Introduction to Survival Analysis

Sandra Taylor, Ph.D.

April 11 & 18, 2018

UCDAVIS
CLINICAL AND TRANSLATIONAL SCIENCE CENTER

UCDAVIS
ENVIRONMENTAL HEALTH SCIENCES CENTER

Seminar Objectives

- **Recognize survival data**
- **Understand the unique aspects of survival data**
- **Be able to generate and interpret survival curves**
- **Learn how to compare two or more survival curves**

What is survival data?

Classically, how long a subject survived

National Vital Statistics Reports, Vol. 53, No. 6, November 10, 2004 5

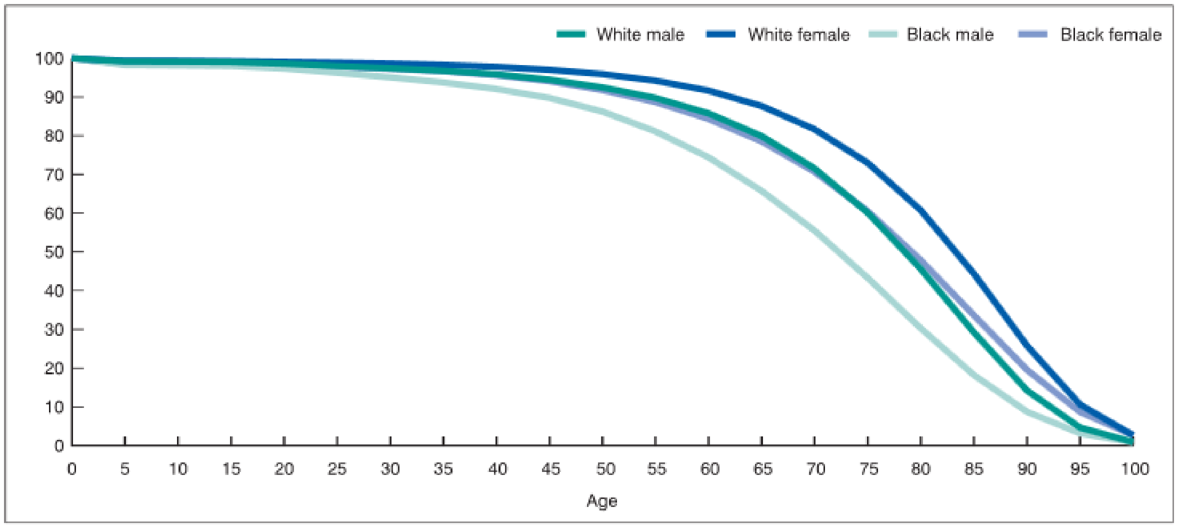


Figure 2. Percent surviving by age, race, and sex: United States, 2002

By obtaining the age at which every person died in the US, we can construct survival curves like these that show the probability that a person will survive until a certain age

Time-to-Event Data

- **Bad Events**
  - Death
  - Recurrence of cancer
  - Disease progression
  - Failure of equipment
- **Good Events**
  - Confirmed pregnancy
  - Return to full function
  - Completion of training
  - Extubation

How does time-to-event data differ from other data types?

- **Consists of 2 pieces of information**
  - Time of observation (i.e., how long did you observe the subject)
  - Outcome at the end of the observation period
- **Differs from other data types in having 2 components**
  - Consider cholesterol levels
  - Consider presence of hypertension

What are challenges to analyzing time-to-event data?

- **Different observation lengths among subjects**

- **Failure to observe the event of interest**

Illustration

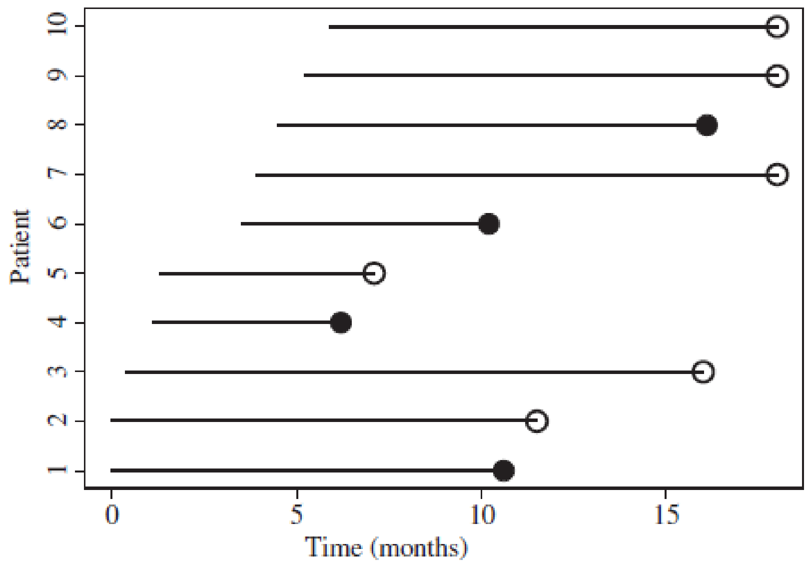


FIGURE 26.1 Diagram of patient accrual and follow-up from the data from Table 26.1. *Solid circles*, uncensored observation; *open circles*, censored observation.

- **Consider a cancer survival study**
- **18-month duration**
- **Accrue patients for 6 months**
- **Follow patients until 18 month end of study**
- **Duration of follow up varies from 12 to 18 months depending on recruitment**
- **Event (death or relapse) not observed in all patients**

Censoring

- **The survival time for a subject is "censored" if the event of interest is not observed.**
- **Right censoring - event occurs after a specified time**
- **Left censoring – event occurred before a specified time**
- **Interval censoring – event known only to have occurred between to time points**

Causes of Right Censoring

- **Administrative**
  - study designed to stop at a certain time
- **Withdrawal of patient from study**
- **Loss to follow up**

All handled the same way analytically

Addressing Varying Follow Up

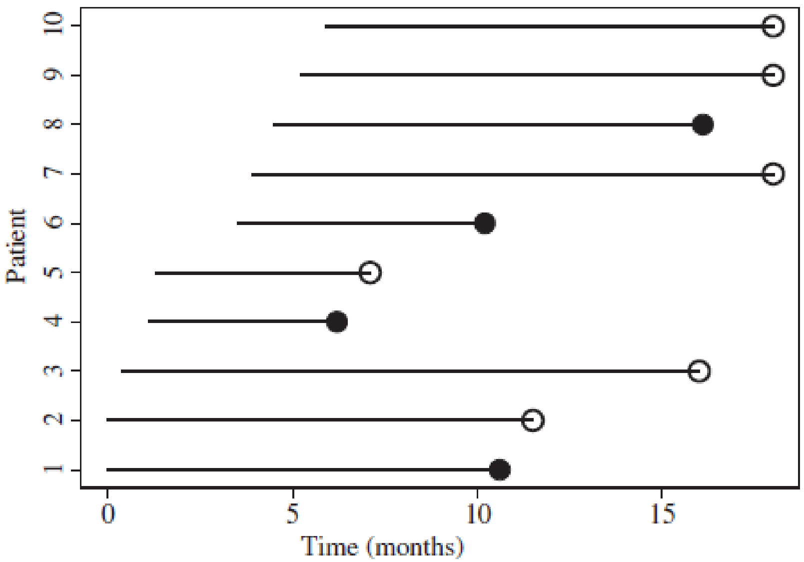


FIGURE 26.1 Diagram of patient accrual and follow-up from the data from Table 26.1. *Solid circles*, uncensored observation; *open circles*, censored observation.

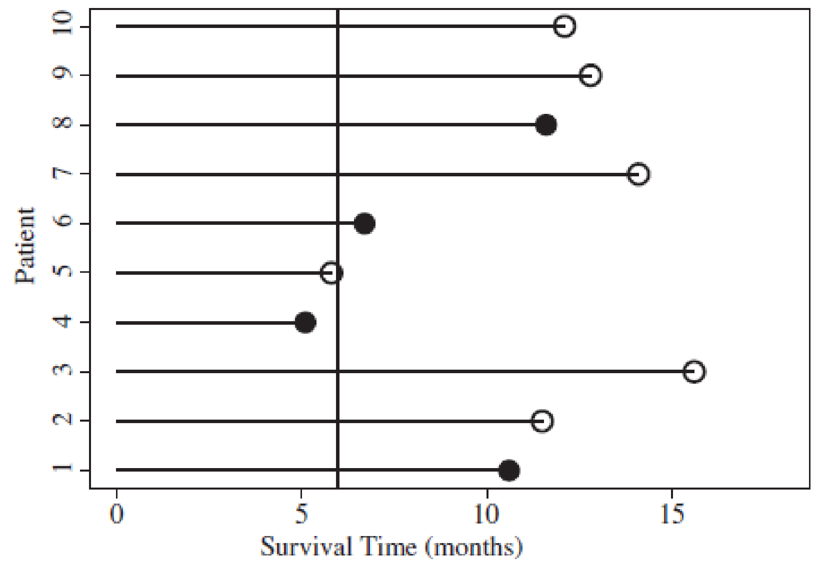
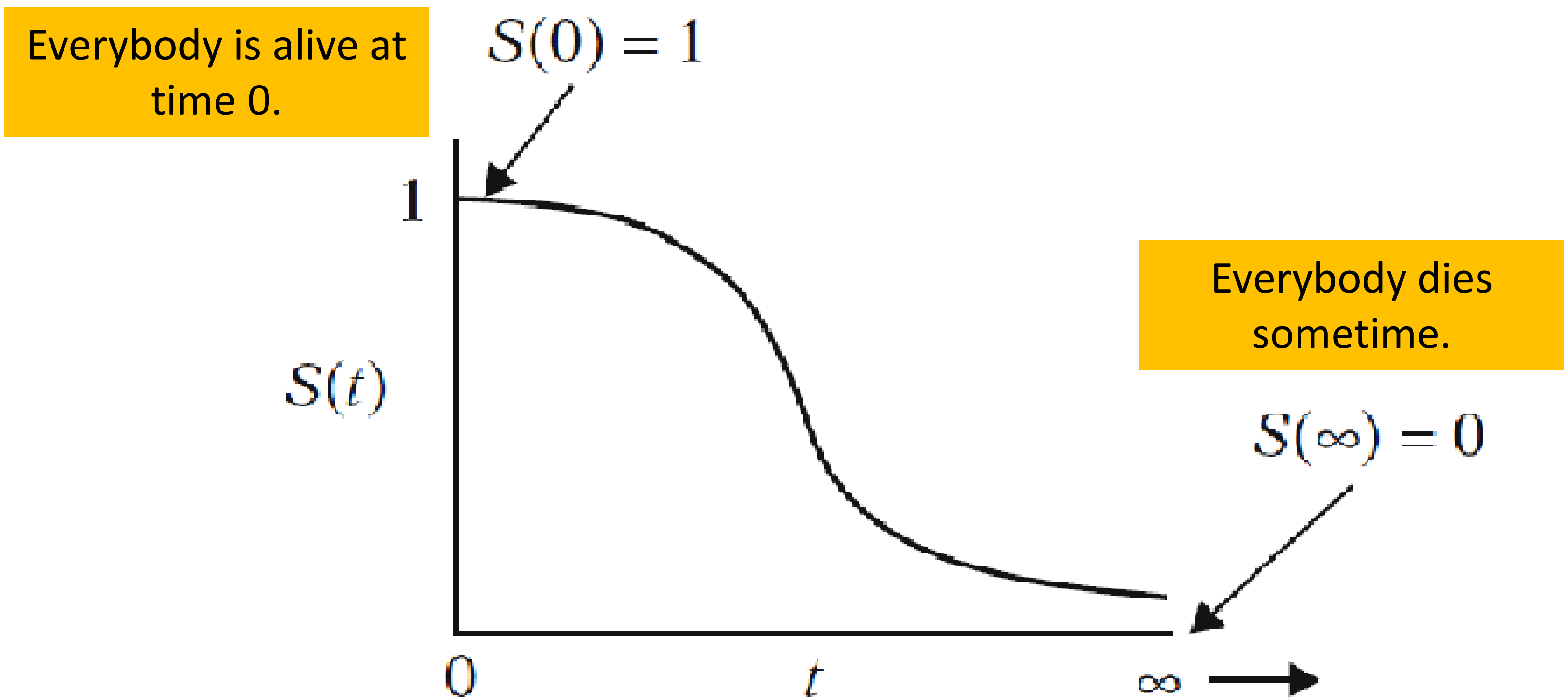


FIGURE 26.2 Diagram of the survival times for Table 26.1.

- **Shift times so every subject starts at time 0**
- **"Survival" time then equals time on study**

Survival Function

- **Survival function is the "summary statistic" for time-to-event data**
- **Summarizes probability of the event occurring over time**
- ***S(t)* = probability of individual surviving until time *t***



Estimating the Survival Function

- **Kaplan-Meier Method (aka Product-Limit Estimator) is most common method for estimating survival function**

$$\widehat{S}(t) = \prod_{t_i \le t} (1 - f_i / r_i)$$

t_i = times of events or censoring ordered from first to last
f_i = the number of events that occur at time t_i
r_i = the number of individuals at risk at time t_i

Construction of KM Curve

TABLE 26.2 Construction of a Product-Limit Estimator

Time, t_i (Month)	No. at Risk, r_i	No. of Events, f_i	Product-Limit Estimator	Cumulative No. Censored, $m_c(t_i)$	Cumulative No. of Events, $m_e(t_i)$
0	20	0	1.00	0	0
5	20	2	$1 - 2/20 = 0.90$	0	2
6	18	0	$(1 - 0/18) \times 0.90 = 0.90$	0	2
10	15	1	$(1 - 1/15) \times 0.90 = 0.84$	3	3
13	14	2	$(1 - 2/14) \times 0.84 = 0.72$	3	5

- **Start with 20 at time 0. S(0) = 1**
- **2 events at 5 months; 20 at risk (f_i=2, r_i= 20)**
- **No events or censoring at 6 months so no change**
- **1 event at 10 months, 3 subjects censored between 6 and 10 months (f_i = 1, r_i= 15 due to 2 events and 3 censored)**
- **2 events at 13 months (f_i = 2, r_i= 14 due to 3 events and 3 censored)**

In this way can calculate survival probabilities over the time period of observation.

Visualizing the Survival Curve

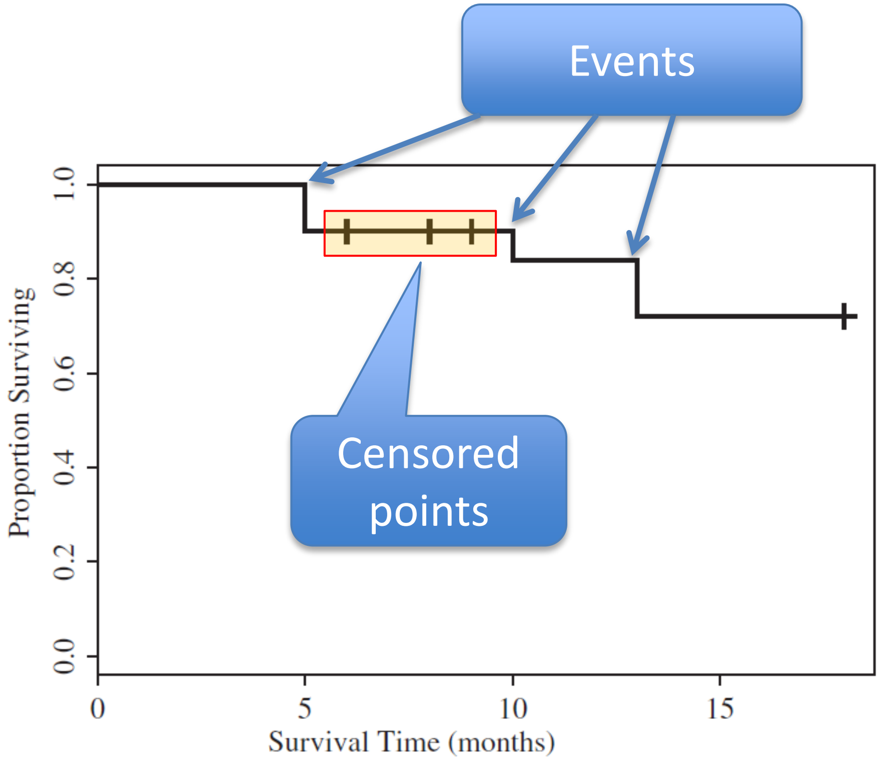


FIGURE 26.3 Product-limit survival curve from the data in Table 26.2.

Month	S(t) Estimate
0	1.00
5	0.90
6	0.90
10	0.84
13	0.72

Understanding the Survival Curve

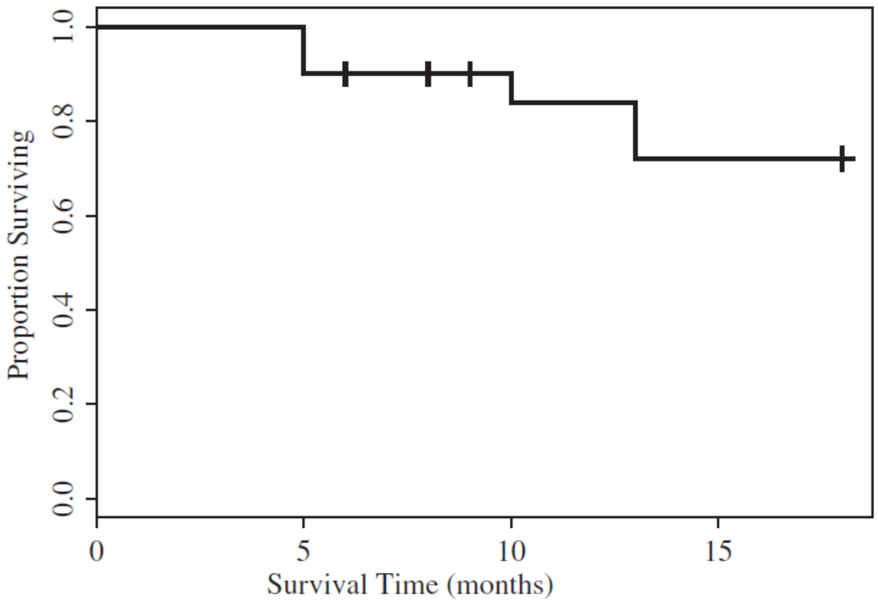


FIGURE 26.3 Product-limit survival curve from the data in Table 26.2.

- Estimated probability of surviving to 5 months is 90%
- Estimated probability of surviving to 10 months is 84%
- Estimated probability of surviving to 13 months is 72%

AIDS Clinical Trials Group Study

- Double-blind trial that compared a 3 drug regimen to a 2 drug regimen
- Eligible patients – CD4 counts < 200 and at least 3 months of prior zidovudine therapy
- N = 1,151 subjects
- Primary outcome: development of AIDS or death

ACTG320 dataset (partial)

Time to event or censoring

Event indicator
0 = censored
1 = AIDS diagnosis or death

ID	Days	AIDS	Trt	Sex	Race
1	189	0	0	1	1
2	287	0	0	2	2
3	242	0	1	1	1
4	199	0	0	1	1
5	286	0	1	1	1
6	285	0	1	1	1
7	270	0	0	1	2
8	285	0	1	1	2
9	276	0	0	1	1
10	306	0	0	1	1
11	334	0	1	2	3
12	285	0	1	2	2
13	265	0	1	1	2
14	206	1	0	2	2
15	305	0	0	1	2
16	110	0	0	2	3
17	298	1	0	1	3

Survival Curves in SAS

- **PROC LIFETEST – Estimate survival curves using Kaplan-Meier method**
- **Compare survival curves between groups**

Plot survival curve

```
ods graphics on;
proc lifetest data=AIDS plots=survival(atrisk);
title "Time to Diagnosis or Death";
    time Days*Aids(0);
    strata trt;
run;
ods graphics off;
```

List # at risk

Survival Curves in SAS

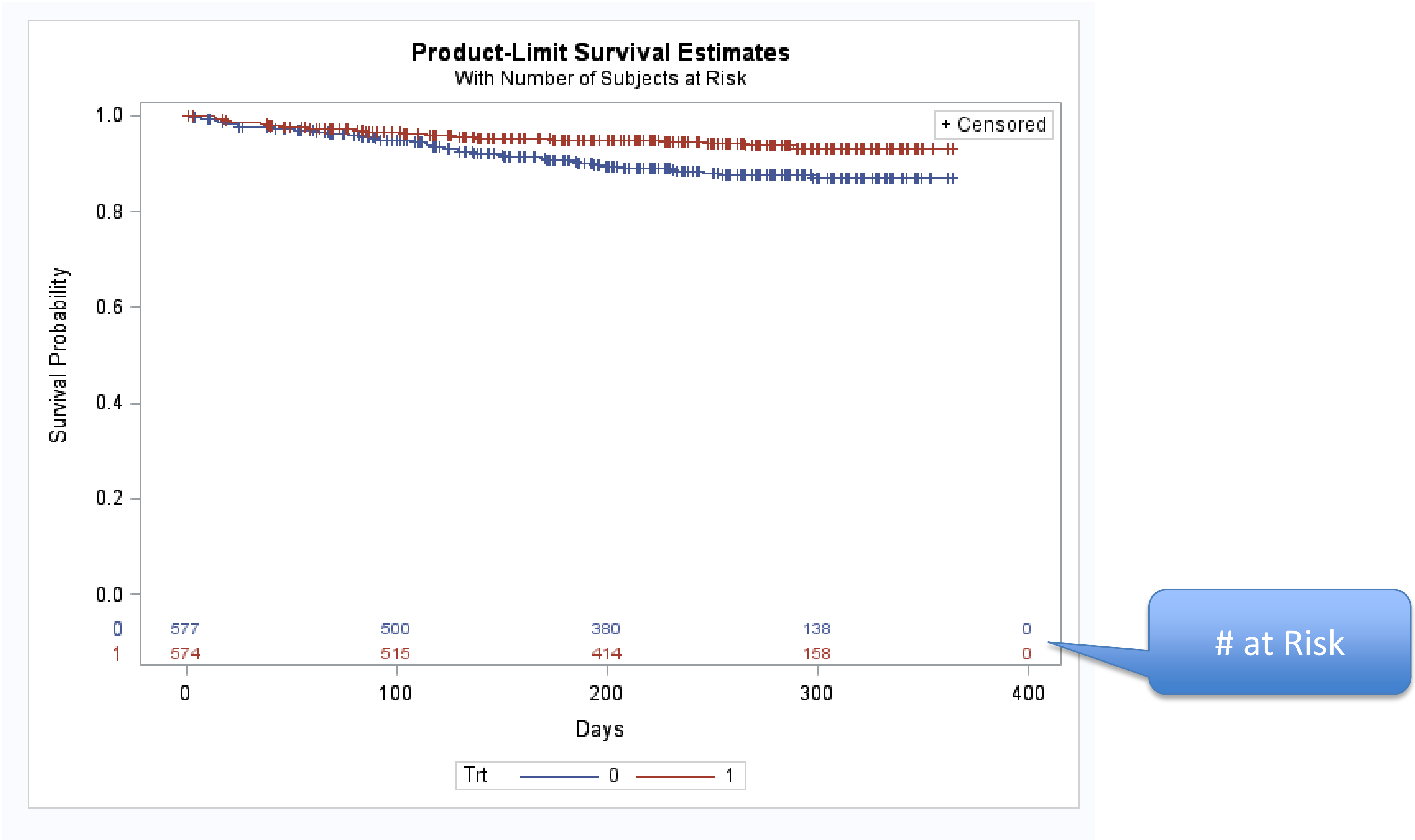
- **PROC LIFETEST – Estimate survival curves using Kaplan-Meier method**
- **Compare survival curves between groups**

```
ods graphics on;
proc lifetest data=AIDS plots=survival(atrisk);
title "Time to Diagnosis or Death";
    time Days*Aids(0);
    strata trt;
run;
ods graphics off;
```

Days = time on study
Aids(0) = event indicator;
0 indicates censored obs

Groups

Survival Curves in SAS

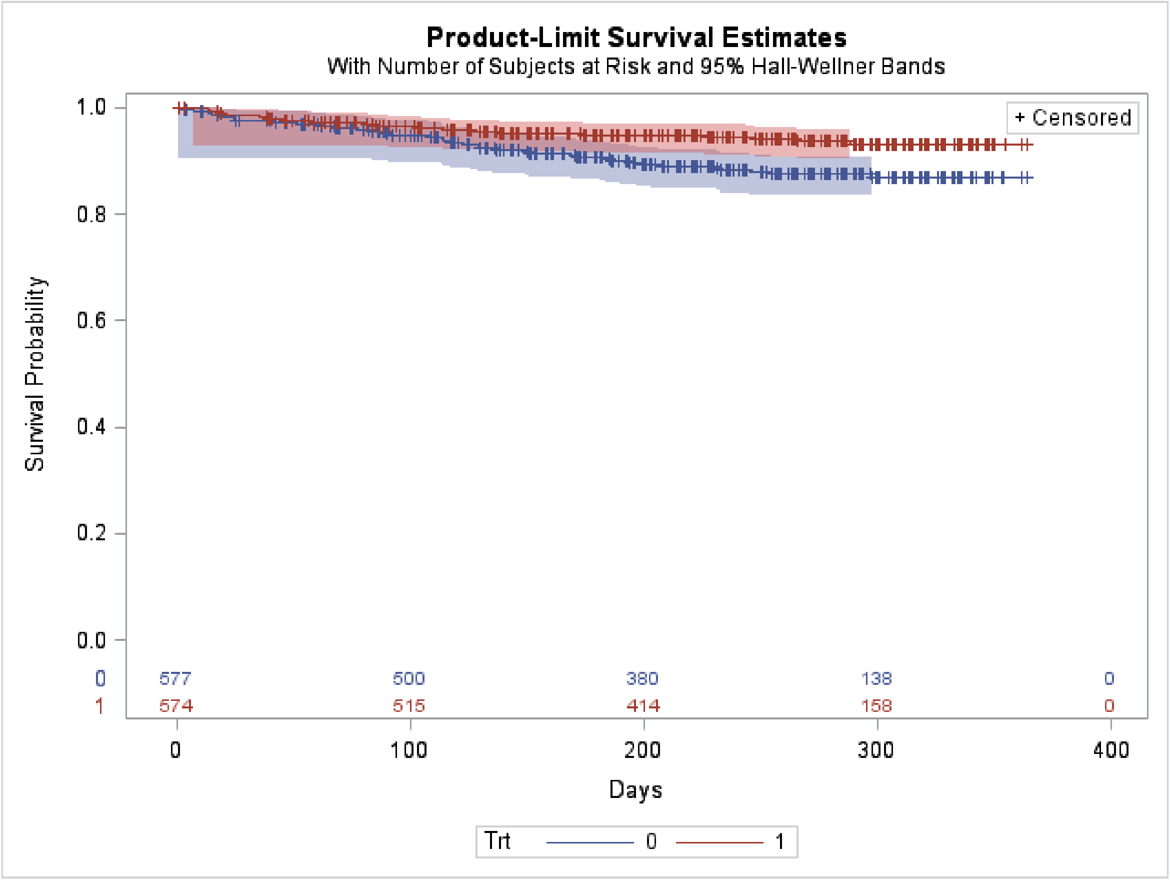


Confidence intervals for Survival Curves in SAS

```
ods graphics on;
proc lifetest data=AIDS plots=survival(cb atrisk);
title "Time to Diagnosis or Death";
     time Days*Aids(0);
     strata trt;
run;
ods graphics off;
```

Add confidence bands

Confidence intervals for Survival Curves in SAS



Comparing Survival Curves

- H_o: Survival curves do not differ between treatment groups
- Here we have only two groups but method can be extended to more
- Log-rank test is most common test
- Other tests exist – differences stem from weights given to different portions of the survival curve

The Log-Rank Test

- **Determine expected number of events if no difference in survival**
  - expected number of events in each group is proportional to number at risk in each group
- **Compare observed to expected number of events**
- **Marked deviation suggests survival curves differ between groups**

The Log-Rank Test

	# failures		# in risk set	
$t_{(j)}$	m_{1j}	m_{2j}	n_{1j}	n_{2j}
1	0	2	21	21
2	0	2	21	19
3	0	1	21	17
4	0	2	21	16
5	0	2	21	14
6	3	0	21	12
7	1	0	17	12
8	0	4	16	12
10	1	0	15	8
11	0	2	13	8
12	0	12	12	6
13	1	0	12	4
15	0	1	11	4
16	1	0	11	3
17	0	1	10	3
22	1	1	7	2
23	1	1	6	1

Expected cell counts:

$$e_{1j} = \underbrace{\left(\frac{n_{1j}}{n_{1j} + n_{2j}} \right)}_{\text{Proportion in risk set}} \times \underbrace{\left(m_{1j} + m_{2j} \right)}_{\text{\# of failures over both groups}}$$

$$e_{2j} = \left(\frac{n_{2j}}{n_{1j} + n_{2j}} \right) \times \left(m_{1j} + m_{2j} \right)$$

Source: Staub & Gekenidie 2011. Seminar in Statistics: Survival Analysis. Chapter 2 Kaplan-Meier Survival Curves and the Log-Rank Test. March 7, 2011

The Log-Rank Test

EXAMPLE

Expanded Table (Remission Data)

		# failures		# in risk set		# expected		Observed–expected	
j	$t_{(j)}$	m_{1j}	m_{2j}	n_{1j}	n_{2j}	e_{1j}	e_{2j}	$m_{1j}-e_{1j}$	$m_{2j}-e_{2j}$
1	1	0	2	21	21	$(21/42)\times 2$	$(21/42)\times 2$	−1.00	1.00
2	2	0	2	21	19	$(21/40)\times 2$	$(19/40)\times 2$	−1.05	1.05
3	3	0	1	21	17	$(21/38)\times 1$	$(17/38)\times 1$	−0.55	0.55
4	4	0	2	21	16	$(21/37)\times 2$	$(16/37)\times 2$	−1.14	1.14
5	5	0	2	21	14	$(21/35)\times 2$	$(14/35)\times 2$	−1.20	1.20
6	6	3	0	21	12	$(21/33)\times 3$	$(12/33)\times 3$	1.09	−1.09
7	7	1	0	17	12	$(17/29)\times 1$	$(12/29)\times 1$	0.41	−0.41
8	8	0	4	16	12	$(16/28)\times 4$	$(12/28)\times 4$	−2.29	2.29
9	10	1	0	15	8	$(15/23)\times 1$	$(8/23)\times 1$	0.35	−0.35
10	11	0	2	13	8	$(13/21)\times 2$	$(8/21)\times 2$	−1.24	1.24
11	12	0	2	12	6	$(12/18)\times 2$	$(6/18)\times 2$	−1.33	1.33
12	13	1	0	12	4	$(12/16)\times 1$	$(4/16)\times 1$	0.25	−0.25
13	15	0	1	11	4	$(11/15)\times 1$	$(4/15)\times 1$	−0.73	0.73
14	16	1	0	11	3	$(11/14)\times 1$	$(3/14)\times 1$	0.21	−0.21
15	17	0	1	10	3	$(10/13)\times 1$	$(3/13)\times 1$	−0.77	0.77
16	22	1	1	7	2	$(7/9)\times 2$	$(2/9)\times 2$	−0.56	0.56
17	23	1	1	6	1	$(6/7)\times 2$	$(1/7)\times 2$	−0.71	0.71
Totals		9	21			19.26	10.74	−10.26	+10.26

- **Calculate expected number of events at each time point**
- **Calculate difference between observed and expected**
- **Sum differences as measure of how different observed values are from expected *if no difference in survival* Calculate difference between observed and expected**

Source: Staub & Gekenidie 2011. Seminar in Statistics: Survival Analysis. Chapter 2 Kaplan-Meier Survival Curves and the Log-Rank Test. March 7, 2011

The Log-Rank Test

Sum the differences between observed and expected

$$O_i - E_i = \sum_{j=1}^{\#\,failure\ times} \left(m_{ij} - e_{ij} \right)$$

$$O_1 - E_1 = -10.26$$

$$O_2 - E_2 = 10.26$$

Create log-rank statistic

$$\boxed{\text{Log-rank statistic} = \frac{(O_2 - E_2)^2}{Var(O_2 - E_2)}}$$

Log-rank test has chi-square distribution so can use to test null hypothesis

$$\frac{(O_2 - E_2)^2}{Var(O_2 - E_2)} \sim \chi_1^2$$

Source: Staub & Gekenidie 2011. Seminar in Statistics: Survival Analysis. Chapter 2 Kaplan-Meier Survival Curves and the Log-Rank Test. March 7, 2011

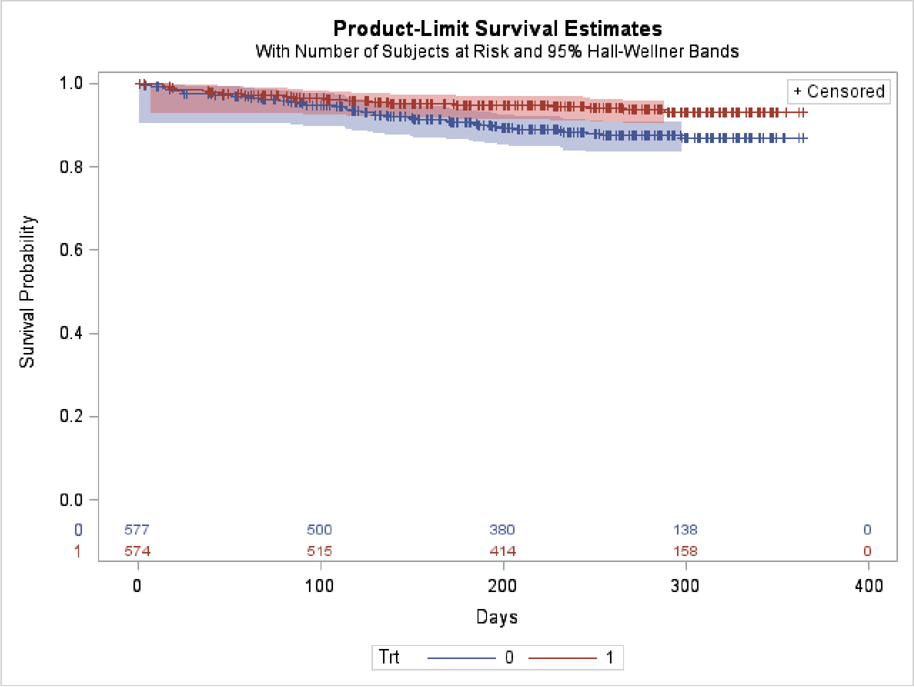
Log-Rank Test in SAS

- **Automatically generated with previous code due to strata command**

```
ods graphics on;
proc lifetest data=AIDS plots=survival(cb atrisk);
title "Time to Diagnosis or Death";
     time Days*Aids(0);
     strata trt;
run;
ods graphics off;
```

Log-Rank Test in SAS

Test of Equality over Strata			
Test	Chi-Square	DF	Pr > Chi-Square
Log-Rank	10.5449	1	0.0012
Wilcoxon	9.4431	1	0.0021
-2Log(LR)	11.1765	1	0.0008



- **Survival curves differ significantly between the two treatment groups**
- **New treatment regimen improved survival**

Survival and Failure Estimates

Time to Diagnosis or Death

The LIFETEST Procedure

Stratum 1: Trt = 0

Product-Limit Survival Estimates						
Days		Survival	Failure	Survival Standard Error	Number Failed	Number Left
0.000		1.0000	0	0	0	577
1.000		0.9983	0.00173	0.00173	1	576
1.000	*	.	.	.	1	575
2.000		0.9965	0.00347	0.00245	2	574
3.000	*	.	.	.	2	573
4.000	*	.	.	.	2	572
7.000		.	.	.	3	571
7.000		0.9930	0.00695	0.00346	4	570
9.000		0.9913	0.00870	0.00387	5	569
10.000	*	.	.	.	5	568
11.000	*	.	.	.	5	567
13.000		0.9896	0.0104	0.00424	6	566
14.000		0.9878	0.0122	0.00458	7	565
15.000		0.9861	0.0139	0.00489	8	564
16.000		0.9843	0.0157	0.00519	9	563
17.000	*	.	.	.	9	562
18.000		0.9826	0.0174	0.00547	10	561
20.000		0.9808	0.0192	0.00573	11	560
24.000		0.9791	0.0209	0.00598	12	559
25.000		0.9773	0.0227	0.00622	13	558

SAS will also provide estimates of survival and failure probabilities at each time point as well as the number of events and number at risk.

Time to Diagnosis or Death

The LIFETEST Procedure

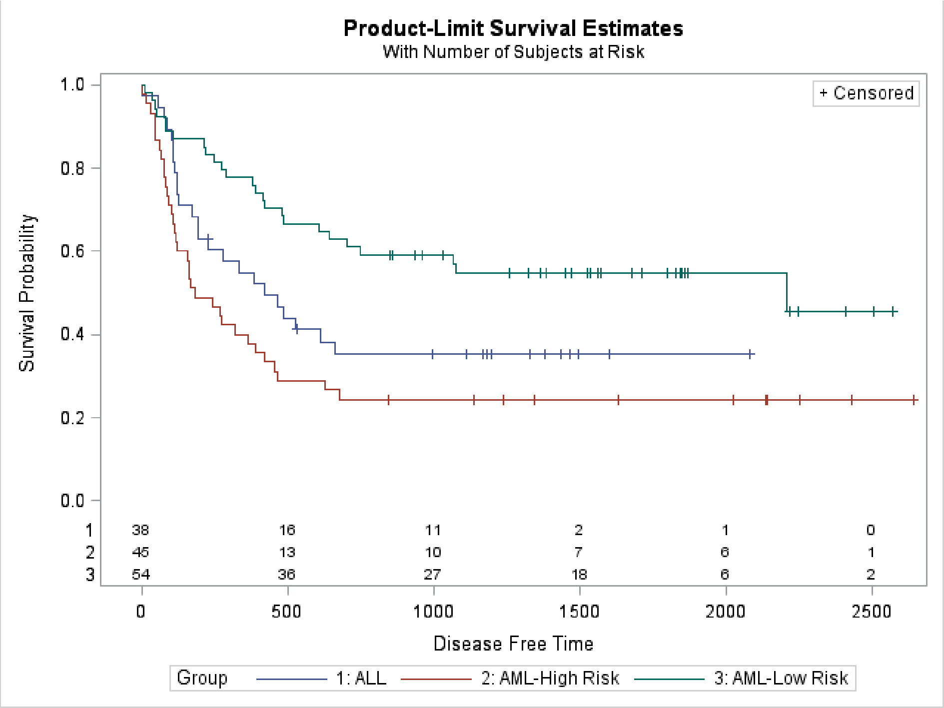
Stratum 2: Trt = 1

Product-Limit Survival Estimates						
Days		Survival	Failure	Survival Standard Error	Number Failed	Number Left
0.000		1.0000	0	0	0	574
1.000	*	.	.	.	0	573
3.000	*	.	.	.	0	572
7.000		0.9983	0.00175	0.00175	1	571
13.000		0.9965	0.00350	0.00247	2	570
14.000		.	.	.	3	569
14.000		0.9930	0.00699	0.00348	4	568
17.000		0.9913	0.00874	0.00389	5	567
17.000	*	.	.	.	5	566
18.000		.	.	.	6	565
18.000		0.9878	0.0122	0.00460	7	564
19.000	*	.	.	.	7	563
20.000		0.9860	0.0140	0.00491	8	562
25.000		0.9842	0.0158	0.00521	9	561
35.000		0.9825	0.0175	0.00549	10	560
38.000	*	.	.	.	10	559
39.000		0.9807	0.0193	0.00575	11	558
39.000	*	.	.	.	11	557
39.000	*	.	.	.	11	556
40.000	*	.	.	.	11	555
41.000	*				11	554

Another Example

- **Disease-free survival after bone marrow transplant**
  - Time to death or disease progression
- **3 risk categories**
  - ALL – acute lymphoblastic leukemia
  - AML Low – Acute myeloctic leukemia
  - AML High – Acute myeloctic leukemia

Disease-free Survival

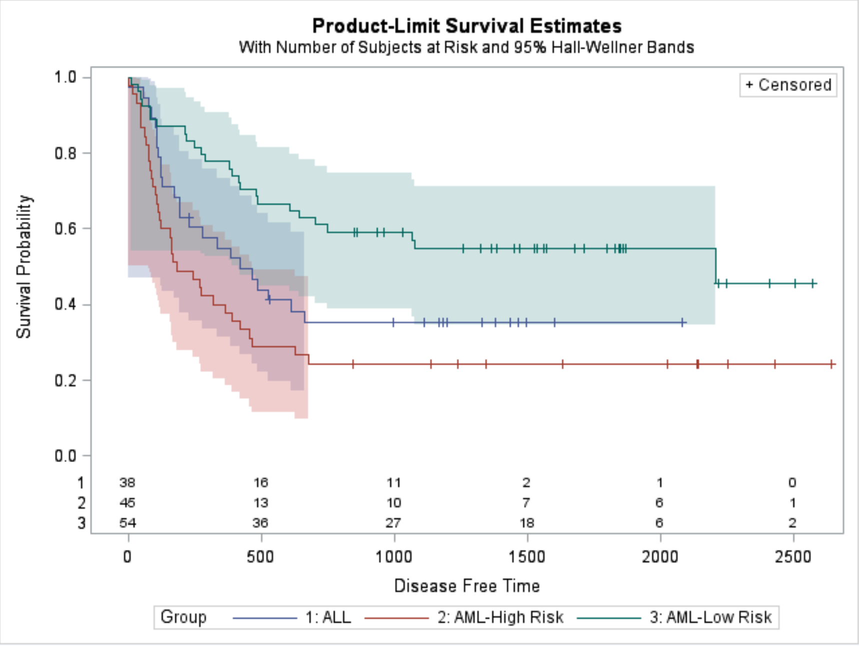


Test	Chi-Square	DF	Pr > Chi-Square
Log-Rank	13.8037	2	0.0010

- **AML – low risk group has best survival**
- **AML – high risk group has poorest survival**
- **Log-rank test indicates that at least 2 curves differ significantly**
- **How to test?**

Multiple Comparisons

Adjustment for Multiple Comparisons for the Logrank Test				
Strata Comparison			p-Values	
Group	Group	Chi-Square	Raw	Tukey-Kramer
ALL	AML-High Risk	2.6610	0.1028	0.2324
ALL	AML-Low Risk	5.1400	0.0234	0.0605
AML-High Risk	AML-Low Risk	13.8011	0.0002	0.0006

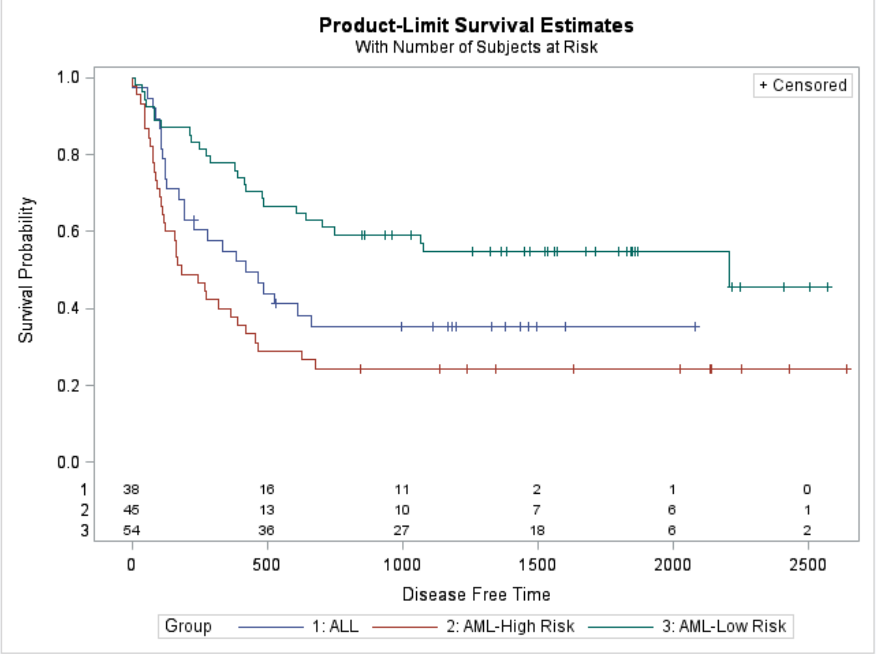


If overall test is significant, follow up with multiple comparisons.

```
ods graphics on;
proc lifetest data=BMT plots=survival(cb atrisk = 0 to 2500 by 500);
title "Disease-free Survival";
      time T * Status(0);
      strata Group / test=logrank adjust=tukey;
run;
ods graphics off;
```

Only do log rank test
Conduct multiple comparisons with a Tukey procedure to control the error rate.

Estimates of Survival Quartiles



AML-High Risk

Summary Statistics for Time Variable T

Quartile Estimates				
	Point	95% Confidence Interval		
Percent	Estimate	Transform	[Lower	Upper)
75	677.00	LOGLOG	363.00	.
50	183.00	LOGLOG	113.00	390.00
25	84.00	LOGLOG	48.00	115.00

AML-Low Risk

Summary Statistics for Time Variable T

Quartile Estimates				
	Point	95% Confidence Interval		
Percent	Estimate	Transform	[Lower	Upper)
75	.	LOGLOG	.	.
50	2204.00	LOGLOG	641.00	.
25	390.00	LOGLOG	105.00	641.00

- SAS will provide estimates by group of median, 25th and 75th quartiles *if available.*
- Median survival - time to which 50% of subjects have survived
- 25th – time by which 25% of subjects have experienced the event
- 75th – time by which 75% of subjects have experienced the event

Summary

- “Survival” analysis methods applicable to variety of “time-to-event” data
- Censoring necessitates special methods
- Kaplan-Meier summarizes survival data
- Log-rank test statistically compares survival between categorical groups
- Next month – regression analysis of survival data allowing evaluation of multiple categorical and continuous predictors

Help is Available

- **CTSC Biostatistics Office Hours**
  - Every Tuesday from 12 – 1:30 in Sacramento
  - Sign-up through the CTSC Biostatistics Website
- **EHS Biostatistics Office Hours**
  - Every Monday from 2-4 in Davis
- **Request Biostatistics Consultations**
  - CTSC - www.ucdmc.ucdavis.edu/ctsc/
  - EHS Center