Medical Statistics: Survival Analysis

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University of Sheffield

MAS6012/MAS361/MAS461
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Contents

Contents

- **Organization of Course**
  - Two Components
    - Clinical trials
      - Experiments on human (and animal) subjects
      - Ethical issues, efficient use of subjects, etc
    - Survival Analysis
      - (analyzing data on length of lifetimes, e.g. times of remission in leukaemia)
  - Approximately 10 lectures each

- **Organization of course material**
  - Two sets of lecture notes (Survival & Clinical)
  - Clinical Chapters 1 – 10 (~ 1 per lecture)
  - Survival Chapters 1 – 4 main part of course
  - Appendix 0: background maths
    - Maximum Likelihood Estimation
      - (but used only in a couple of places)
  - Appendix 1 use of computer packages
    - SAS, SPSS, Minitab, S-PLUS
  - Exercises & Task Sheets are in Course Booklet
    - Solutions follow later as appropriate

- **Task Sheets & Exercises**
  - Task sheets:–
    - ~ each week
    - simple quick short exercises/reading
    - reinforce / consolidate lecture material
  - Exercises:–
    - 3 sets during semester in weeks 5,8,10
    - Work submitted within 2 weeks will be marked and returned
  - **See Study Guide**
    - **recommendations on time to spend**

Task Sheets & Exercises

- Task sheets:–
  - are designed for you to test **your own understanding** of the course material
  - *you are responsible* for your own learning on the course — task sheets help you in self-assessment
- Exercises:–
  - **Prime route for individual feedback**
  - Task sheets often provide guide for exercises
- Unacceptable reasons for not submitting anything
  - I did not have enough time
  - I knew I could do them so I did not need to submit
  - I could not do anything so did not think it was worth it

Solutions to Task Sheets & Exercises

- Exercises:–
  - Solutions available on web soon after submission
    - Printed solutions will be provided to those who submit
- Task sheets:–
  - are designed for you to test your own understanding of the course material
  - if necessary go back to lecture notes (etc) & re-read relevant sections
    - (and if necessary re-read again & … …)
  - Solutions will be provided on web pages in due course (for revision etc)
    - but ***deliberately*** these will not appear very quickly

- Course web page

  http://nickfieller.staff.shef.ac.uk/

  - Click on Teaching & then on [MAS6012/MAS461/MAS361 Medical Statistics]
- Lecture notes, task sheets, solutions & data sets available here after distribution in lectures
  - (I don't keep back copies)

Books

- **Campbell, M. J. (2001)**
  Statistics at Square Two. BMJ
- **Collett, D. (2003)**
  Modelling Survival Data in Medical Research. (2nd Edition) Chapman & Hall
- **Everitt, Brian & Rabe-Heskith, Sophia (2001)** *Analyzing Medical Data Using S-PLUS*. Springer. Support material at

http://web1.iop.kcl.ac.uk/IoP/Departments/BioComp/splusBook.shtml

Contents

- **Objectives**
  - statistical modelling & analysis of *lifetime data*.
  - Lifetime data arise especially in medical statistics and in reliability studies.
    - *survival time:-*
      - time from diagnosis to death of a patient
      - *time to recovery* or *remission* of a patient or
      - *time to failure* of an electronic component.

- **Outline**
  - Types of survival data
  - Censoring
  - Parametric & non-parametric approaches
- **Single Sample Methods**
  - survivor & hazard functions
  - Lifetables
  - Kaplan-Meier estimators

- **Two Sample Comparisons:-**
  - log rank test
  - maximum likelihood test
  - likelihood ratio test
  - proportional hazards

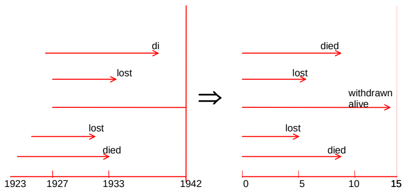
- **Regression Models**
  - parametric models
    - exponential & Weibull
  - non-parametric methods
    - proportional hazards or Cox regression
    - partial likelihood

- **Aims of survival analysis**
  - describe/model a single sample
    - making inferences on a single population
  - compare two or more groups
    - effect of treatments on survival time
  - investigate relationship with covariates
    - effects on survival time of covariates
    - adjust for covariates in comparisons

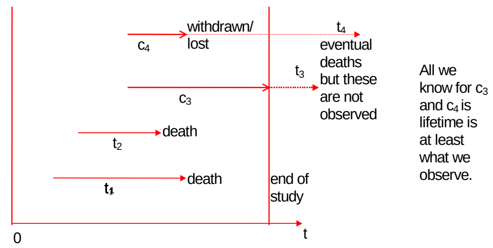
Contents

- **Censoring**
  - event of interest not yet occurred
  - observe only survival time is ***at least*** t
  - some observations t_i (i=1,…,n) are ***censored***
  - censored observations provide information on survival so cannot be ignored

Censoring



Censoring



Censoring

- ***Right censoring***
  - lifetime exceeds some value
- ***Left censoring***
  - lifetime less than some value
- ***Interval censoring***
  - failure occurred during an interval

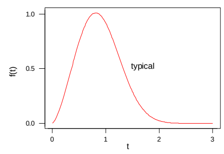
- **Aims**:
  - **estimate lifetime distributions**
    - ⇒ estimate properties of distribution
    - (median lifetime, prob of surviving > 5 years,…)
  - **Censoring**
    - non-parametric — lifetables, Kaplan-Meier
    - parametric — exponential, Weibull.

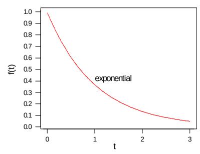
- survival time is a random variable T
- T>0, continuous variable
  - **p.d.f.** f(t) (t>0)
  - **d.f.** $F(t)=P[T\leq t]$
  - (so $f(t)=F'(t)$ and $F(t)=\int_0^t f(u)\,du$)

- **Survivor function**
  - $S(t)=P[T>t]=1-F(t)$
  - (so $S'(t) = -f(t)$, $S(t) = \int_t^{\infty} f(u)du$)
- **Hazard function**
  - $h(t)=\lim_{\delta t\to 0}\left[\frac{P[t\leq T<t+\delta t\,|\,T\geq t]}{\delta t}\right]$
  - "P[die at time T given survived until T]"

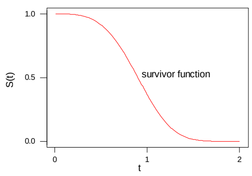
- **Cumulative hazard function**
  - $H(t)=\int_0^t h(u)du=-\log_e S(t)$
  - f(t), S(t), H(t) and h(t) are equivalent characterizations of a survival distribution
  - all inter-related

- **Typical patterns**

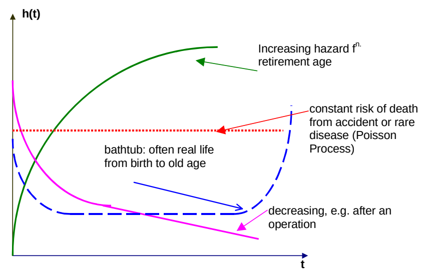




- **Survivor function**



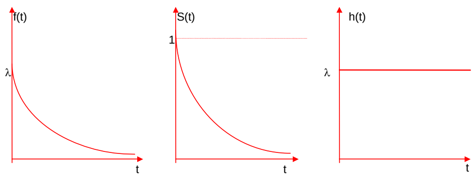
Hazard functions:



- Choose appropriate family of models by recognizing form of hazard function
  - practical situation
  - initial investigation of the data
- then can estimate parameters in model

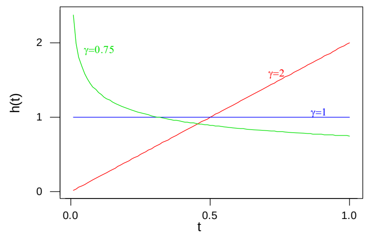
- **Example:-** exponential
  - $f(t) = \lambda e^{-\lambda t}$
  - $S(t) = e^{-\lambda t}$
  - $h(t) = \lambda$ (**NB** constant)
    - $[= f(t)/S(t)]$
- ***only*** constant for exponential survival distribution

- exponential



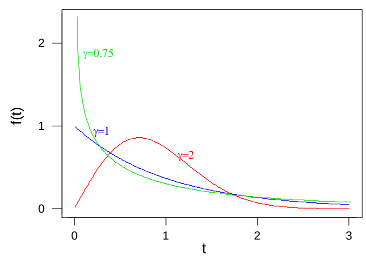
- **Example:-**Weibull
  - $f(t) = \lambda\gamma t^{\gamma-1}\exp(-\lambda t^{\gamma})$
  - $S(t) = \exp(-\lambda t^{\gamma})$
  - $h(t) = \lambda\gamma t^{\gamma-1}$
    - $\gamma > 1$: increasing
    - $\gamma = 1$: constant (exponential)
    - $\gamma < 1$: decreasing

- e.g. $\lambda = 1$; Weibull hazard functions



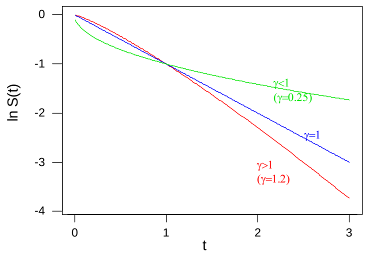
Weibull hazard functions

- e.g. $\lambda = 1$; Weibull density functions



Weibull Density Functions

- e.g. $\lambda = 1$; Weibull log-survivor functions



Weibull log survivor functions

- Weibull family
  - very flexible models
  - allows both increasing ($\gamma>1$) & decreasing ($\gamma<1$) hazard functions
- Difficult to estimate if γ close to 1
  - (numerical instability)

Contents

- **Lifetables**
  - 3 types :-
    - **Population** (from census or survey)
    - **Cohort** (follow a group throughout lifetimes)
    - **Clinical** (or follow-up)
      survival pattern of specific group of individuals.

- **Example**
  - every patient followed up after treatment either until death or up to the end of 1992
  - aim is to estimate probability of surviving for k years in separate steps:
    - first estimate probability of surviving another year given survived up to start of year, for each year
    - then multiply conditional probabilities together

Year of treatment	number treated	Number alive on each anniversary				
		1^{st}	2^{nd}	3^{rd}	4^{th}	5^{th}
1987	62	58	51	46	45	42
1988	39	36	33	31	28	
1989	47	45	41	38	73	
1990	58	53	48	115		
1991	42	40	173			
	248	232				

- prob survive first year =232/248 =0.936

Year of treatment	number treated	Number alive on each anniversary				
		1^{st}	2^{nd}	3^{rd}	4^{th}	5^{th}
1987	62	58	51	46	45	42
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	248	**232**				

- prob survive second year, given alive at start 173/(232 – **40**) = 0.901

Year of treatment	number treated	Number alive on each anniversary				
		1^{st}	2^{nd}	3^{rd}	4^{th}	5^{th}
1987	62	**58**	51	46	45	42
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1990	58	**53**	48	115		
1991	42	**40**	**173**			
	248	**232**				

- prob survive third year, given alive at start 115/(173 – 48) = 0.920

Year of treatment	number treated	Number alive on each anniversary: 1^{st}	2^{nd}	3^{rd}	4^{th}	5^{th}
1987	62	58	**51**	46	45	42
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1990	58	53	**48**	**115**		
1991	42	40	**173**			
	248	232				

Year after treatment	Prob. of surviving each year	Prob. of dying each year	Lifetable (per 1000): Number alive on each anniversary	Number dying during each year
x	p_x	q_x	l_x	d_x
0	0.936	0.064	1000	64
1	0.901	0.099	936	93
2	0.920	0.080	843	67
3	0.948	0.052	776	40
4	0.933	0.067	736	49
5			687	

$0.901 \times 936 = 843$

- n_x — number alive at start of $(x,x+1)$
  d_x — number dying in $(x,x+1)$
  estimate of conditional probability of dying in $(x,x+1)$, given alive at x, is
  $$p_x=d_x/n_x$$
- What if subjects are lost to follow-up?
  - (and not known if still alive or not)

- w_x — number lost to follow-up
  - includes those who have disappeared
    - (i.e. last report last year)
  - +'withdrawn alive'
- assume withdrawals are uniformly spread over $(x,x+1)$
- adjusted number at risk $n_x'=n_x-½w_x$

- adjusted number at risk $n_x'=n_x-½w_x$
- adjusted estimate of conditional probability of dying in $(x,x+1)$, given alive at x, is $p_x=d_x/n_x'$
- Then $n_{x+1}=n_x-d_x-w_x$

Interval since operation years x to x+1	Last reported during this interval: Died d_x	withdrawn w_x	Living at start of interval n_x	Adjusted number at risk n_x'	Estimated probability of death q_x	Estimated probability of survival p_x	% of survivors after x years l_x	Estimate of p.d.f. $\hat{p}_{x+\frac{1}{2}}$	Estimate of hazard function $\hat{h}_{x+\frac{1}{2}}$
0 – 1	90	0	374	374.0	0.2406	0.7594	100	0.241	0.274
1 – 2	76	0	284	284.0	0.2676	0.7324	75.9	0.203	0.309
2 – 3	51	0	208	208.0	0.2452	0.7548	55.6	0.136	0.279
3 – 4	25	12	157	151.0	0.1656	0.8344	42.0	0.070	0.181
4 – 5	20	5	120	117.5	0.1702	0.8298	35.0	0.059	0.186
5 – 6	7	9	95	90.5	0.0773	0.9227	29.1	0.023	0.080
6 – 7	4	9	79	74.5	0.0537	0.9463	26.8	0.014	0.055
7 – 8	1	3	66	64.5	0.0155	0.9845	25.4	0004	0.016
8 – 9	3	5	62	59.5	0.0504	0.9496	25.0	0.013	0.052
9 – 10	2	5	54	51.5	0.0388	0.9612	23.7	0.009	0.040
10 –	21	26	47	—	—	—	22.8		

120 = 157 – 25 – 12

Interval since operation years x to x+1	Last reported during this interval: Died d_x	withdrawn w_x	Living at start of interval n_x	Adjusted number at risk n_x'	Estimated probability of death q_x	Estimated probability of survival p_x	% of survivors after x years l_x	Estimate of p.d.f. $\hat{p}_{x+\frac{1}{2}}$	Estimate of hazard function $\hat{h}_{x+\frac{1}{2}}$
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10 –	21	26	47	—	—	—	22.8		

120 = 157 – 25 – 12

117.5 = 120 – ½ x 5

- Estimated survivor function is

$$\hat{S}_x = p_0 p_1 \ldots\ldots p_{x-1}$$

- estimate of pdf is

$$\hat{f}_{x+\frac{1}{2}} := \hat{S}_x - \hat{S}_{x+1} = \hat{S}_x q_x$$

- Estimate of hazard is $\hat{h}_{x+\frac{1}{2}} := \dfrac{2q_x}{1+p_x}$

- Estimate of hazard is

$$\hat{h}_{x+\frac{1}{2}} = \frac{\hat{f}_{x+\frac{1}{2}}}{\hat{S}_{x+\frac{1}{2}}} = \frac{\hat{S}_x q_x}{\frac{1}{2}(\hat{S}_x + \hat{S}_{x+1})} = \frac{2q_x}{1+p_x}$$

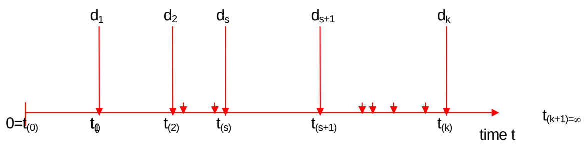
noting $\hat{S}_{x+1} = p_x \hat{S}_x$

- assumed
  - withdrawals have same probability of death as non-withdrawals.
    - Is loss to follow-up connected with condition?
  - p_x and q_x constant over study
    - (estimated by combining data from several years)
- estimates are subject to sampling error:

$$\mathrm{Var}(\hat{S}_x) = \hat{S}_x^2 \sum_{j=1}^{x-1} \frac{d_j}{n_j(n_j - d_j)}$$

- **Clinical life tables suggest the form of the hazard function**
- Lifetable methods take data in groups. Information is lost if actual lifetimes (perhaps censored) are available & have been grouped

- **Kaplan–Meier estimates**
  - k ordered distinct lifetimes $t_{(1)} < t_{(2)} < \ldots < t_{(k)}$
  - d_i — number of deaths at $t_{(i)}$ (so $\Sigma d_i = n$)



- $\hat{F}(t)$ = proportion of lifetimes < t

  $= \frac{1}{n}\sum_{j=1}^{s} d_j$ for $t_{(s)} \leq t < t_{(s+1)}$

- so $\hat{S}(t) = 1 - \hat{F}(t) = \dfrac{n - \sum_1^s d_j}{n}$

  for $t_{(s)} \leq t < t_{(s+1)}$

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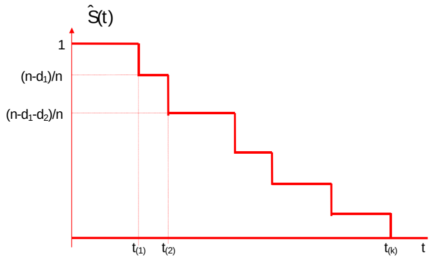

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- Let r_j be the number at risk (≡number alive) just before $t_{(j)}$,
  Then $r_{j+1} = r_j - d_j$, so

$$\hat{S}(t) = \frac{n-d_1}{n} \cdot \frac{n-d_1-d_2}{n-d_1} \cdot \frac{n-d_1-d_2-d_3}{n-d_1-d_2} \cdots \frac{n-d_1-d_2-\ldots-d_s}{n-d_1-\ldots-d_{s-1}}$$

$$= \left(1-\frac{d_1}{r_1}\right)\left(1-\frac{d_2}{r_2}\right)\cdots\left(1-\frac{d_s}{r_s}\right)$$

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$$= \prod_{j=1}^{s}\left(1-\frac{d_j}{r_j}\right) \text{ for } t_{(s)} \leq t < t_{(s+1)}$$

- What if some observations censored?
  - adjust numbers at risk r_i by allowing for censoring

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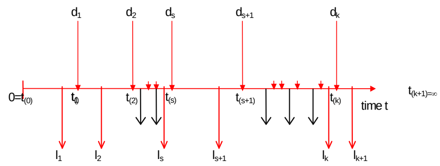
- l_1 l_2 l_3 .... l_k numbers censored before time $t_{(j)}$



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l_j = # censored in the previous interval
now $r_1 = n - l_1$; $r_{j+1} = r_j - d_j - l_{j+1}$ for j=1,2,...,k-1
[or $r_j = n - (d_1+d_2+\ldots+d_{j-1}) - (l_1+l_2+\ldots+l_j)$ for j≥2]
⇨ Kaplan-Meier product limit

$$\hat{S}(t) = \prod_{j=1}^{s}\left(1-\frac{d_j}{r_j}\right) \text{ for } t_{(s)} \leq t < t_{(s+1)}$$

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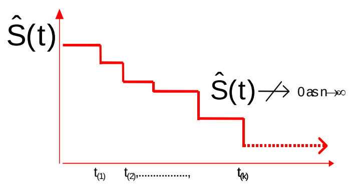
- **Notes**
  - assumes that the l_j censorings survive up to just after $t_{(j-1)}$ and then are removed
  - uncensored case is just a special case with l_j=0 all j
  - If l_{k+1}>0 then, since r_k>d_k

$$\hat{S}(t) = \prod_{j=1}^{k}\left(1-\frac{d_j}{r_j}\right) > 0 \quad \text{when } t>t_{(k)}$$



But we know that $S(\infty) = 0$

⇨ Kaplan-Meir estimates are ***biased*** if maximum observation is censored

- $\hat{S}(t)$ is subject to sampling error

$$\text{var}(\hat{S}(t)) = [\hat{S}(t)]^2 \sum_{j=1}^{s} \frac{d_j}{r_j(r_j-d_j)} \quad \text{for } t_{(s)} \le t < t_{(s+1)}$$

- so can get confidence bands for S(t) with +/- 2 x st.error

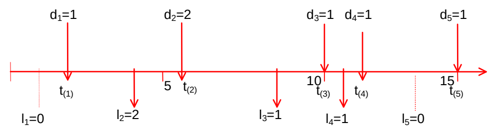
- estimate cumulative hazard H(t) by

$$\hat{H}(t) = -\log_e(\hat{S}(t))$$

or simpler is to use

$$\tilde{H}(t) = \sum_{j=1}^{s} \frac{d_j}{r_j} \quad \text{for } t_{(s)} \le t < t_{(s+1)}$$

- **Example**
  - Remission times for 10 patients
  - 6 relapse 3.0, 6.5,6.5,10,12,15 months
  - **1** lost to follow-up at 8.4 months
  - **3** still in remission at end after 4.0, 5.7, 10.1 months
- **i.e. 4 censored observations**



j	$t_{(j)}$	l_j	r_j	d_j	$\hat{S}(t)$		notes
					1	$0\le t<3.0$	
1	3.0	0	10	1	0.9	$3.0\le t<6.5$	9/10
2	6.5	2	7	2	0.643	$6.5\le t<10.0$	9/10x5/7
3	10.0	1	4	1	0.482	$10.0\le t<12.0$	9/10x5/7x3/4
4	12.0	1	2	1	0.241	$12.0\le t<15.0$	9/10x5/7x3/4x1/2
5	15.0	0	1	1	0	$15\le t$	

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5	15.0	0	1	1	0	$15\le t$	

7 = 10 – 1 –2

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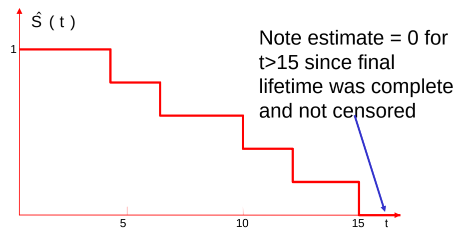
3	10.0	1	4	1	0.482	$10.0\le t<12.0$	9/10x5/7x3/4
4	12.0	1	2	1	0.241	$12.0\le t<15.0$	9/10x5/7x3/4x1/2
5	15.0	0	1	1	0	$15\le t$	

4 = 7 – 2 –1



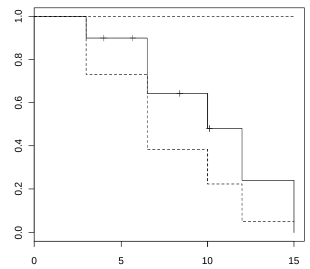
- Implementation in **R**:
  - Need to load library `survival`
    - `> library(survival)`
  - Need to create 'survival object' with `Surv()` `Surv(time,censor,type='right')`
  - t hen use `survfit()` to estimate a survival curve
  - and `plot()` and `summary()` to see details


```
> library(survival)
Loading required package: splines
> load("tumour.Rdata")
> attach(tumour)
> tumour
   time censor
1   3.0      1
2   4.0      0
3   5.7      0
4   6.5      1
5   6.5      1
6   8.4      0
7  10.0      1
8  10.1      0
9  12.0      1
10 15.0      1
```

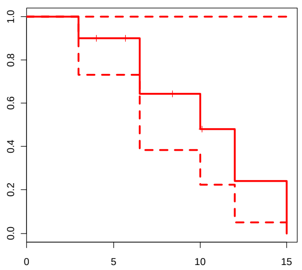
```
# create survival object in tumour.sv:
> tumour.sv <—Surv(time, censor, type = "right")
# estimate survival curve in tumourSurv:
> tumourSurv <-survfit(tumour.sv ~1, data=tumour)
# note 'regressing'/'relating' survival object on a
  constant with ~ 1
# look at summary calculations
> summary(tumourSurv)
Call: survfit(formula = tumour.sv, data = tumour)
 time n.risk n.event survival std.err lower 95% CI upper 95% CI
  3.0     10       1    0.900  0.0949       0.7320            1
  6.5      7       2    0.643  0.1679       0.3852            1
 10.0      4       1    0.482  0.1877       0.2248            1
 12.0      2       1    0.241  0.1946       0.0496            1
 15.0      1       1    0.000     NaN           NA           NA
# Note confidence interval for the K-M estimates
  and that in this small data set the interval is
  truncated at 1
```



```
# plot curve:
> plot(tumourSurv)
```



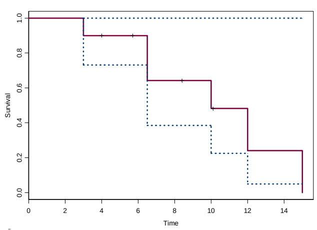

```
# plot curve:
> plot(tumourSurv,lwd=3,col=2)
```



- S-plus implementation:
  - Statistics>Survival>Nonparametric Survival…
  - Need to create formula in dialogue box such as `Surv(time,censor,type='right')~1`

S-plus output:

```
time n.risk n.event survival std.err lower 95% CI upper 95% CI
 3.0     10       1    0.900  0.0949       0.7320            1
 6.5      7       2    0.643  0.1679       0.3852            1
10.0      4       1    0.482  0.1877       0.2248            1
12.0      2       1    0.241  0.1946       0.0496            1
15.0      1       1    0.000      NA           NA           NA
```



Note confidence intervals by default

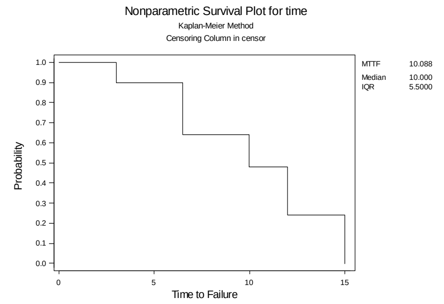
- Minitab implementation:
  - Stat>Reliability/Survival>Nonparametric Dist Analysis-Right Censoring
  - Need to specify value indicating **censored** observations

Minitab output:

Kaplan-Meier Estimates

Time	Number at Risk	Number Failed	Survival Probability	Standard Error	95.0% Normal CI Lower	Upper
3.0000	10	1	0.9000	0.0949	0.7141	1.0000
6.5000	7	2	0.6429	0.1679	0.3137	0.9720
10.0000	4	1	0.4821	0.1877	0.1142	0.8501
12.0000	2	1	0.2411	0.1946	0.0000	0.6225
15.0000	1	1	0.0000	0.0000	0.0000	0.0000

Minitab graph:



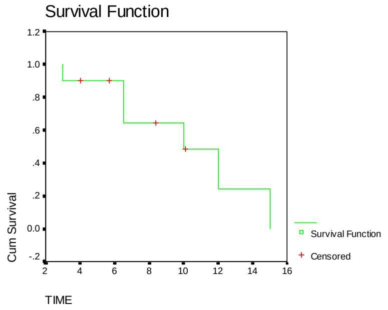
- SPSS implementation:
  - Analyze>Survival>Kaplan-Meier
  - Need to specify value indicating **uncensored** values
  - Note indication of censored values
    - Also indicated by S-PLUS

SPSS Output:

Survival Analysis for TIME

Time	Status	Cumulative Survival	Standard Error	Cumulative Events	Number Remaining
3	0	.9000	.0949	1	9
4	1			1	8
6	1			1	7
7	0			2	6
7	0	.6429	.1679	3	5
8	1			3	4
10	0	.4821	.1877	4	3
10	1			4	2
12	0	.2411	.1946	5	1
15	0	.0000	.0000	6	0

SPSS Graph



- **Summary**
  - Life tables
    - Grouped data
    - Allow for censoring by adjusting # at risk
  - Kaplan-Meier
    - Individual data
    - Uncensored case = 1 – empirical CDF
    - Express as a product of terms $[1 - d_i/r_i]$
    - Censored case by adjusting # at risk

- Kaplan-Meier estimates are the key exploratory tool for censored data
  - Cannot draw histograms of censored data
    - Don't know which bin to put a censored in
- Kaplan-Meier Plot is always step 1 in analysing censored data