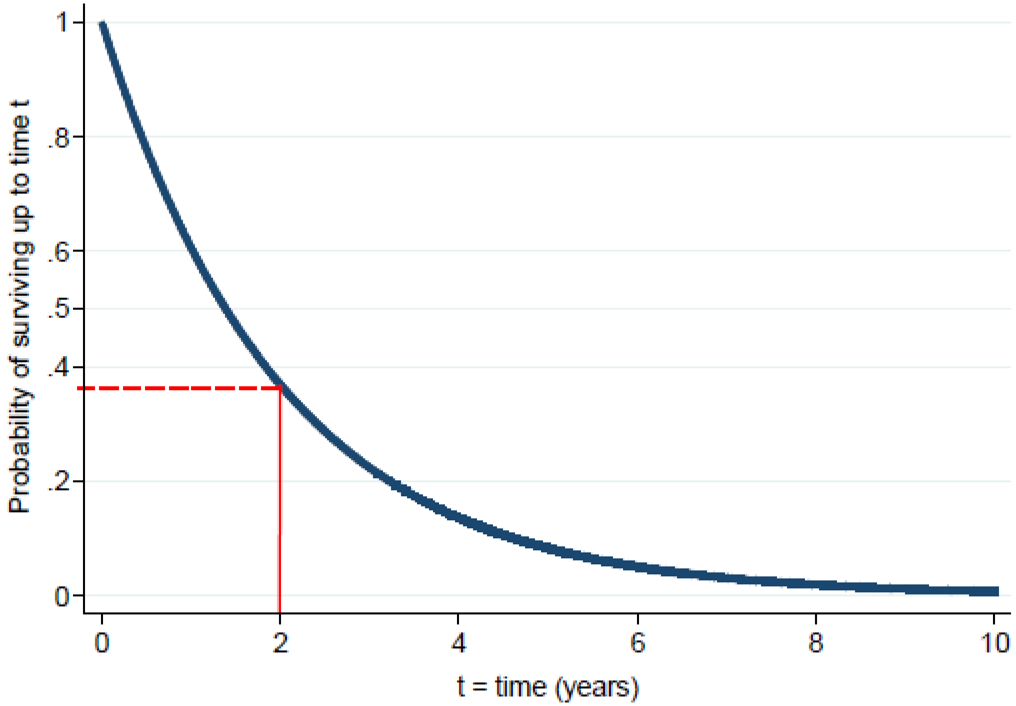
- **Survivor function**: Probability of not experiencing event of interest (“surviving”) up to time t.

Example:



Estimating a survival rate

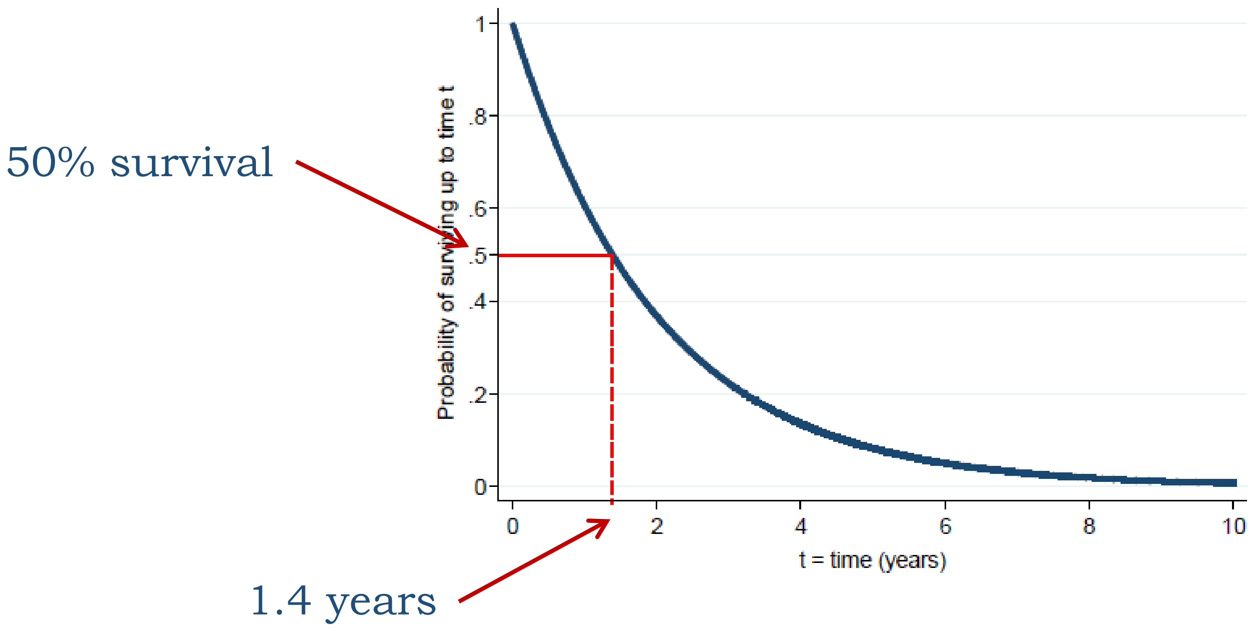
- Probability of surviving up to 2 years = 0.37.



Median survival time

- It is the time (expressed in months or years) when half the patients are expected to be alive. It means that the chance of surviving beyond that time is 50%.

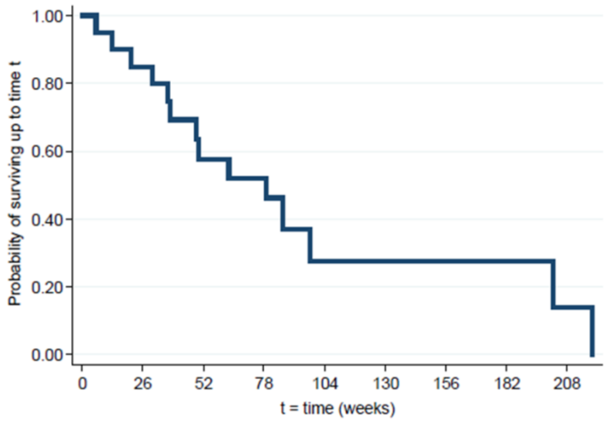
- Median survival time = 1.4 years, since the probability of surviving up to 1.4 years is 0.5.



Kaplan-Meier (KM) estimation of survivor function

First death

6	13	21	30	31*	37	38	47*	49	50
63	79	80*	82*	82*	86	98	149	202	219



- **20** individuals in study at t=0.
- First death at t=6 weeks.
- No individuals censored before t=6.
- Probability of death for each individual: **1/20=0.05**
- Therefore probability of surviving beyond t=6 is **(1-0.05)=0.95=19/20**.

Weeks in follow-up (t)	N at risk at time t	N of deaths at time t	Prob. of death at time t	Prob. of no death at time t	Prob. of surviving up to and including time t
0	20	0	0	1	1
6	20	1	0.05	0.95	1 x 0.95 = 0.95

"Risk set" at time t

1/20

19/20

K-M estimation of survivor function

Second death

	13	21	30	31*	37	38	47*	49	50
63	79	80*	82*	82*	86	98	149	202	219

- **19** individuals in study between t=6 and t=13.
- Second death at t=13.
- No individuals censored between t=6 and t=13.
- Probability of death for each individual: **1/19=0.053**
- Therefore probability of surviving beyond t=13 is **0.95 x 0.947 =0.90**.
  - with **0.95=(1-(1/20))** and **0.947=(1-(1/19))**

19/20

18/19

Weeks in follow-up (t)	N at risk at time t	N of deaths at time t	Prob. of death at time t	Prob. of no death at time t	Prob. of surviving up to and including time t
6	20	1	0.05	0.95	0.95
13	19	1	0.053	0.947	0.95 x 0.947 = 0.90

1/19

1-(1/19)=18/19

K-M estimation of survivor function

Third and fourth death

		21	30	31*	37	38	47*	49	50
63	79	80*	82*	82*	86	98	149	202	219

- **18** individuals in study between t=13 and t=21.
- Probability of death for each individual: **1/18=0.056**
- Probability of surviving beyond t=21 is **0.90 x (1-(1/18)) =0.85**.

From t=13: 0.95*0.947

- **17** individuals in study between t=21 and t=30.
- Probability of death for each individual: **1/17=0.059**
- Probability of surviving beyond t=30 is **0.85 x (1-(1/17)) =0.80**.

Weeks in follow-up (t)	N at risk at time t	N of deaths at time t	Prob. of death at time t	Prob. of no death at time t	Prob. of surviving up to and including time t
13	19	1	1/19= 0.053	0.947	0.90
21	18	1	1/18= 0.056	0.944	0.85
30	17	1	1/17= 0.059	0.941	0.80

K-M estimation of survivor function

Fifth and sixth death

				31*	37	38	47*	49	50
63	79	80*	82*	82*	86	98	149	202	219

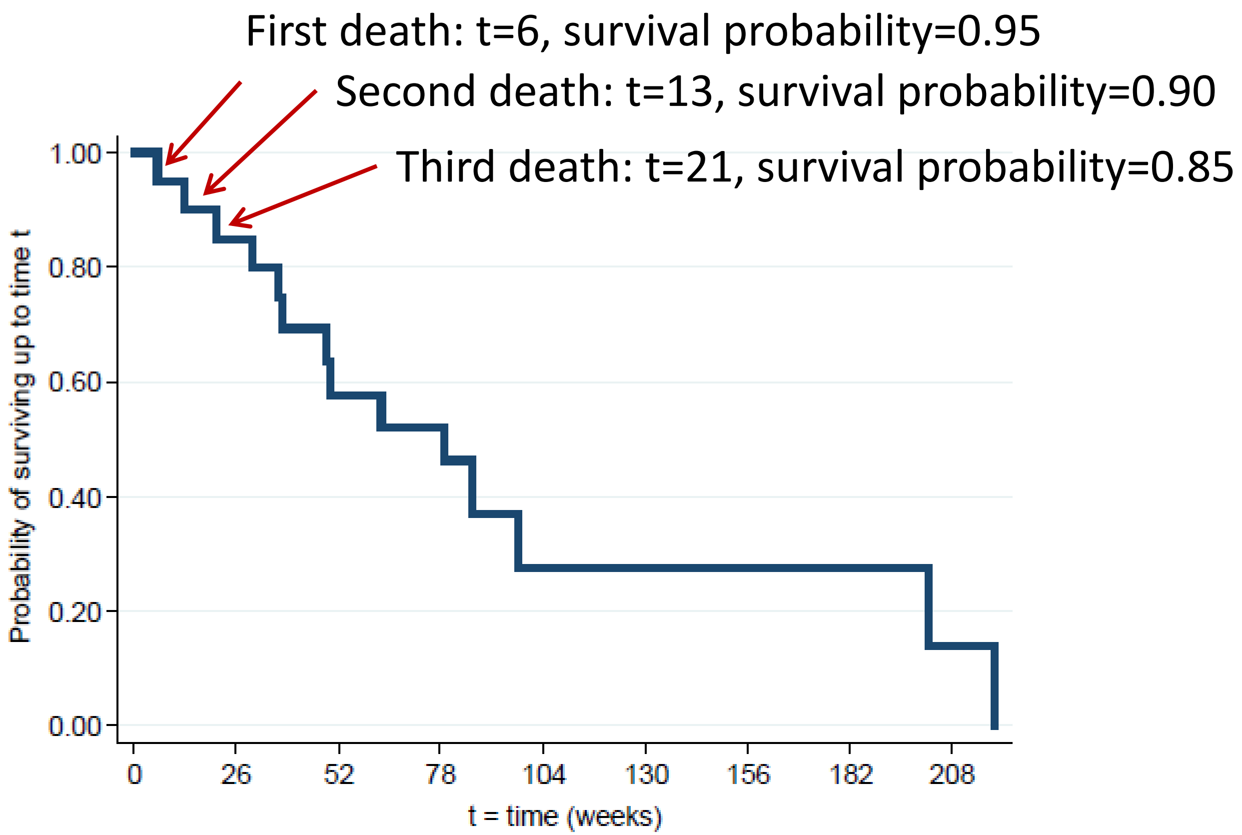
- **16** individuals in study between t=30 and t=31.
- 1 individual censored at t=31.
- **Probability of surviving beyond t=31 remains at 0.80**.

- **15** individuals in study between t=31 and t=37.
- Probability of surviving beyond t=37 is **0.80 x (1-(1/15)) =0.747**.

Weeks in follow-up (t)	N at risk at time t	N of deaths at time t	Prob. of death at time t	Prob. of no death at time t	Prob. of surviving up to and including time t
30	17	1	0.059	0.941	0.80
31	16	0	0	1	0.80 x 1 = 0.80
37	15	1	1/15=0.067	0.933	0.80 x 0.933 = 0.747

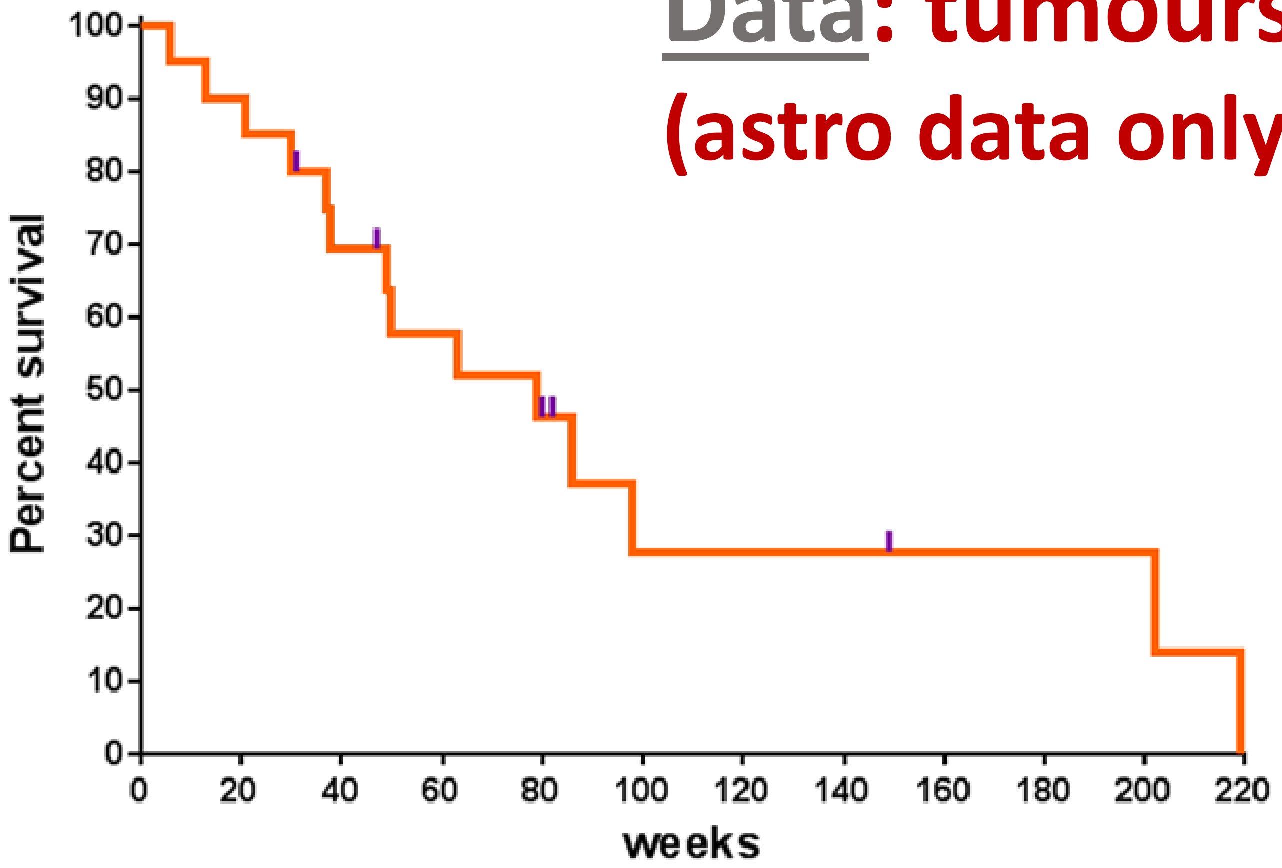
K-M plot of survivor function

- Continue these calculations until reaching the longest event time.
- K-M plot drawn as a step function:



K-M plot of survivor function

- Add ticks to indicate where censoring occurred.



Data: tumours.slsx

(astro data only)

Comparing 2 groups

- Weeks to death or censoring (*) in **20 adults** with recurrent astrocytoma:

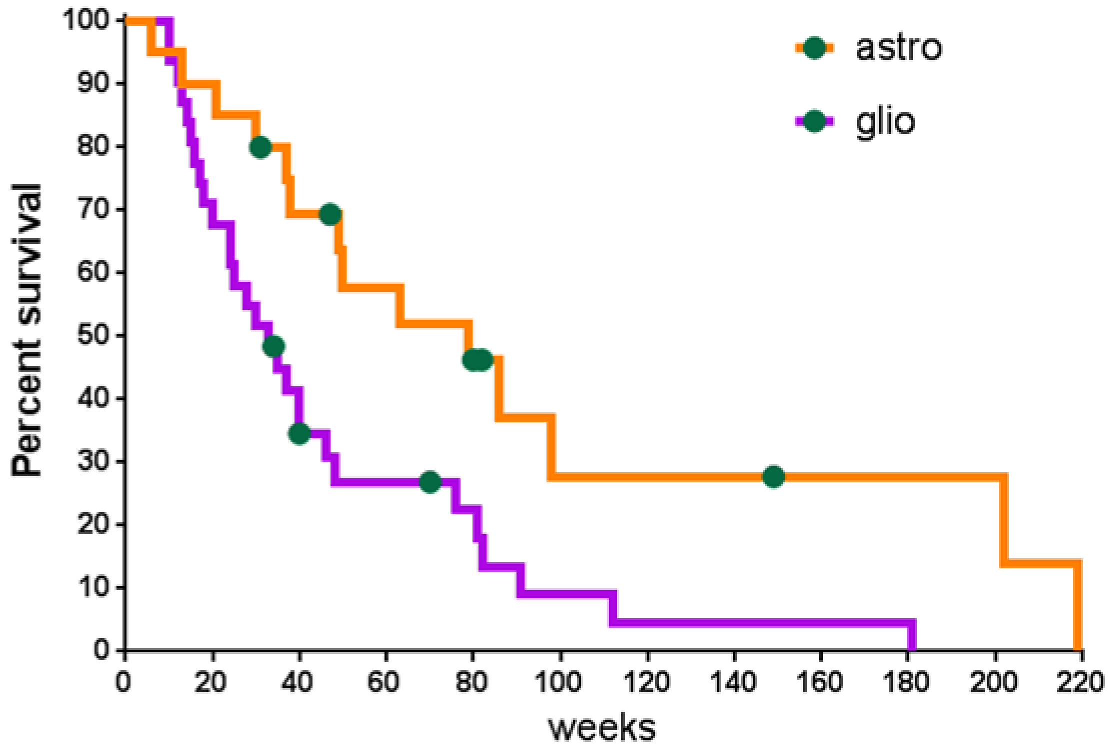
6	13	21	30	31*	37	38	47*	49	50
63	79	80*	82*	82*	86	98	149	202	219

- Weeks to death or censoring (*) in **31 adults** with recurrent glioblastoma:

10	10	12	13	14	15	16	17	18	20
24	24	25	28	30	33	34*	35	37	40
40	40*	46	48	70*	76	81	82	91	112
181									

Data reproduced from BMJ 2004; 328:1073.

K-M plot of survivor function by tumour type



- Survival chances appear better in individuals with astrocytoma than with glioblastoma, but is the **difference between groups statistically significant**?

Comparing 2 samples

- Could compare **median survival time**, or **probability of surviving** up to any particular time.
- Better to use a test which compares survivor functions over whole follow-up period.
- **Log rank test:** tests null hypothesis of no difference between samples in probability of an event (death in this example) at any time point during follow-up.
- **Log rank test statistic**:
    - based on calculating expected number of events that would occur under null hypothesis at each event time, and comparing to observed number of events.
    - under null hypothesis has a Chi^2 distribution with 1 degree of freedom.

Log rank test to compare 2 groups

Astro	Death (=1)	Glio	Death (=1)
6	1	10	1
13	1	10	1
21	1	12	1
30	1	13	1
31	0	14	1
37	1	15	1
38	1	16	1
47	0	17	1
49	1	18	1
50	1	20	1
63	1	24	1
79	1	24	1
80	0	25	1
82	0	28	1
82	0	30	1
86	1	33	1
98	1	34	0
149	0	35	1
202	1	37	1
219	1	40	1
		40	1
		40	0
		46	1
		48	1
		70	0
		76	1
		81	1
		82	1
		91	1
		112	1
		181	1

=14 deaths

=28 deaths

20/51

31/51

Week	Overall Observed Deaths	Expected Deaths – Astro	Expected Deaths – Glio	Observed Remainder – Astro	Observed Remainder – Glio
6	1/51	0.392157	0.607843	19	31
10	2/50	0.76	1.24	19	29
12					
13					
14					
15					
...					
Total (Expected)		Sum	Sum		
Total (Observed)		14	28		

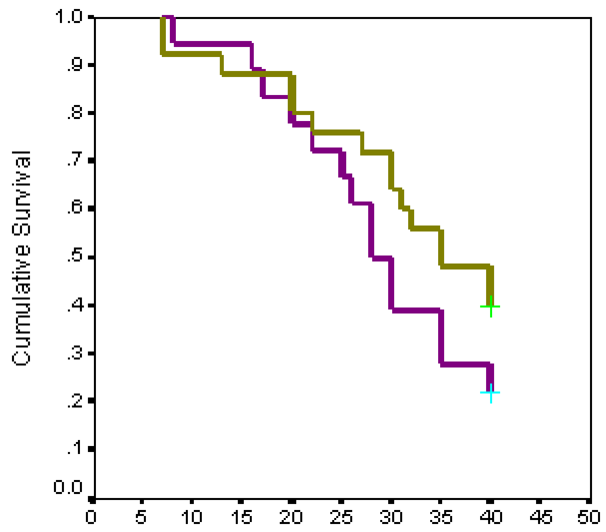
(19/50)*2

(31/50)*2

Log rank test statistic has a Chi^2 distribution:

$$Z = \frac{\sum_{j=1}^{J} (O_{1j} - E_{1j})}{\sqrt{\sum_{j=1}^{J} V_j}}$$

Log rank test



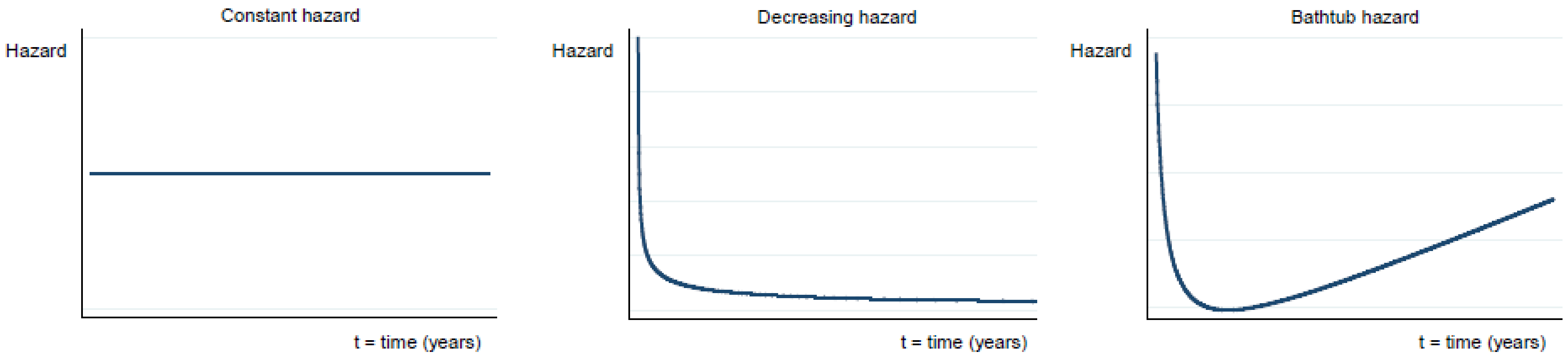
- Unlikely to detect a difference between Groups if survivor functions cross over during follow-up.
- Assumes **non-informative censoring**
- Can be extended to compare more than 2 groups.

<u>But</u>

- Only provides a p-value, not an estimate of size of difference between groups or a confidence interval.
  - Estimate of size of difference = **Hazard Ratio**

Hazard function

- **Hazard** is defined as the slope of the survival curve :a measure of how rapidly subjects are dying.
- Hazard function describes how hazard varies over time.

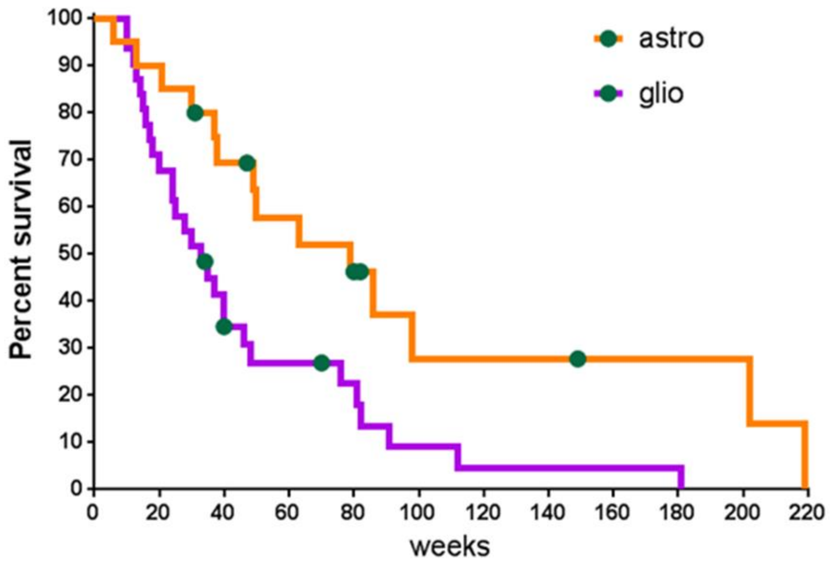


Hazard Ratio (HR)
for comparing 2 samples

- Hazards may vary over time, but assume that **HR is constant over time**.
- The hazard ratio is not directly related to the ratio of median survival times.
- When comparing 2 groups (a and b):
  - observed events (deaths) in each group: **Oa** and **Ob**,
  - expected events (deaths) in each group: **Ea** and **Eb,**
    - assuming a null hypothesis of no difference in survival.
- **HR= (Oa/Ea)/(Ob/Eb)**
- No assumption is needed about shape of hazard functions or underlying distribution of time to event data.
- HR is obtained from **Cox regression**

Hazard Ratio (HR)

Data: tumours.xlsx



	Survival Curve comparison		
1	Comparison of Survival Curves		
2			
3	Log-rank (Mantel-Cox) test		
4	Chi square	7.497	
5	df	1	
6	P value	0.0062	
7	P value summary	**	
8	Are the survival curves sig different?	Yes	
9			
10	Gehan-Breslow-Wilcoxon test		
11	Chi square	5.828	
12	df	1	
13	P value	0.0158	
14	P value summary	*	
15	Are the survival curves sig different?	Yes	
16			
17	Median survival		
18	astro	79	
19	glio	33	
20	Ratio (and its reciprocal)	2.394	0.4177
21	95% CI of ratio	1.26 to 4.547	0.2199 to 0.7934
22			
23	Hazard Ratio (Mantel-Haenszel)	A/B	B/A
24	Ratio (and its reciprocal)	0.4132	2.42
25	95% CI of ratio	0.2194 to 0.7779	1.286 to 4.557
26			
27	Hazard Ratio (logrank)	A/B	B/A
28	Ratio (and its reciprocal)	0.4341	2.304
29	95% CI of ratio	0.2367 to 0.7961	1.256 to 4.224
30			

- **HR = 2.3** (95% CI [1.32;4.44])

- At any point in time, hazard (i.e. instantaneous rate) of dying in individuals with recurrent glioblastoma is **2.3 times** higher than in individuals with recurrent astrocytoma.

Comparing more than 2 samples

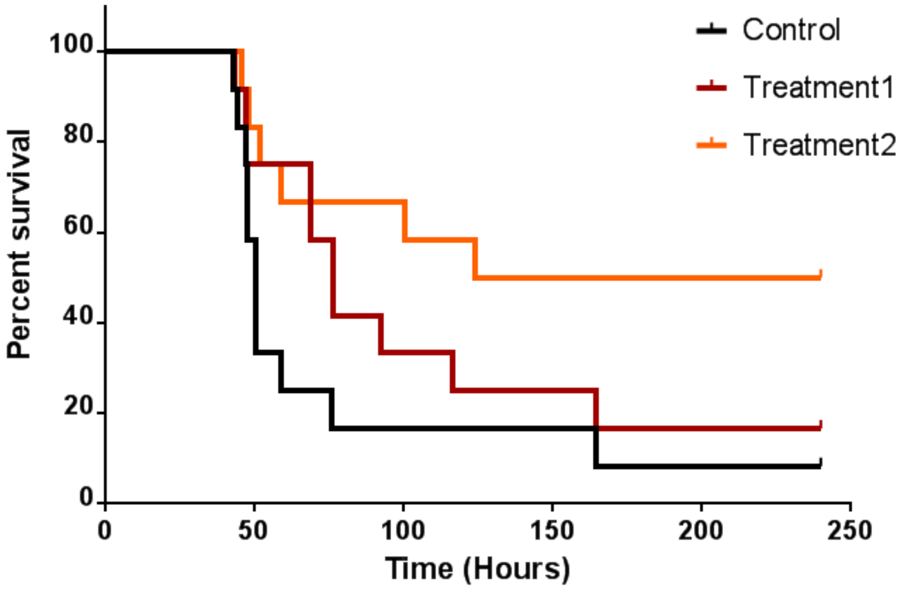
- **Issue with GraphPad:** cannot compare more than 2 groups directly
  - As in: does not run post-hoc pairwise comparisons

- **So how do we do it?**
  - Step 1: All groups comparisons (equivalent omnibus step in ANOVA)
  - Step 2: Make all pairwise comparisons of interest
  - Step 3: Apply Bonferroni correction

- **Example dataset**: **Lung infection**
  - Mice are infected with *Streptococcus pneumoniae*
    - 3 groups: Control, treatment 1 and treatment 2

Comparing more than 2 groups

- Step 1: All groups comparisons



Comparison of Survival Curves	
Log-rank (Mantel-Cox) test (recommended)	
Chi square	7.112
df	2
P value	0.0286
P value summary	*
Are the survival curves sig different?	Yes
Logrank test for trend (recommended)	
Chi square	7.044
df	1
P value	0.0080
P value summary	**
Sig. trend?	Yes
Gehan-Breslow-Wilcoxon test	
Chi square	6.743
df	2
P value	0.0343
P value summary	*
Are the survival curves sig different?	Yes

- There is an overall difference in survival between the 3 groups but which group is different from which?

Comparing more than 2 groups

- Step 2: Make all pairwise comparisons of interest

Control vs. T1

Comparison of Survival Curves		
Log-rank (Mantel-Cox) test		
Chi square	1.800	
df	1	
P value	0.1798	
P value summary	ns	
Are the survival cur		
Gehan-Breslow-Wilcoxon test		
Chi square	2.227	
df	1	
P value	0.1356	
P value summary	ns	
Are the survival curves sig different?	No	
Median survival		
Control	50.50	
Treatment1	76.50	
Ratio (and its reciprocal)	0.6601	1.515
95% CI of ratio	0.2804 to 1.554	0.6433 to 3.567
Hazard Ratio (Mantel-Haenszel)	A/B	B/A
Ratio (and its reciprocal)	1.898	0.5270
95% CI of ratio	0.7443 to 4.838	0.2067 to 1.344
Hazard Ratio (logrank)	A/B	B/A
Ratio (and its reciprocal)	1.720	0.5813
95% CI of ratio	0.7895 to 4.560	0.2193 to 1.267

Adjusted p-value = 0.5394

Control vs. T2

Comparison of Survival Curves		
Log-rank (Mantel-Cox) test		
Chi square	6.101	
df	1	
P value	0.0135	
P value summary	*	
Are the surv		
Gehan-Breslow-Wilcoxon test		
Chi square	5.825	
df	1	
P value	0.0158	
P value summary	*	
Are the survival curves sig different?	Yes	
Median survival		
Control	50.50	
Treatment2	182.0	
Ratio (and its reciprocal)	0.2775	3.604
95% CI of ratio	0.1026 to 0.7503	1.333 to 9.745
Hazard Ratio (Mantel-Haenszel)	A/C	C/A
Ratio (and its reciprocal)	3.642	0.2746
95% CI of ratio	1.306 to 10.16	0.09847 to 0.7658
Hazard Ratio (logrank)	A/C	C/A
Ratio (and its reciprocal)	3.130	0.3195
95% CI of ratio	1.360 to 9.751	0.1026 to 0.7353

Adjusted p-value = 0.0405

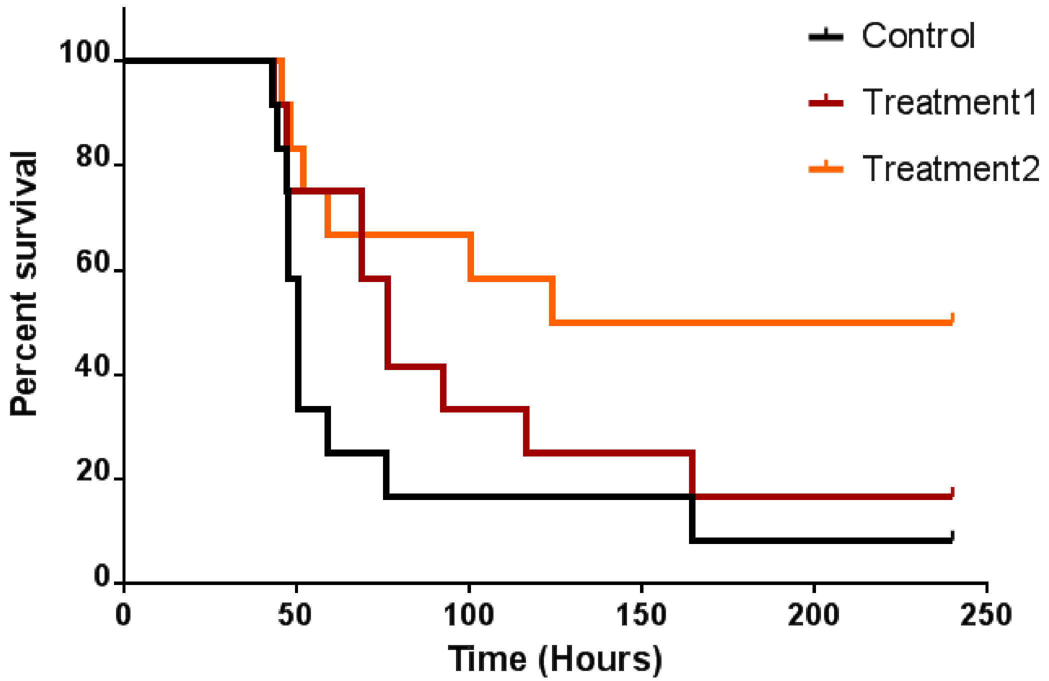
T1 vs. T2

Comparison of Survival Curves		
Log-rank (Mantel-Cox) test		
Chi square	2.214	
df	1	
P value	0.1367	
P value summary	ns	
Are the survival		
Gehan-Breslow-Wilcoxon test		
Chi square	1.528	
df	1	
P value	0.2164	
P value summary	ns	
Are the survival curves sig different?	No	
Median survival		
Treatment1	76.50	
Treatment2	182.0	
Ratio (and its reciprocal)	0.4203	2.379
95% CI of ratio	0.1528 to 1.157	0.8647 to 6.546
Hazard Ratio (Mantel-Haenszel)	B/C	C/B
Ratio (and its reciprocal)	2.151	0.4649
95% CI of ratio	0.7843 to 5.899	0.1695 to 1.275
Hazard Ratio (logrank)	B/C	C/B
Ratio (and its reciprocal)	2.084	0.4797
95% CI of ratio	0.8024 to 5.767	0.1734 to 1.246

Adjusted p-value = 0.4101

- Step 3: Apply Bonferroni correction: 0.05/3=0.06 or initial **p-values*3**

Comparing more than 2 groups



- At any point in time, hazard of dying in mice with lung infection is:
  - almost 2 times higher in the control than in the treatment 1 group (p=0.54)
  - 3.6 times higher in the control than in the treatment 1 group (p=0.04)