

Biost 517
Applied Biostatistics I
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Lecture 6:
(Right) Censored Data Descriptives

October 14, 2011

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Lecture Outline
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- Graphical Depiction of the Entire Distn
- Methods for Right Censored Data
 - Setting
 - Motivating example
 - Estimation of survivor functions
 - Life table methods
 - Kaplan-Meier estimates

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**Graphical Characterizations
of an Entire Distribution**
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Probability Distribution Function
.....

- For ordered variables, we define
 - Cumulative distribution function (cdf):
 - $F(x) = \Pr(X \leq x)$
 - Survivor function:
 - $S(x) = \Pr(X > x) = 1 - F(x)$

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Empirical Distribution Function

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- Sample cumulative distribution function or survivor function can be used as an estimate
 - (Just treat the sample as if it were the population)
- These functions can sometimes be estimated for censored data (unlike histograms, densities, etc.)

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Empirical CDF: No Censoring

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- Definition:

For uncensored data $\{X_1, X_2, \dots, X_n\}$

Empirical cumulative distribution function

$$\hat{F}(x) = \frac{1}{n} \sum_{i=1}^n 1_{[X_i \leq x]} = \frac{\text{\# observations } \leq x}{n}$$

Empirical survivor function

$$\hat{S}(x) = 1 - \hat{F}(x)$$

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Empirical CDF: Properties

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- The empirical cdf assigns probability mass of $1/n$ at each observation
 - Step function:
 - jumps at each observation
 - level between observations
- The empirical cdf can be graphed for an ordered variable
 - Because we draw conclusions from the spacing of the x-axis, this makes most sense when the measurements are on an interval or ratio scale

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Stata: Empirical CDF

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- `"cumul var, gen(Fvar) equal"`
 - Generates a new variable named *Fvar* with empirical CDF
 - (Note the need to use the "equal" option to handle ties)
- `"line Fvar var, sort connect(stairstep)"`
 - Produces empirical CDF (as a step function)
 - (Note the need to use the "sort" option)

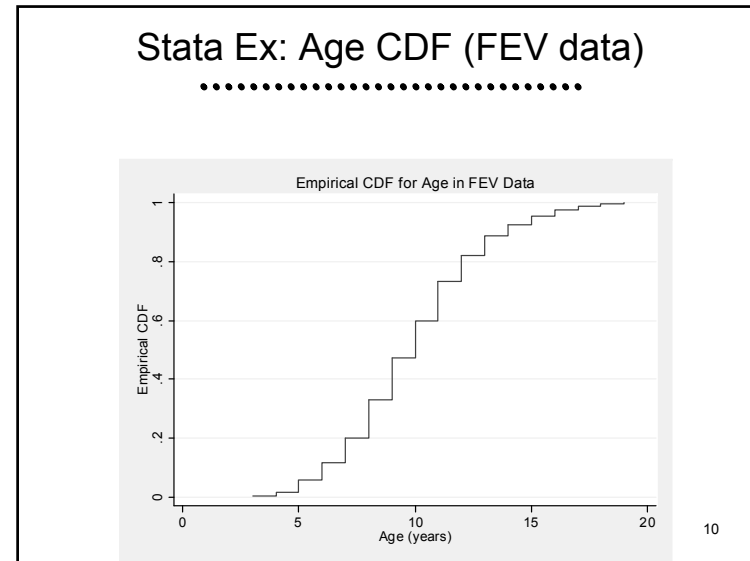
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Stata Ex: Age CDF (FEV data)

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- `cumul age, gen(Fage) equal`
- `line Fage age, connect(stairstp) sort`
`xtitle("Age (years)") ytitle("Empirical CDF")`
`t1("Empirical CDF for Age in FEV Data")`

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Setting for Right Censored Data

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Missing Data

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- Ideal:

"Just say no."
 - Nancy Reagan
- Real life:

"Missing data happens."
 - Bumper sticker (rough translation)

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Missing Data Classifications

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- Mechanistic classification
 - Missing completely at random (MCAR)
 - Missing at random (MAR)
 - Missingness can depend on other observed data
 - Missing not at random (MNAR)

- Functional classification
 - Ignorable (MCAR and sometimes MAR)
 - Discarding cases with missing data does not bias results
 - Nonignorable (MNAR and most times MAR)
 - Omitting cases with missing data leads to erroneous conclusions

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Sad Facts of Life

.....

“Bloodsuckers hide beneath my bed”
- Eyepennies, Mark Linkous (Sparklehorse)

- Typically, nothing in your data can tell you whether missing data is ignorable or nonignorable
 - You just have to deal with what you worry about

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Censored Data

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- Special type of nonignorable missing data
 - The value is known to be in some interval, but the exact value is not always known
 - Commonly arises when measuring time to some event
 - Can also arise when measuring laboratory values due to nondetectable levels or saturation of the device

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Types of Censored Data

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- Right censoring:
 - For some observations it is only known that the true value exceeds some threshold
- Left censoring:
 - For some observations it is only known that the true value is below some threshold
- Interval censoring:
 - For some observations it is only known that the true value is between some thresholds

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Example: Setting

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- A clinical trial of aspirin in prevention of cardiovascular mortality
 - 10,000 subjects are randomized equally to receive either aspirin or placebo
 - Subjects are randomized over a three year period
 - Subjects are followed for fatal events for an additional three year period following accrual of the last subject

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Example: Right Censoring

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- Problem:
 - At the end of the clinical trial, some subjects have been observed to die
 - True time to death is known for these subjects
 - At the end of the clinical trial, most subjects are likely to be still alive
 - Death times of these subjects are only known to be longer than the observation time
 - “(Right) Censored observations”

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Example: Wrong Approach

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- Cannot ignore censored data
 - These are our treatment successes
 - If we throw these cases out of the dataset, we will underestimate the probability of longer survival

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Example: Bad Solution #1

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- Cannot just treat as binary (live/die) data
 - Potential time of follow-up (censoring time) differs across subjects
 - Administrative censoring (alive at time of analysis)
 - Loss to follow-up due to adverse events
 - Confounding vs loss of precision
 - Confounding if pattern of censoring differs across groups

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Example: Bad Solution #2

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- Should not just treat as binary (live/die) data at time of earliest censoring
 - May not answer the scientific question
 - Detecting short term versus long term effects
 - Statistically less efficient

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Right Censored Data

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- Notation:
 - Unobserved :
 - True times to event : $\{T_1^0, T_2^0, \dots, T_n^0\}$
 - Censoring Times : $\{C_1, C_2, \dots, C_n\}$
 - Observed data :
 - Observation Times : $T_i = \min(T_i^0, C_i)$
 - Event indicators : $D_i = \begin{cases} 1 & \text{if } T_i = T_i^0 \\ 0 & \text{otherwise} \end{cases}$

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Motivating Example

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Motivating Example

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- Hypothetical study of subject survival
 - Subjects accrued to study and followed until time of analysis
 - Study done at three centers, which started the studies in three successive years
 - Censoring time thus differs across centers

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Data by Date (Real Time)

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Staggered study entry by site

Year		Accrual Group		
		A	B	C
1990	On study	100	--	--
	Died	43		
	Surviving	57		
1991	On study	57	100	--
	Died	27	53	
	Surviving	30	47	
1992	On study	30	47	100
	Died	13	22	55
	Surviving	17	25	45

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Data by Study Time

.....

Realign data according to time on study

Year		Accrual Group		
		A	B	C
1	On study	100	100	100
	Died	43	53	55
	Surviving	57	47	45
2	On study	57	47	--
	Died	27	22	
	Surviving	30	25	
3	On study	30	--	--
	Died	13		
	Surviving	17		

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Combined Data

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Year		Accrual Group			Combined
		A	B	C	
1	On study	100	100	100	300
	Died	43	53	55	151
	Surviving	57	47	45	149
2	On study	57	47	--	104
	Died	27	22		49
	Surviving	30	25		55
3	On study	30	--	--	30
	Died	13			13
	Surviving	17			17

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- ### Problem Posed by Missing Data
-
- Sampling scheme causes (informative) missing data
 - Potentially, we might want to estimate three year survival probabilities
 - Different centers contribute information for varying amounts of time
 - One year survival can be estimated at A, B, C
 - Two year survival can be estimated at A, B
 - Three year survival can be estimated at A
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Possible Remedies

- WRONG: Ignore missing
 - E.g., 17 of 300 subjects alive at three years

- RIGHT BUT WRONG QUESTION: Use data only up to earliest censoring time
 - E.g., 149 of 300 subjects alive at one year

- RIGHT BUT INEFFICIENT: Use only center A
 - E.g., 17 of 100 subjects alive at three years

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Best Approach

- RIGHT AND EFFICIENT
 - Use all available data to estimate that portion of survival for which it is informative
 - Use Centers A, B, and C to estimate one year survival
 - Use Centers A and B to estimate proportion of one-year survivors who survive to two years
 - Use Center A to estimate proportion of two-year survivors who survive to three years

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Theoretical Basis for Approach

- Properties of probabilities
 - Probability of event A and B occurring is product of
 - Probability that A occurs when B has occurred
 - Probability that B has occurred

$$\Pr(A \cap B) = \Pr(A | B) \times \Pr(B)$$

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Application of Theory to Survival

- For times $T_1 < T_2$, probability of surviving beyond time T_2 is the product of
 - Probability of surviving beyond time T_2 given survival beyond time T_1 , and
 - Probability of surviving beyond time T_1

For $t_0 \leq t_1 \leq t_2 \leq \dots \leq t_k$

$$\begin{aligned} \Pr(T^0 \geq t_j) &= \Pr(T^0 \geq t_j \cap T^0 \geq t_{j-1}) \\ &= \Pr(T^0 \geq t_j | T^0 \geq t_{j-1}) \Pr(T^0 \geq t_{j-1}) \end{aligned}$$

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Estimate Conditional Survival

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- Condition on surviving up until the start of the time interval
 - Denominator is number of subjects at start of interval
 - Numerator is deaths during the interval
- Requirement for validity
 - Subjects available at the start of each time interval are a random sample of the population surviving to that time
 - “Missing at Random” (MAR)
 - “Noninformative censoring”

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Estimate Survival Probability

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- Estimate probability of survival at the endpoint of each time interval
 - Multiply the conditional probabilities for all intervals prior to the time point of interest

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Application to Example

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- Within interval conditional probabilities
 - Use A, B, C to estimate $Pr(T^0 \geq 1)$
 - Use A, B to estimate $Pr(T^0 \geq 2 | T^0 \geq 1)$
 - Use A to estimate $Pr(T^0 \geq 3 | T^0 \geq 2)$
- Multiply to obtain unconditional cumulative survival
 - $Pr(T^0 \geq 1)$
 - $Pr(T^0 \geq 2) = Pr(T^0 \geq 2 | T^0 \geq 1) Pr(T^0 \geq 1)$
 - $Pr(T^0 \geq 3) = Pr(T^0 \geq 3 | T^0 \geq 2) Pr(T^0 \geq 2)$

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Motivating Example Results

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Survival Probabilities

Yr	Combined	Each Year	Cumulative
1	On study 300 Died 151 Surviving 149	149/300 = 49.67%	49.67%
2	On study 104 Died 49 Surviving 55	55/104 = 52.88%	.4967* .5288 = 26.27%
3	On study 30 Died 13 Surviving 17	17/30 = 56.67%	.2627* .5667 = 14.88%

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Estimation of Survivor Functions

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Noninformative Censoring

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- When estimating survivor functions using censored data:
 - Censoring must not be informative
 - Censored subjects neither more nor less likely to have an event in the immediate future
 - Censored individuals must be a random sample of those at risk at time of censoring: MAR
 - Missingness depends on time last observed
 - But random among all subjects at that time
 - Later: a random sample from all subjects at risk having similar modeled covariates: MAR
 - Missingness depends on time last observed and some other measured and modeled covariates

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Informative Censoring Examples

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- Subjects in a RCT are withdrawn due to treatment failure
 - (likely they would die sooner than those remaining)
- Subjects in a RCT in a fatal condition are lost to follow up when they go on vacation
 - (likely they are healthier than those remaining)
- Leukemia patients in a RCT of bone marrow transplantation are censored if they die of infections rather than dying of cancer
 - (they might have had a more effective regimen to wipe out existing cancer)

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Detecting Informative Censoring

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- As a general rule it is impossible to use the data to detect informative censoring
- The necessary data is almost certainly missing in the data set
- In some cases, it is impossible to ever observe the missing data: “Competing Risks”
 - Nonfelines can only die once
 - We cannot observe whether subjects dying of one cause are more or less likely to die of another if we cure them of the first cause

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Life Table Methods

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- In the actuarial (e.g., insurance) setting
 - The time intervals are often chosen by years, decades, etc.

- The data are presented for each year as
 - N_j : Number of subjects at risk at start of interval
 - C_j : Number censored during interval (these will contribute half a person)
 - D_j : Number of events in interval

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Life Table Methods: Notation

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- Number at risk, censored, failed in each interval

Time interval : $(t_{j-1}, t_j]$

Number at risk : N_j

Number censored : C_j

Number of events : D_j

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Life Table Methods: Formula

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- Computation of probability of survival

Conditional probability of survival in interval :

$$\Pr(T^0 \geq t_j | T^0 \geq t_{j-1}) = 1 - \frac{D_j}{N_j - 0.5 \times C_j}$$

Cumulative probability of survival :

$$\Pr(T^0 \geq t_j) = \Pr(T^0 \geq t_j | T^0 \geq t_{j-1}) \Pr(T^0 \geq t_{j-1})$$

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Kaplan-Meier Estimates

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- Kaplan-Meier (Product Limit) Estimates

- With more precisely measured individual data
 - The time intervals are defined by unique observation times
 - The data are presented for each year as
 - N_j : Number of subjects at risk at start of interval
 - D_j : Number of events at end of interval
 - (Note no censoring or events during interval by definition)
 - (Note also that for ties, censoring occurs after deaths)

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Kaplan-Meier Notation

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- Definition of intervals, number at risk, failures

Ordered distinct observation times :

$$t_1 \leq t_2 \leq \dots \leq t_k$$

Time interval : $(t_{j-1}, t_j]$

Number at risk at t_j : N_j

Number of events at t_j : D_j

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Kaplan-Meier Hazard Estimates

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- Computation of hazard and conditional probability of survival in interval

Hazard for event in interval : $\frac{D_j}{N_j}$

Conditional probability of survival in interval :

$$\Pr(T^0 \geq t_j | T^0 \geq t_{j-1}) = 1 - \frac{D_j}{N_j}$$

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Kaplan-Meier Survival Estimate

.....

- Estimating survival probability

$$S(t) = \Pr(T^0 > t)$$

Cumulative probability of survival :

$$\Pr(T^0 > t_j) = \Pr(T^0 > t_j | T^0 > t_{j-1}) \Pr(T^0 > t_{j-1})$$

$$\hat{S}(t_j) = \left(1 - \frac{D_j}{N_j}\right) \times \left(1 - \frac{D_{j-1}}{N_{j-1}}\right) \times \dots \times \left(1 - \frac{D_1}{N_1}\right)$$

$$= \prod_{i=1}^j \left(1 - \frac{D_i}{N_i}\right)$$

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If Last Observation Censored

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- For an interval which ends in a censored observation with no observed events, the conditional probability of surviving within the interval is 1.
- Note also that if the largest observation time is censored, the KM (PLE) survivor function never goes to zero
 - We generally regard the KM (PLE) survivor function to be undefined for times beyond the largest observation time in this situation

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Kaplan-Meier Properties

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- The KM (PLE) survivor functions can be shown to be
 - Consistent: As sample sizes go to infinity, they estimate the true value
 - Nonparametric maximum likelihood estimates
 - But usual asymptotic (large sample) theory for regular, parametric MLE's does not apply
 - Asymptotic (large sample) normal distribution for estimates was established differently

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Other Derivations of KM

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- The KM (PLE) survivor functions can also be derived as the
 - Self-consistent estimator
 - (see Miller, Survival Analysis)
 - “Redistribute to the right” estimator

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Redistribute to the Right

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- Basic idea
 - Recall the empirical cdf assigns probability $1/n$ to each observation
 - A censored observation should be equally likely to have event time like any of the remaining uncensored observations
 - Recursively redistribute the mass of each censored observation among the subjects remaining at risk

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Ex: Redistribute to the Right

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- Data: 1, 3, 4*, 5, 7*, 9, 10
 - (asterisk means censored)
- Initially: each point has mass $1/7$
- Determine probability of events at earliest observed (uncensored) event times
 - $\Pr(T^0 = 1) = 1/7$
 - $\Pr(T^0 = 3) = 1/7$

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Ex: Redistribute to the Right

.....

- Censored observation at 4
 - Divide the mass at 4 equally among the remaining subjects at risk
 - Now mass of $1/7 + 1/28 = 5/28$ for each of 5, 7, 9, 10
- Determine probability of events at next observed (uncensored) event times
 - $\Pr(T^0 = 5) = 5/28$

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Ex: Redistribute to the Right

.....

- Censored observation at 7
 - Divide the mass at 7 equally among the remaining subjects at risk
 - Now mass of $5/28 + 5/56 = 15/56$ for each of 9, 10
- Determine probability of events at next observed (uncensored) event times
 - $\Pr(T^0 = 9) = 15/56$
 - $\Pr(T^0 = 10) = 15/56$

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Ex: Redistribute to the Right

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Kaplan-Meier estimate of Survival

t	$\Pr(T^0 = t)$	$\Pr(T^0 > t)$
0		1.000
1	$1/7 = 0.143$.857
3	$1/7 = 0.143$.714
4	0.000	.714
5	$5/28 = 0.179$.536
7	0.000	.536
9	$15/56 = 0.268$.268
10	$15/56 = 0.268$.000

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Stata: Kaplan-Meier Commands

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- First step is declaring data to be of censored survival type
- Potentially three variables may be used
 - Start of interval
 - Assumed to be at time 0 if nothing supplied
 - End of interval
 - Status at end of interval
 - 0 = censored
 - Nonzero = event occurred at end of interval

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Stata: Kaplan-Meier Commands

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- Syntax for “setting survival data”
 - “`stset endtime eventind, t0(entrytime)`”
 - *endtime*: name of the variable measuring the time at the end of the interval
 - *eventind*: name of an indicator (0 or 1) variable indicating event status at the end of the interval
 - *entrytime*: name of the variable specifying the time at the start of the interval
 - (does not need to be supplied)
 - “`stset, clear`” resets the data set

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Stata: Kaplan-Meier Commands

.....

- Syntax for getting estimates, plots
 - Plotting survival curves
 - “`sts graph`”
 - “`sts graph, atrisk`”
 - “`sts graph, cens(s)`”
 - Listing survival estimates
 - “`sts list`”
 - Saving survival estimates
 - “`sts gen newvar = s`”

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Example: PSA Data

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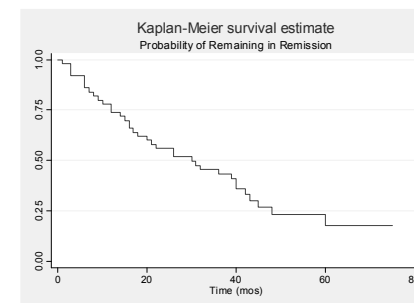
- PSA data set
 - `infile ... obstime str8 inrem using psa.txt`
 - `g relapse = 0`
 - `replace relapse = 1 if inrem=="no"`
 - `stset obstime relapse`
 - `sts graph, xtitle("Time from Treatment (mos)")`
 - `sts list`
 - `sts gen estremt = s`

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Example: KM Graph

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- `sts graph, xtitle("Time (mos)") t1("Probability of Remaining in Remission")`



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Example: KM Graph

.....

- sts graph, atrisk xtitle("Time (mos)") t1("Probability of Remaining in Remission")

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Example: KM Graph

.....

- sts graph, cens(s) xtitle("Time (mos)") t1("Probability of Remaining in Remission")

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Example: KM Listing

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- sts list

Time	Beg.		Net		Survivor		Std.	
	Total	Fail	Lost	Function	Error	[95% Conf. Int.]		
1	50	1	0	0.9800	0.0198	0.8664	0.9972	
3	49	3	0	0.9200	0.0384	0.8007	0.9692	
6	46	3	0	0.8600	0.0491	0.7286	0.9307	
7	43	1	0	0.8400	0.0518	0.7054	0.9166	
8	42	1	0	0.8200	0.0543	0.6826	0.9020	
9	41	1	0	0.8000	0.0566	0.6602	0.8870	
10	40	1	0	0.7800	0.0586	0.6381	0.8716	
12	39	2	0	0.7400	0.0620	0.5947	0.8399	
14	37	1	0	0.7200	0.0635	0.5735	0.8236	
15	36	1	0	0.7000	0.0648	0.5525	0.8070	
16	35	2	0	0.6600	0.0670	0.5114	0.7730	
17	33	1	0	0.6400	0.0679	0.4911	0.7557	

--more--

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Example: KM Listing

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- sts list, at(24 27 30 33 36)

Time	Beg.		Survivor		Std.	
	Total	Fail	Function	Error	[95% Conf. Int.]	
24	28	22	0.5600	0.0702	0.4124	0.6842
27	27	2	0.5185	0.0709	0.3725	0.6461
30	25	1	0.4978	0.0710	0.3529	0.6267
33	22	2	0.4545	0.0711	0.3124	0.5860
36	20	1	0.4318	0.0711	0.2913	0.5645

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Example: Restricted Means

- Stata will give an estimate of the restricted mean
 - Restricted to maximum follow-up time

```
. stci, rmean
      failure _d: relapse
      analysis time _t: obstime

      | no. of restrictd
      | subj   mean      Std. Err. [95% Conf. Intrvl]
-----+-----
total |   50   33.92(*)   3.65323   26.76   41.08
```

(*) largest observed analysis time is censored, mean is underestimated

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