

Lecture #11

- Kaplan and Meier procedure
- Comparisons of survival curve, Log rank test
- Cox Proportional Hazard models

Many studies in medicine are designed to determine whether a new medication, a new treatment, or a new procedure will perform better than the one in use.

Although measures of short-term effects are of interest, long-term outcomes, such as mortality and major morbidity, are also important.

For example in a study of the effect of adjuvant chemotherapy on bladder cancer patients after cystectomy. A clinical trial was started to study the effect of postoperative chemotherapy. After cystectomy, patients were randomized to two groups: one group received adjuvant chemotherapy and the other received placebo.

The investigator wants to examine survival experience in the two groups. The outcome variable is a qualitative variable, survival or death of the patient and the desire is to estimate and compare the length of time patients survive in each treatment group.

Survival Analysis

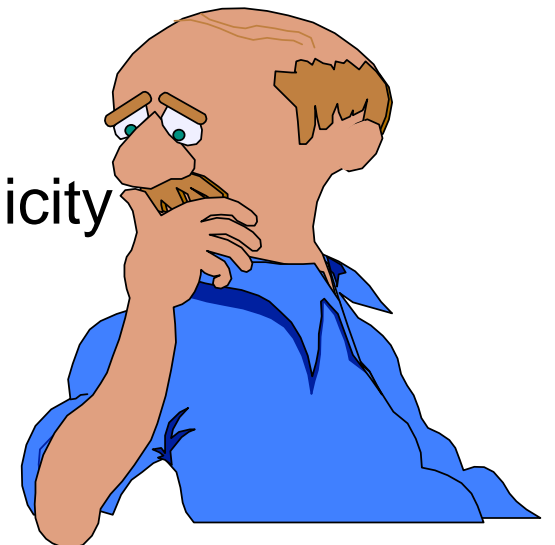
The methods of data analysis discussed before are not appropriate for measuring length of survival time for two reasons.

First, investigators frequently must analyze data before all patients have died; otherwise, it may be many years before they know which treatment is better.

The second reason is that patients do not typically begin treatment or enter the study at the same time, not all patients had surgery on the same day or had chemotherapy on the same day.

Methods are called “survival” analysis for historical reasons, but are useful for analyzing time to events other than death--e.g.,

- ~ time to relapse (pediatric ALL)
- ~ time to neutropenia (bactrim vs. amoxicillin for otitis media, serial WBC's)
- ~ time to pregnancy (infertility studies)
- ~ time to palpable tumor (animal carcinogenicity studies)



Censoring

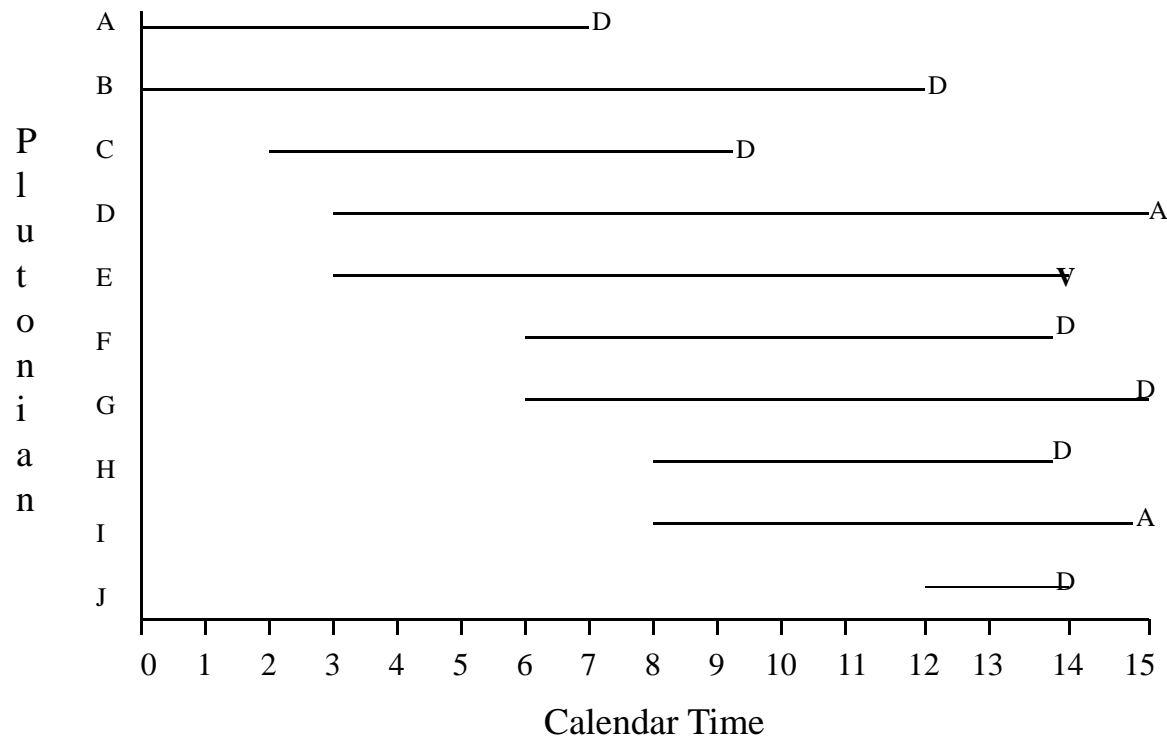
Censoring occurs when a subject is observed for some period of time without the event of interest (death, relapse, bone marrow engraftment, etc.) occurring.

Censoring may result from:

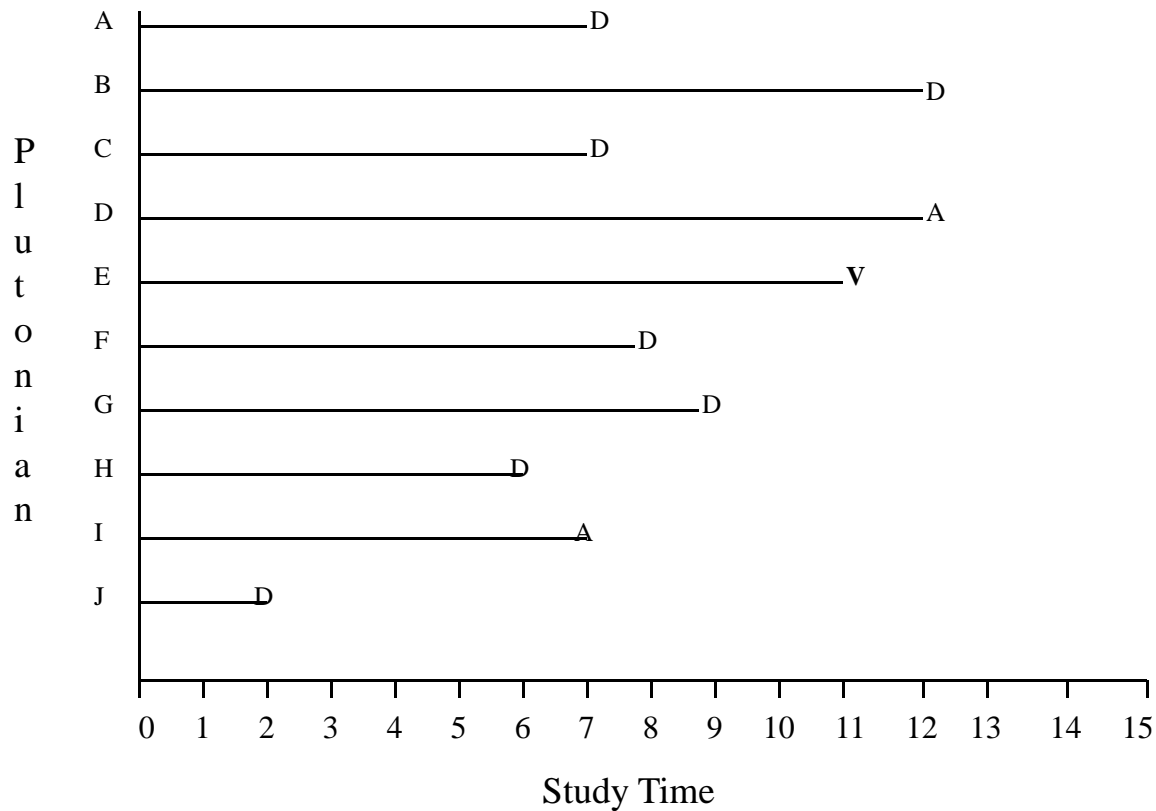
- Loss to follow-up
- Follow-up ends before event occurs
- Competing risks -- e.g. bone marrow transplant patient dies of opportunistic infection before engraftment; ALL patient dies in automobile accident before relapsing

Problem: The tobacco industry, driven far from Earth by public health protectors, invades Pluto. It is very cold so Plutonians spend most time inside and are dropping dead from exposure to second hand tobacco smoke.

Figure shows 10 randomly selected nonsmoking Plutonians observed during 15 Pluto time units. Subjects entered the study when they started hanging out at smoky bars and were followed until they dropped dead, were lost to follow-up or the study ended.



This figure shows the same data in a study time format instead of calendar time. It can be seen, for example, that subject A lived exactly 7 time units(uncensored) while subject I lived at least 7 time units(censored). Subject E is censored at time unit 11 since the vaporization death had nothing to do with second hand smoke.



When the prolonged observation of an individual is not necessary to assess occurrence of the event (as in surgical mortality), 2x2 contingency chi-square analysis may be used to assess differences in survival between groups of subjects.

Example:

Surgical Priority	Discharge Status		Total
	Dead	Alive	
Emergency	24	9	33
Non-Emergency	289	100	389
Total	313	109	422

Chi-Square = 0.04

Degrees of Freedom = (2-1)(2-1) = 1

p = 0.084

Assumptions in Survival Analysis

The interpretation of survival curves (and their CIs) depends on these assumptions:

Random sample:

If your sample is not randomly selected from a population, then you must assume that your sample is representative of that population.

Independent observations: Choosing any one subject in the population should not affect the chance of choosing any other particular subject.

Consistent entry criteria: Patients are enrolled into studies over a period of months or years.

In these studies it is important that the starting criteria don't change during the enrollment period.

Imagine a cancer survival curve starting from the date that the first metastasis was detected. What would happen if improved diagnostic technology detected metastases earlier?

Even with no change in therapy or in the natural history of the disease, survival time will apparently increase (patients die at the same age they otherwise would but are diagnosed at an earlier age and so live longer with the diagnosis).

Assumptions in Survival Analysis (cont)

Consistent criteria for defining "survival " If the curve is plotting time to death, then the ending criterion is pretty clear. If the curve is plotting time to some other event, it is crucial that the event be assessed consistently throughout the study.

Time of censoring is unrelated to survival.

Estimation of Survival (or Hazard) Function

- Suppose we have follow-up data on a sample of (independent) individuals that describes the *time* at which they became an incidence case (or died)
- How do we use the data to estimate $S(t)$ or $h(t)$



Kaplan-Meier or Product-Limit Estimator

Simple Example

Interval from lung cancer diagnosis to death

Patient	Survival (months)
1	2
2	3
3	6
4	6
5	7
6	10
7	15
8	15
9	16
10	27
11	30
12	32

Product Limit Method

Event Number	Time of Death (t)	# who fail at time t	# at risk at time t	q	$p=1-q$	$S(t^+)$
0	0	0	12	0	1	1
1	2	1				
2	3	1				
3	6	2				
4	7	1				
5	10	1				
6	15	2				
7	16	1				
8	27	1				
9	30	1				
10	32	1				

Product Limit Method

Event Number	Time of Death (t)	# who fail at time t	# at risk at time t	q	$p=1-q$	$S(t+)$
0	0	0	12	0	1	1
1	2	1	12			
2	3	1	11			
3	6	2	10			
4	7	1	8			
5	10	1	7			
6	15	2	6			
7	16	1	4			
8	27	1	3			
9	30	1	2			
10	32	1	1			

Product Limit Method

Event Number	Time of Death (t)	# who fail at time t	# at risk at time t	q	$p=1-q$	$S(t^+)$
0	0	0	12	0	1	1
1	2	1	12	$1/12=.083$		
2	3	1	11			
3	6	2	10			
4	7	1	8			
5	10	1	7			
6	15	2	6			
7	16	1	4			
8	27	1	3			
9	30	1	2			
10	32	1	1			

Product Limit Method

Event Number	Time of Death (t)	# who fail at time t	# at risk at time t	q	$p=1-q$	$S(t^+)$
0	0	0	12	0	1	1
1	2	1	12	0.083	0.917	
2	3	1	11			
3	6	2	10			
4	7	1	8			
5	10	1	7			
6	15	2	6			
7	16	1	4			
8	27	1	3			
9	30	1	2			
10	32	1	1			

Product Limit Method

Event Number	Time of Death (t)	# who fail at time t	# at risk at time t	q	$p=1-q$	$S(t^+)$
0	0	0	12	0	1	1
1	2	1	12	0.083	0.917	
2	3	1	11	1/11=.091	0.909	
3	6	2	10			
4	7	1	8			
5	10	1	7			
6	15	2	6			
7	16	1	4			
8	27	1	3			
9	30	1	2			
10	32	1	1			

Product Limit Method

Event Number	Time of Death (t)	# who fail at time t	# at risk at time t	q	$p=1-q$	$S(t^+)$
0	0	0	12	0	1	1
1	2	1	12	0.083	0.917	
2	3	1	11	0.091	0.909	
3	6	2	10	2/10=.2	0.8	
4	7	1	8			
5	10	1	7			
6	15	2	6			
7	16	1	4			
8	27	1	3			
9	30	1	2			
10	32	1	1			

Product Limit Method

Event Number	Time of Death (t)	# who fail at time t	# at risk at time t	q	$p=1-q$	$S(t^+)$
0	0	0	12	0	1	1
1	2	1	12	0.083	0.917	
2	3	1	11	0.091	0.909	
3	6	2	10	0.2	0.8	
4	7	1	8	$1/8=.125$	0.875	
5	10	1	7	$1/7=.143$	0.857	
6	15	2	6	$2/6=.333$	0.667	
7	16	1	4	$1/4=.25$	0.75	
8	27	1	3	$1/3=.333$	0.667	
9	30	1	2	$1/2=.5$	0.5	
10	32	1	1	$1/1=1$	1	

Product Limit Method

Event Number	Time of Death (t)	# who fail at time t	# at risk at time t	q	p=1-q	S(t+)
0	0	0	12	0	1	1
1	2	1	12	0.083	0.917	1x.917=.917
2	3	1	11	0.091	0.909	
3	6	2	10	0.2	0.8	
4	7	1	8	0.125	0.875	
5	10	1	7	0.143	0.857	
6	15	2	6	0.333	0.667	
7	16	1	4	0.25	0.75	
8	27	1	3	0.333	0.667	
9	30	1	2	0.5	0.5	
10	32	1	1	1	1	

Product Limit Method

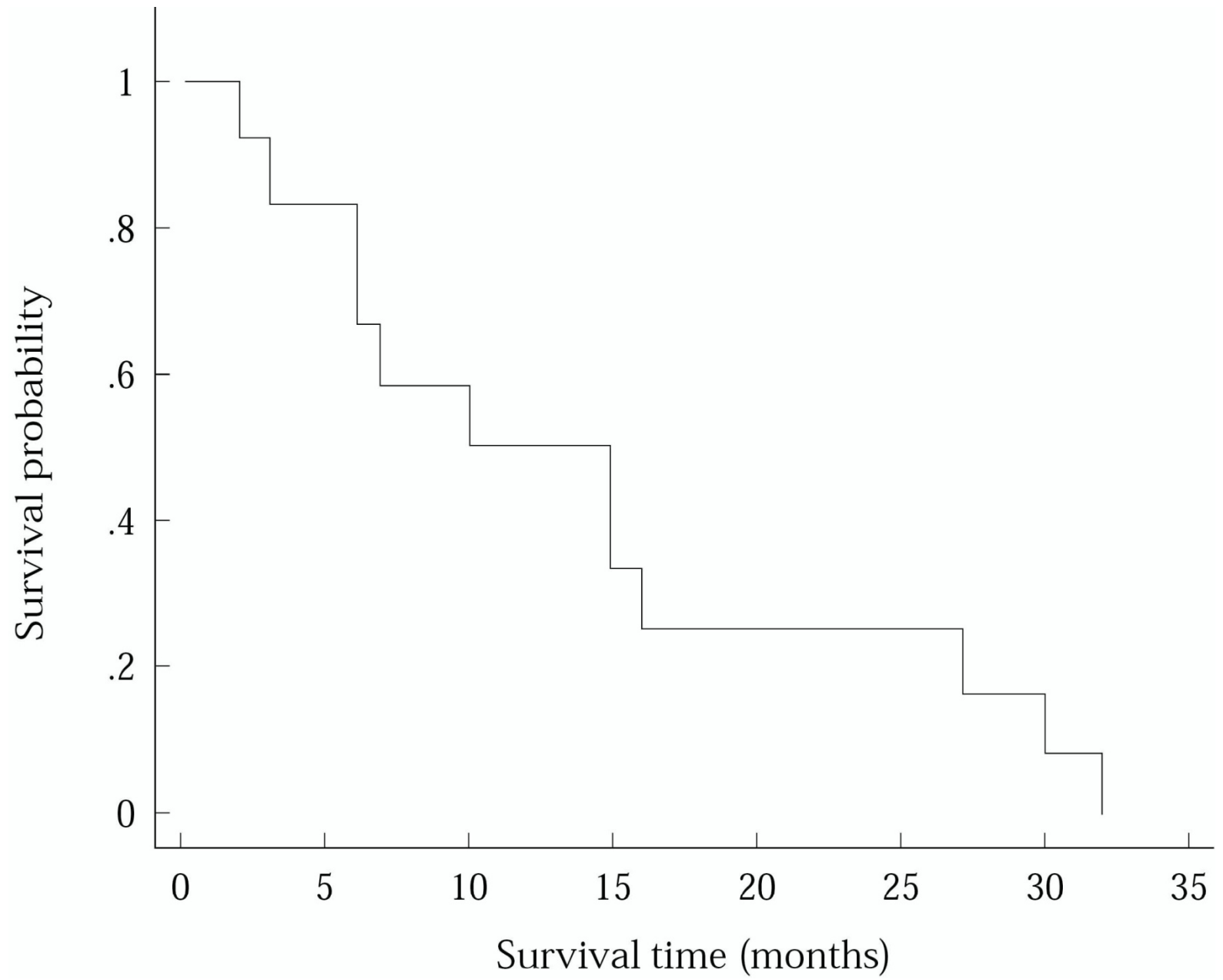
Event Number	Time of Death (t)	# who fail at time t	# at risk at time t	q	p=1-q	S(t+)
0	0	0	12	0	1	1
1	2	1	12	0.083	0.917	0.917
2	3	1	11	0.091	0.909	.917x.909=.833
3	6	2	10	0.2	0.8	
4	7	1	8	0.125	0.875	
5	10	1	7	0.143	0.857	
6	15	2	6	0.333	0.667	
7	16	1	4	0.25	0.75	
8	27	1	3	0.333	0.667	
9	30	1	2	0.5	0.5	
10	32	1	1	1	1	

Product Limit Method

Event Number	Time of Death (t)	# who fail at time t	# at risk at time t	q	p=1-q	S(t+)
0	0	0	12	0	1	1
1	2	1	12	0.083	0.917	0.917
2	3	1	11	0.091	0.909	0.833
3	6	2	10	0.2	0.8	.833x.8=.667
4	7	1	8	0.125	0.875	
5	10	1	7	0.143	0.857	
6	15	2	6	0.333	0.667	
7	16	1	4	0.25	0.75	
8	27	1	3	0.333	0.667	
9	30	1	2	0.5	0.5	
10	32	1	1	1	1	

Product Limit Method

Event Number	Time of Death (t)	# who fail at time t	# at risk at time t	q	p=1-q	S(t+)	
0	0	0	12	0	1	1	
1	2	1	12	0.083	0.917	0.917	
2	3	1	11	0.091	0.909	0.833	
3	6	2	10	0.2	0.8	0.667	
4	7	1	8	0.125	0.875	.67x.875=.583	
5	10	1	7	0.143	0.857	.583x.857=.5	
6	15	2	6	0.333	0.667	.5x.667=.333	
7	16	1	4	0.25	0.75	.333x.75=.25	
8	27	1	3	0.333	0.667	.25x.667=.167	
9	30	1	2	0.5	0.5	.167x.5=.083	
10	32	1	1	1	0	.083x0=0	



Variation in Follow-up Periods

-- Censoring

Suppose some of the patients
are still not "dead" at the time
the analysis is done --

censored observations

In example, suppose individuals who "failed"
at times 3 and 10 months actually dropped out
at that point (lost to follow-up)

Simple Example

Interval from lung cancer diagnosis to death

Patient	Survival (months)
1	2
2	3+
3	6
4	6
5	7
6	10+
7	15
8	15
9	16
10	27
11	30
12	32

Product Limit Method

Event Number	Time of Death or censoring (t)	# who fail at time t	# at risk at time t	q	$p=1-q$	$S(t+)$
0	0	0	12	0	1	1
1	2	1				
2	3+	0				
3	6	2				
4	7	1				
5	10+	0				
6	15	2				
7	16	1				
8	27	1				
9	30	1				
10	32	1				

Product Limit Method

Event Number	Time of Death (t)	# who fail at time t	# at risk at time t	q	$p=1-q$	$S(t+)$
0	0	0	12	0	1	1
1	2	1	12			
2	3+	0	11			
3	6	2	10			
4	7	1	8			
5	10+	0	7			
6	15	2	6			
7	16	1	4			
8	27	1	3			
9	30	1	2			
10	32	1	1			

Product Limit Method

Event Number	Time of Death (t)	# who fail at time t	# at risk at time t	q	$p=1-q$	$S(t^+)$
0	0	0	12	0	1	1
1	2	1	12	$1/12=.083$		
2	3+	0	11			
3	6	2	10			
4	7	1	8			
5	10+	0	7			
6	15	2	6			
7	16	1	4			
8	27	1	3			
9	30	1	2			
10	32	1	1			

Product Limit Method

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0	0	0	12	0	1	1
1	2	1	12	0.083	0.917	
2	3+	0	11			
3	6	2	10			
4	7	1	8			
5	10+	0	7			
6	15	2	6			
7	16	1	4			
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2	3+	0	11	0/11=0	1	
3	6	2	10			
4	7	1	8			
5	10+	0	7			
6	15	2	6			
7	16	1	4			
8	27	1	3			
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2	3+	0	11	0	1	
3	6	2	10	2/10=.2	0.8	
4	7	1	8			
5	10+	0	7			
6	15	2	6			
7	16	1	4			
8	27	1	3			
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Product Limit Method

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2	3+	0	11	0	1	
3	6	2	10	0.2	0.8	
4	7	1	8	1/8=.125	0.875	
5	10+	0	7	0/7=0	1	
6	15	2	6	2/6=.333	0.667	
7	16	1	4	1/4=.25	0.75	
8	27	1	3	1/3=.333	0.667	
9	30	1	2	1/2=.5	0.5	
10	32	1	1	1/1=1	1	

Product Limit Method

Event Number	Time of Death (t)	# who fail at time t	# at risk at time t	q	p=1-q	S(t+)
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2	3+	0	11	0	1	
3	6	2	10	0.2	0.8	
4	7	1	8	0.125	0.875	
5	10+	0	7	0	1	
6	15	2	6	0.333	0.667	
7	16	1	4	0.25	0.75	
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Product Limit Method

Event Number	Time of Death (t)	# who fail at time t	# at risk at time t	q	p=1-q	S(t+)
0	0	0	12	0	1	1
1	2	1	12	0.083	0.917	0.917
2	3+	0	11	0	1	.917x1=.917
3	6	2	10	0.2	0.8	
4	7	1	8	0.125	0.875	
5	10+	0	7	0	1	
6	15	2	6	0.333	0.667	
7	16	1	4	0.25	0.75	
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Product Limit Method

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1	2	1	12	0.083	0.917	0.917
2	3+	0	11	0	1	0.917
3	6	2	10	0.2	0.8	.917x.8=.733
4	7	1	8	0.125	0.875	
5	10+	0	7	0	1	
6	15	2	6	0.333	0.667	
7	16	1	4	0.25	0.75	
8	27	1	3	0.333	0.667	
9	30	1	2	0.5	0.5	
10	32	1	1	1	1	

Product Limit Method

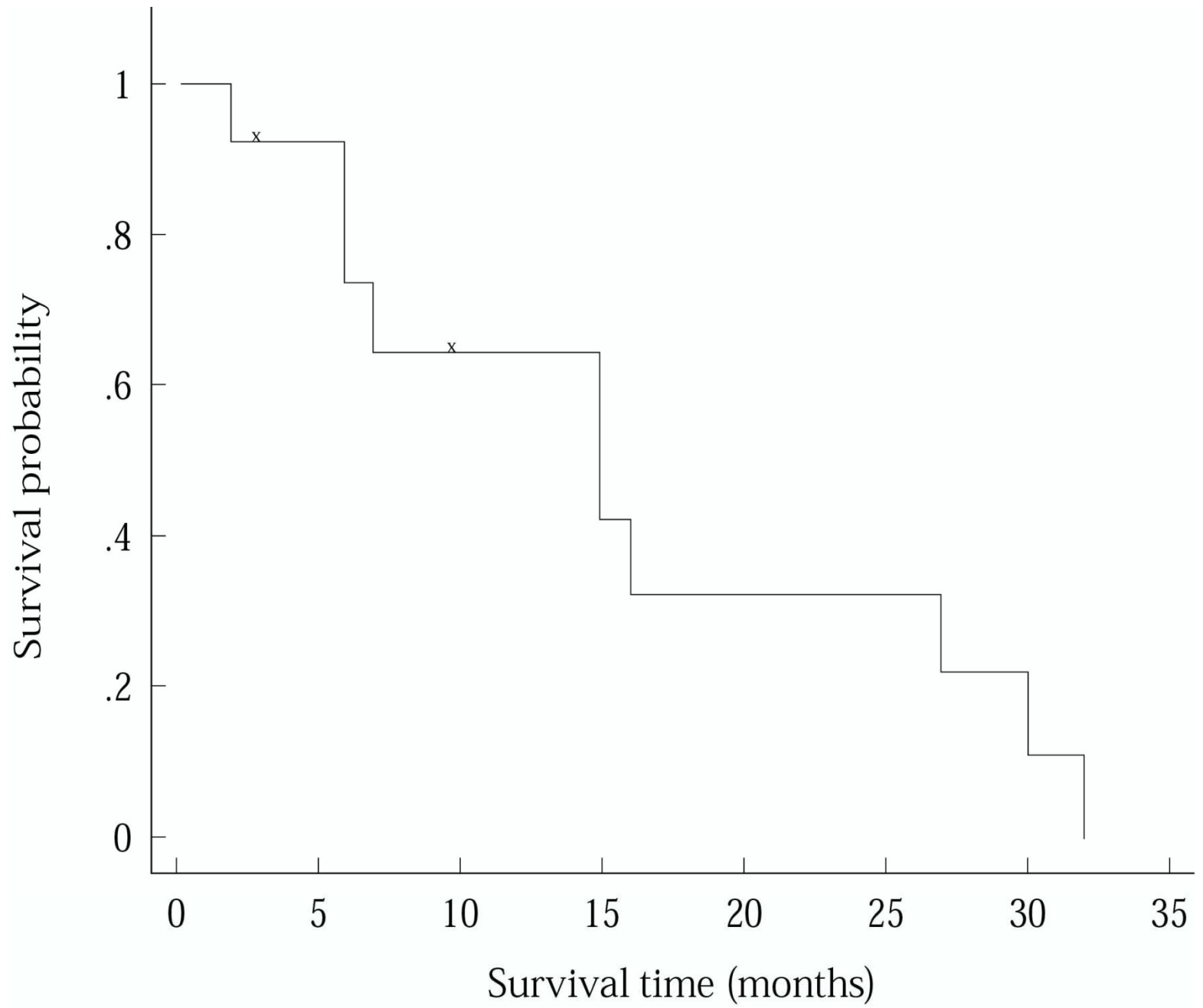
Event Number	Time of Death (t)	# who fail at time t	# at risk at time t	q	p=1-q	S(t+)
0	0	0	12	0	1	1
1	2	1	12	0.083	0.917	0.917
2	3+	0	11	0	1	0.917
3	6	2	10	0.2	0.8	0.733
4	7	1	8	0.125	0.875	.733x.875=.642
5	10+	0	7	0	1	.642x1=.642
6	15	2	6	0.333	0.667	.642x.667=.428
7	16	1	4	0.25	0.75	.428x.75=.321
8	27	1	3	0.333	0.667	.321x.667=.214
9	30	1	2	0.5	0.5	.214x.5=.107
10	32	1	1	1	0	.107x0=0

Basis:

Probability of surviving 2 days is probability of surviving day 2 given survival of day 1, multiplied by the probability of surviving day 1.

Probability of surviving 3 days is probability of surviving day 3 given survival of day 2, multiplied by the probability of surviving day 2 (see above).

Etc.



Standard Error and 95% Confidence Interval for Survival Curve
 (approximation based on Greenwoods Formula)

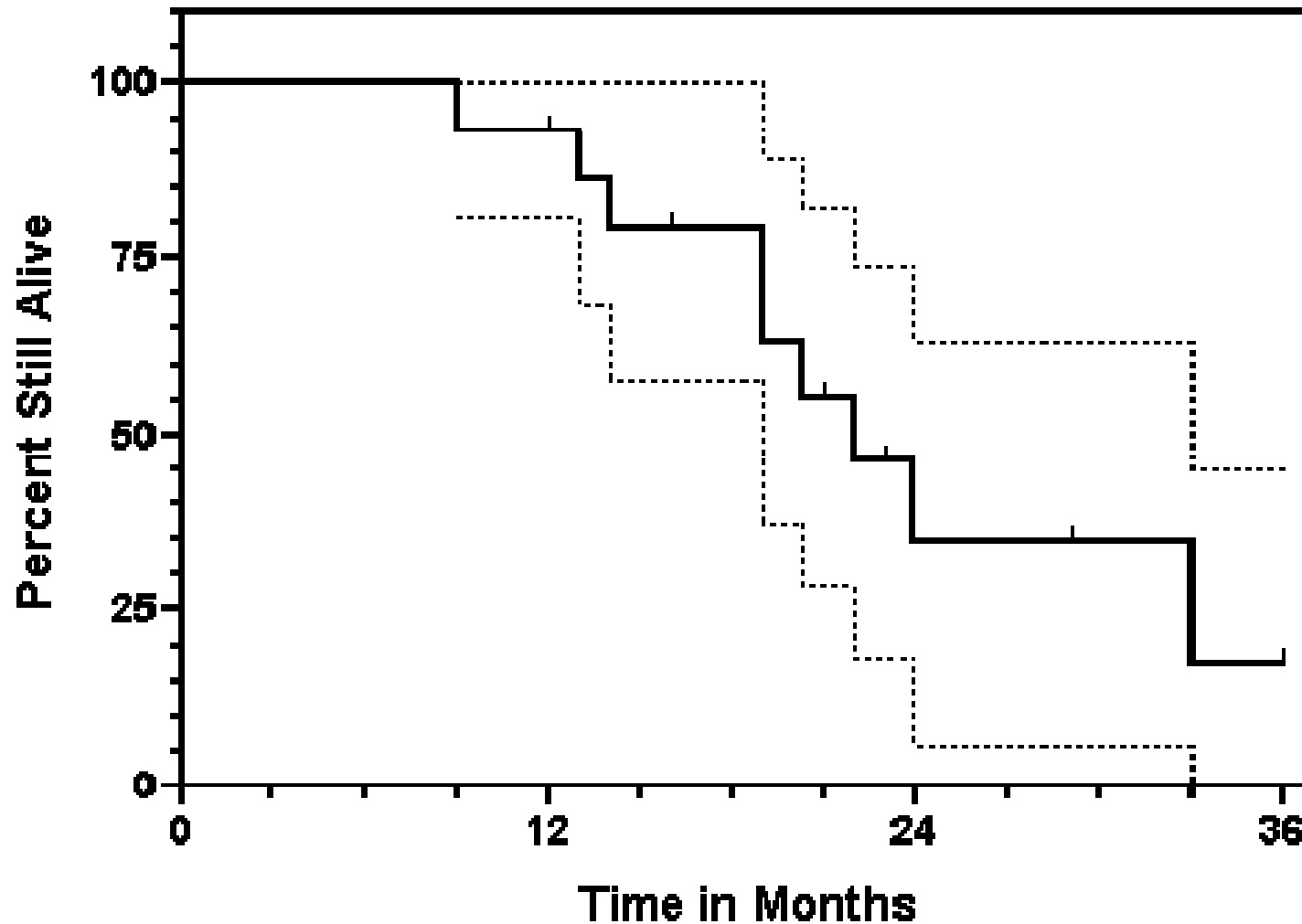
Plutonian	Survival Time t	No. Alive Begin Interval n	No. Deaths d	Fraction Surviving (n-d) / n	Cumulative Survival, S(t) \prod (n-d) / n	Standard Error	Lower 95% CI	Upper 95% CI
J	2	10	1	0.90	0.90	0.10	0.70	1.00*
H	6	9	1	0.89	0.80	0.13	0.54	1.00*
A & C	7	8	2	0.75	0.60	0.15	0.30	0.90
I	7+							
F	8	5	1	0.80	0.48	0.16	0.16	0.80
G	9	4	1	0.75	0.36	0.16	0.04	0.68
E	11+							
B	12	2	1	0.50	0.18	0.15	0.00*	0.48
D	12+							

$$SE_t = S(t) * \sqrt{\sum_1^t [d / (n-d) / n]}$$

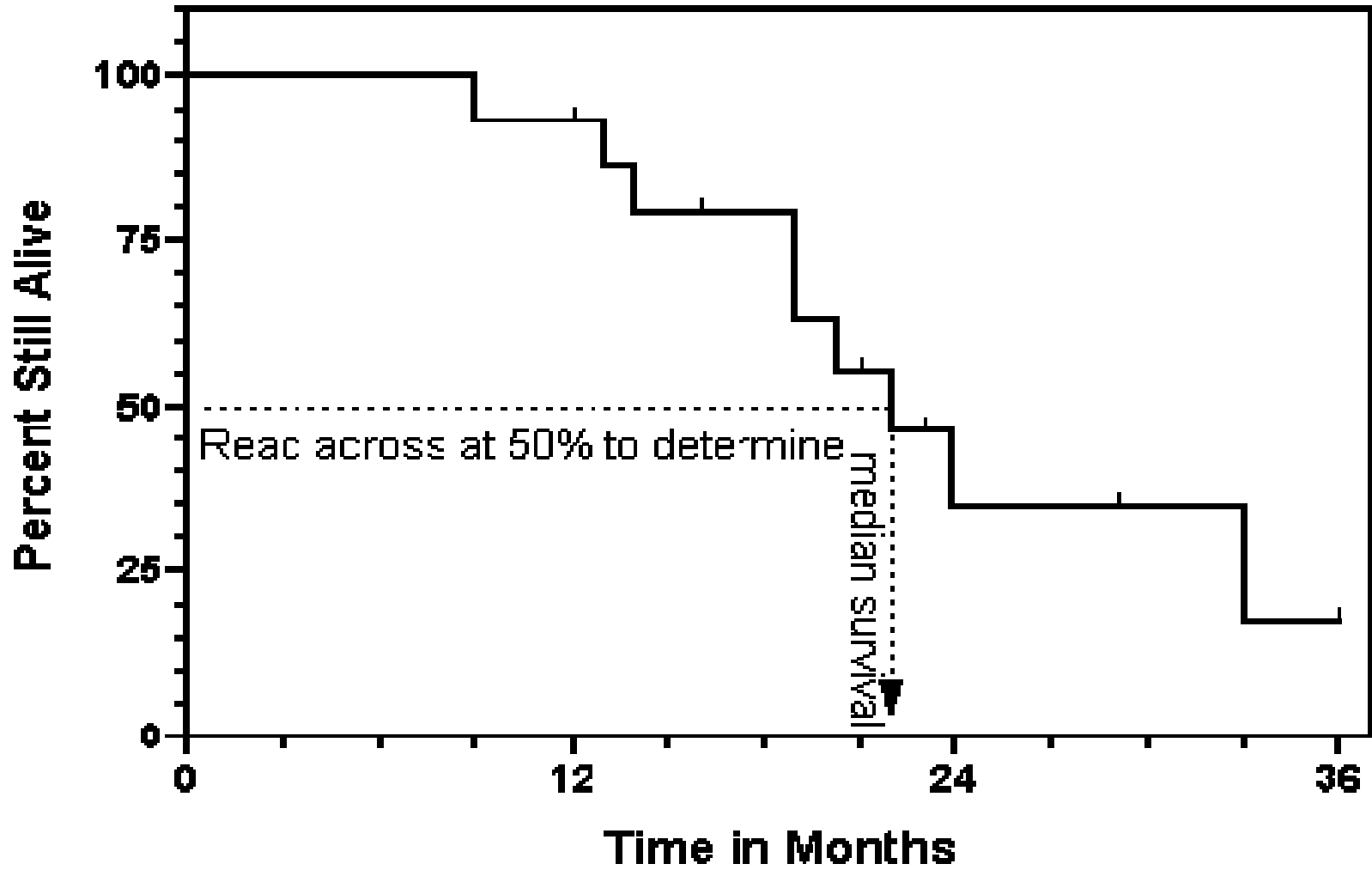
$$CI = S(t) +/- 2SE$$

* Truncated at 1.0 and 0.0 since S(t) cannot go beyond these limits

A survival curve with 95% CIs. The solid line shows the survival curve of a sample of 15 subjects. You can be 95% sure that the overall survival curve for the entire population lies within the dotted lines. The CIs are wide because the sample is so small.



Median Survival



Example:

- ~ Remission time of acute leukemia**
- ~ Patients randomly assigned**
- ~ Purpose: evaluate drug's ability to maintain remissions**
- ~ Study terminated after 1 year**
- ~ Different follow up times due to sequential enrollment**

6-MP

**6,6,6,7,10,22,23,6+,9+,10+,11+,17+,19+,
20+,25+,32+,32+,34+,35+**

Placebo

1,1,2,2,3,4,4,5,5,8,8,8,8,11,11,12,12,15,17,22,23

• The LIFETEST Procedure

• Stratum 1: group = 1

• Product-Limit Survival Estimates

•	•	•	•	Survival	Number	Number
•	•	•	•	Standard	Failed	Left
•	time	Survival	Failure	Error		
•	0.0000	1.0000	0	0	0	21
•	6.0000	.	.	.	1	20
•	6.0000	.	.	.	2	19
•	6.0000	0.8571	0.1429	0.0764	3	18
•	6.0000*	.	.	.	3	17
•	7.0000	0.8067	0.1933	0.0869	4	16
•	9.0000*	.	.	.	4	15
•	10.0000	0.7529	0.2471	0.0963	5	14
•	10.0000*	.	.	.	5	13
•	11.0000*	.	.	.	5	12
•	12.0000	0.6902	0.3098	0.1068	6	11
•	17.0000*	.	.	.	6	10
•	19.0000*	.	.	.	6	9
•	20.0000*	.	.	.	6	8
•	22.0000	0.6039	0.3961	0.1235	7	7
•	23.0000	.	.	.	8	6
•	23.0000	0.4314	0.5686	0.1357	9	5
•	25.0000*	.	.	.	9	4
•	32.0000*	.	.	.	9	3
•	32.0000*	.	.	.	9	2
•	34.0000*	.	.	.	9	1
•	35.0000*	.	.	.	9	0

- Summary Statistics for Time Variable time

- Quartile Estimates

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-
-
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-
-

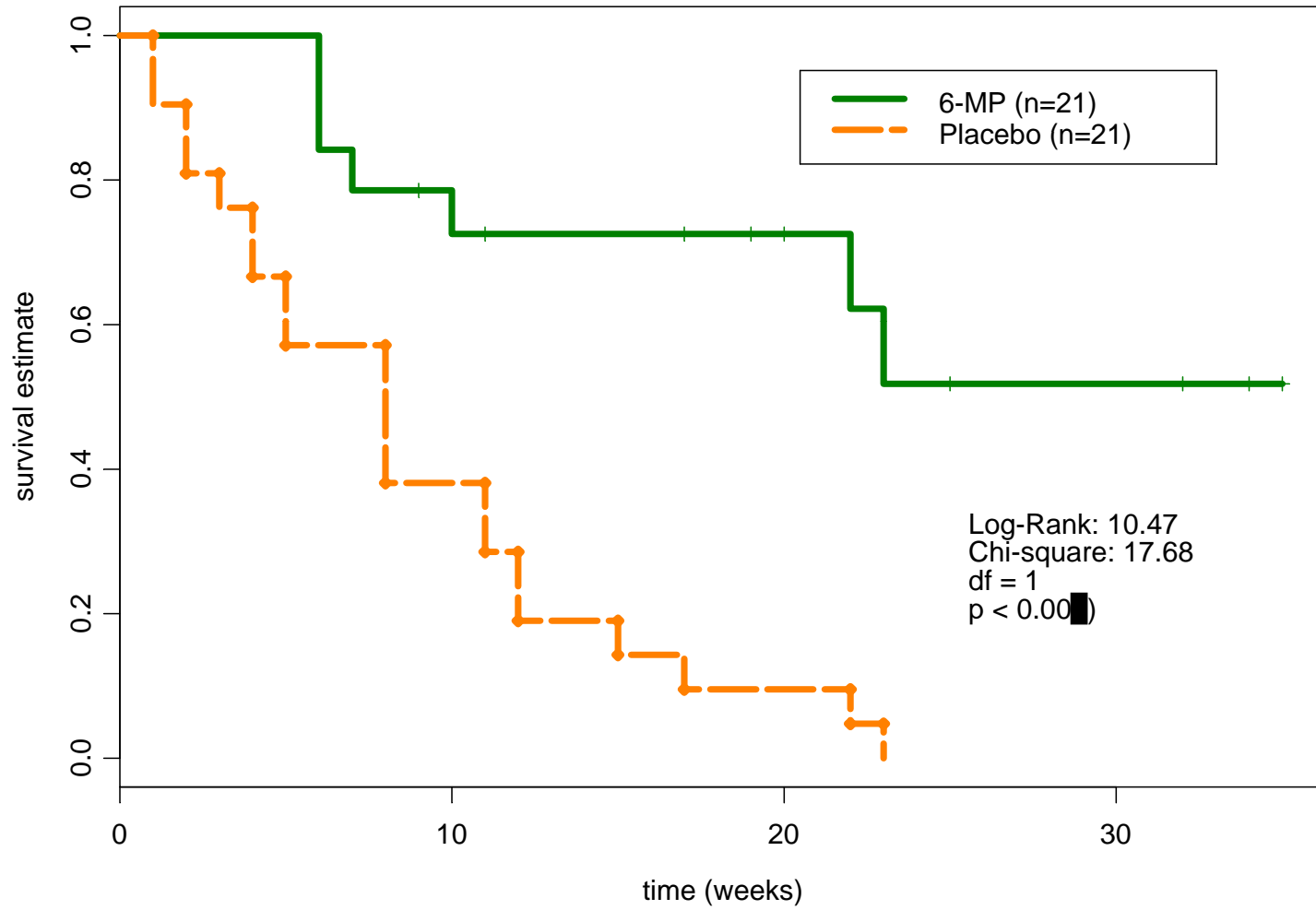
	Point	95% Confidence Interval	
Percent	Estimate	(Lower	Upper)
75	.	23.0000	.
50	23.0000	12.0000	.
25	12.0000	6.0000	23.0000

- Test of Equality over Strata

-
-
-
-
-
-

	Test	Chi-Square	DF	Pr > Chi-Square
	Log-Rank	17.6844	1	<.0001
	Wilcoxon	13.7928	1	0.0002
	-2Log(LR)	16.8486	1	<.0001

Gehan 6-MP Example



A potential trap:

Comparing survival of responders versus nonresponders

- This approach sounds reasonable but is invalid.
- I treated a number of cancer patients with chemotherapy.
- The treatment seemed to work with some patients because the tumor became smaller.
- The tumor did not change size in other patients.
- I plotted separate survival curves for the responders and nonresponders, and compared them with the log-rank test.
- The two differ significantly, so I conclude that the treatment prolongs survival.

A potential trap: Comparing survival of responders versus nonresponders

- This analysis is not valid, because you only have one group of patients, not two.
- Dividing the patients into two groups based on response to treatment is not valid for two reasons:
- A patient cannot be defined to be a "responder" unless he or she survived long enough for you to measure the tumor.
 - Any patient who died early in the study was defined to be a nonresponder
 - In other words, survival influenced which group the patient was assigned to.
 - Therefore you can't learn anything by comparing survival in the two groups.
- The cancers may be heterogeneous. The patients who responded may have a different form of the cancer than those who didn't respond. The responders may have survived longer even if they hadn't been treated.

A potential trap:
Comparing survival of responders versus nonresponders

- The general rule is clear.
- You must define the groups you are comparing (and measure the variables you plan to adjust for) before starting the experimental phase of the study.
- Be very wary of studies that use data collected during the experimental phase of the study to divide patients into groups or to adjust the data.

Covariates and Prognostic Factors

- **“Regression” models for “survival” data allow us to:**
 - evaluate more than one “risk” factor at a time
 - evaluate relative treatment effects while controlling for potential confounding factors
 - investigate interactive effects among factors

The model most often used is the proportional hazards model developed by Cox in 1972, often referred to simply as the Cox model.

Why Study Prognostic Factors?

- 1. To learn about natural history of disease**
- 2. To adjust for imbalances in comparing treatments**
- 3. To aid in designing future studies**
- 4. To look for treatment-covariate interaction**
- 5. To predict outcome for individual patients**
- 6. To intervene in the course of disease**
- 7. To explain variation and detect interaction**

Rule of Thumb for using regression analysis

Need 10 times as many observed events as factors in the model.

e.g., 3 factors, 30 events

The distribution across categories is important as well as the total sample size.

For example, if lymph node positivity is a factor you wish to control for but you only have two patients out of your sample of 100 who have +ve lymph nodes, the estimated effect of lymph nodes will be unreliable.