

Lecture One: Why and What Survival Analysis?

1. An Example: Treatment induced mortality (example 1.4, p8)

- **Design:**
 - A randomized controlled clinical trial (placebo vs 1.0mg DES)
 - Patients with prostatic cancer followed some time after treatment.
- **Measure:**
 - Outcome: Months after Tx (treatment) to Death
 - Measured covariates: Tx assignment, age, ..., Gleason index.
- **Question:** Any association between death and Tx?
- **Analysis Objectives:**
 - Different mortality under different Tx?
 - Different effects of Tx 1(placebo) and 2 (DES)?
 - Time window of analysis? 30 months? 50 months?

2. Snapshot Analysis (ignore censoring)

- Comparing two treatments
- Mortality at the end of 50 months can be summarized by the following 2 by 2 table:

	Tx 1	Tx 2
Alive	10	16
Dead	8	4

- Odds ratio is a measure of association between Tx and mortality
- Fisher's exact test for the null hypothesis of unity odds ratio (i.e. equal death rate for both Tx's)
- Results: p-value (two-sided) = 0.16 (odds ratio = 0.31)
- Conclusion: Some of treatment difference in terms of 50 months mortality
- Comparing mortality at the end of 30 months
Death frequencies are summarized by following 2 by 2 table:

	Tx 1	Tx 2
Alive	13	17
Dead	5	3

- P-value from Fisher's test: $p = 0.44$ (odds ratio = 0.46)
- Absence of treatment difference in terms of 30 month mortality.

- Shall we look at more fixed time points (snapshots)? How many different 2 by 2 tables we can have?
 - Snapshot sensitive to the time window chosen
 - Snapshot ignores the actual time an event (death) occurs
 - A single snapshot alone doesn't show the whole picture
 - How to connect snapshots together in sequence so we can see the trend over the entire course?

3. Survival Analysis: An Illustration of How To Piece snapshots Together (camera vs camcorder)

- Survivorship (Kaplan-Meier Curve) over time
km.ps here
- Log-rank test:
Comparing survival patterns over life span, not just at a particular time point
 - Generalized Wilcoxon test: $p = 0.065$
 - Log-rank (Mantel-Haenszel) test (equal weight): $p = 0.036$
- Summary
 - Tx 2 did not have effect in reducing early death as compared to Tx 1. Wilcoxon test is design to detect difference in early survival.
 - Log-rank test on the other hand attempts to detect difference that is consistent (equal weight) over time. It revealed the significant difference of the effects of two treatments.

4. Survival Data Structure

- Time Origin or beginning of "life"
 - A well define point in a "life" process
 - Needs not be the same clock time (staggered entry)
 - Means the same for all subjects (e.g. subjects are comparable/similar at this beginning time in terms disease prognosis)
 - Examples: Physical failure, time after transplant, biological death
 - Theoretically measurable
 - If not measured: left-censoring (see censoring)
Put figures from the textbook here
- Event/Failure
 - Represented by measurable symptom(s)
 - Examples: development of the disease, failure of equipment, unemployment, death.
 - Multiple events may exist
 - Recurrence of symptom(s), repeated arrests, stop of remission of a leukemia patient

- Time to Event or failure time (survival time)
 - “time” (e.g. clock time) elapsed from the beginning of “life” to the occurrence of the event
 - “space” (e.g. cumulative usage or exposure) traveled from the initial point to where the event occurs
- Censoring

Actual failure time may not always be observed due to the limitation(s) in a study design. When follow-up observation terminates before observing any event, the elapsed “time” from the “beginning” to the termination point is a right censored failure time or simply censoring time.

 - Type I: censoring occurs at pre-determined time.
 - Type II: censoring occurs when pre-specified proportion of failures is observed.
 - Independent random censoring: the censored subject is similar to those alive at the time (i.e. censoring does not depend on the chance of survival). This is a clinically important and statistically desirable feature/assumption.
- Left-censoring

Failure time is to the left of the observed time. Example: I have used it can not recall when the first time was.
- Interval censoring (special case: current status data)

Failure time is not observed, but must be in an observed interval. Example: visits scheduled half year apart, event maybe happened between two visits.
- Other type of censoring: left truncation (delayed entry), right truncation (if the random variable of interest falls outside some interval, even its existence is unobserved).

Question: Is loss to follow-up a type of censoring, how about drop out?

5. Unix and statistical packages (SAS, Splus and R)

6. Appendix: SAS and Splus programs for snapshot analysis and Survival analysis

SAS code:

```
libname fu './sdata';
data tmp;
  set fu.prostat;
  if st >= 30 then snap1 = 'alive';
  else snap1 = 'dead';
  if st >= 50 then snap2 = 'alive';
  else snap2 = 'dead';
proc print;
  var pid snap1 snap2 st censor;
proc freq;
  tables (snap1 snap2)*treat/chisq relrisk;
proc lifetest;
  time st*censor(0);
  strata treat;
run;
```

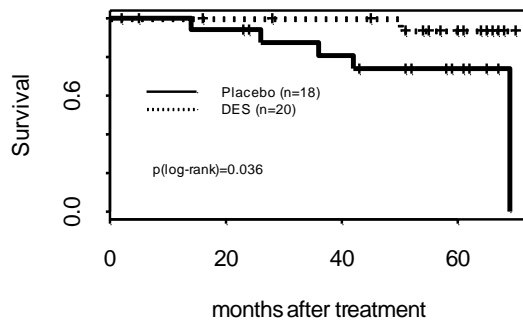
Splus code:

```

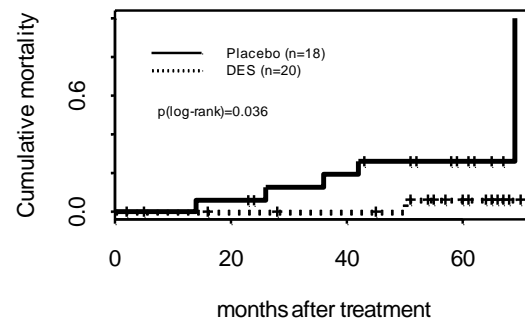
km.s<-function(){
  tmpdf <- importData("../sdata/prostat.sas7bdat")
  motif()
  #   postscript("km.ps")
  par(mfrow=c(2,2))
  treat.km <- survfit(Surv(st, censor)~treat, data=tmpdf)
  plot(treat.km,xlab="days after treatment", lty=1:2,
       ylab="Survival", xlim=c(0, 72), ylim=c(0,1),mark.time=T, lwd=2)
  title("Survival by treatment")
  legend(2,0.7, paste(c("treatment 1","treatment 2"),
                      c("(n=18)","(n=20)")), lty=1:2,cex=0.6)
  legend(2,0.3,"p(log-rank)=0.036",cex=0.6)
  plot(treat.km,xlab="days after treatment",fun="event", lty=1:2,
       ylab="Cumulative mortality", xlim=c(0, 72), ylim=c(0,1),
       mark.time=T, lwd=2)
  title("Mortality by treatment")
  legend(2,0.9, paste(c("treatment 1","treatment 2"),
                      c("(n=18)","(n=20)")), lty=1:2,cex=0.6)
  legend(2,0.6,"p(log-rank)=0.036",cex=0.6)
  #   dev.off()
}

```

Survival by treatment



Mortality by treatment



Assignment one: Forty-six patients with advanced stage non-small cell lung cancer (NSCLC) and relapsed from erlotinib were randomized to receive chemotherapy (pemetrexed or docetaxel, arm A) or chemotherapy plus erlotinib (arm B) between 2008 and 2012. Survival outcomes of those patients were collected (see the Excel file). The data contain following variables:

ARM: treatment arm (A or B)
DOTX: the date of onset of treatment
DOD: the date of death
DOLS: the date of last seen for survivors
DOP: the date of disease progression

The overall survival (OS) was measured from the date of onset of treatment to the date of death, and was censored at the date of last seen for survivors; and the progression-free survival (PFS) was measured from the date of onset of treatment to the date of disease progression or the date of death whichever occurred earlier, and was censored at the date of last seen for survivors without disease progression.

Write a program (SAS or Splus/R) to calculate OS, PFS and their corresponding censoring indicators (use 0 for censored, 1 for event). Generate a working dataset (e.g. SAS dataset) for future survival analysis of the data.

1. Read section 1.2 and Appendix B.