

Bootstrap simulations to estimate Overall Survival based on the distribution of a historical control

Antonio Nieto / Javier Gómez



Background

Trials measuring initial hints of activity (e.g oncology phase II)

- Non comparative single arm study
- Time-to-event endpoints
 - Bidimensional variable (X,Y) with X=length and Y=status
 - Analyzed by means of Kaplan-Meier method
 - Example: Overall survival defined as time from first dose administration date to death date or last contact

Introduction

- After obtaining median overall survival we would like to put our estimate into perspective
 - Main limitation is the different distribution of well known prognostic baseline characteristics
- Obtain a rough estimation using the historical distribution by means of bootstrap replications.
 - Background idea based on Mazumdar et al paper*
 - May be applied to any time-to-event variable (e.g. PFS/TTP)

* A standardization method to adjust for the effect of patient selection in phase II clinical trials-Mazumdar M, Fazzari M, Panageas KS (Statistics in Medicine 2001 20:883-892)

Hypothetical Scenario

- A new compound with promising activity has been evaluated in a single-arm phase II clinical trial with 137 patients
 - Fictitious example based on a slightly modified lung SAS dataset*

```
data VALung;
  drop check m;
  retain Therapy Cell;
  infile cards column=column;
  length Check $ 1;
  label SurvTime='failure or censoring time'
        Kps='karnofsky index'
        DiagTime='months till randomization'
        Age='age in years'
        Prior='prior treatment?'
        Cell='cell type'
        Therapy='type of treatment'
        Treatment='treatment indicator';
  M=Column;
  input Check $ @@;
  if M>Column then M=1;
  if Check='s'|Check='t' then input @M Therapy $ Cell $ ;
  else input @M SurvTime Kps DiagTime Age Prior @@;
  if SurvTime > . ;
  censor=(SurvTime<0);
  SurvTime=abs(SurvTime);
  Treatment=(Therapy='test');
  datalines;
standard squamous
72 60 7 69 0 411 70 5 64 10 228 60 3 38 0 126 60 9 63 10
118 70 11 65 10 10 20 5 49 0 82 40 10 69 10 110 80 29 68 0
...
```

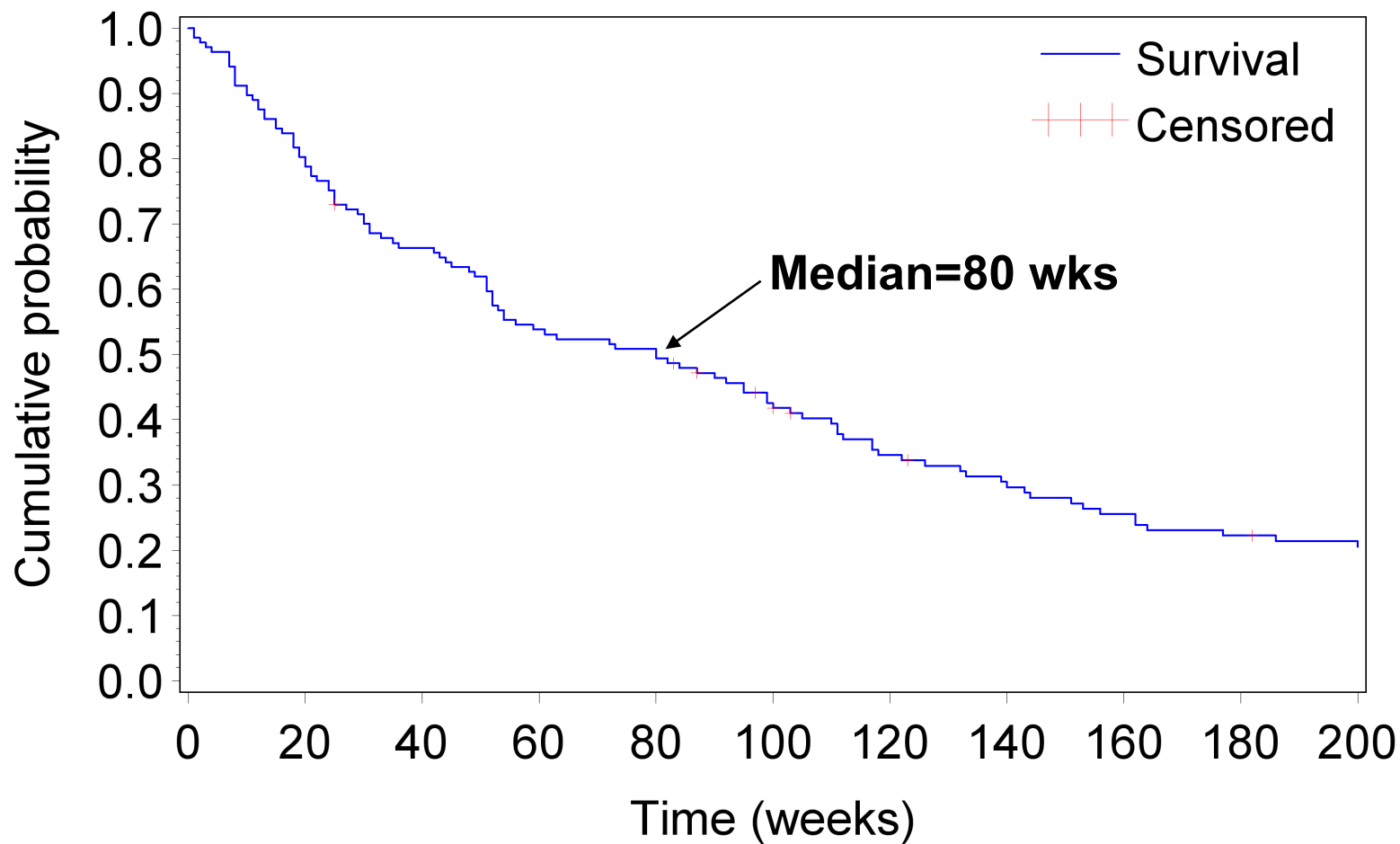
```
...
52 60 4 45 0 164 70 15 68 10 19 30
15 30 5 63 0 43 60 11 49 10 340 80
111 60 5 64 0 231 70 18 67 10 378 80
;
run;

*Minor edits;

Data lung;
length Therapy Cell $15.;
set VALung;
Therapy='Experimental';
If Cell='adeno' then Cell='Adenocarcinoma';
else If Cell='squamous' then Cell='Squamous';
else Cell='Other';
run;
```

* http://support.sas.com/documentation/cdl/en/statug/63033/HTML/default/viewer.htm#statug_lifetest_sect018.htm

Kaplan-Meier



Comparison vs Standard

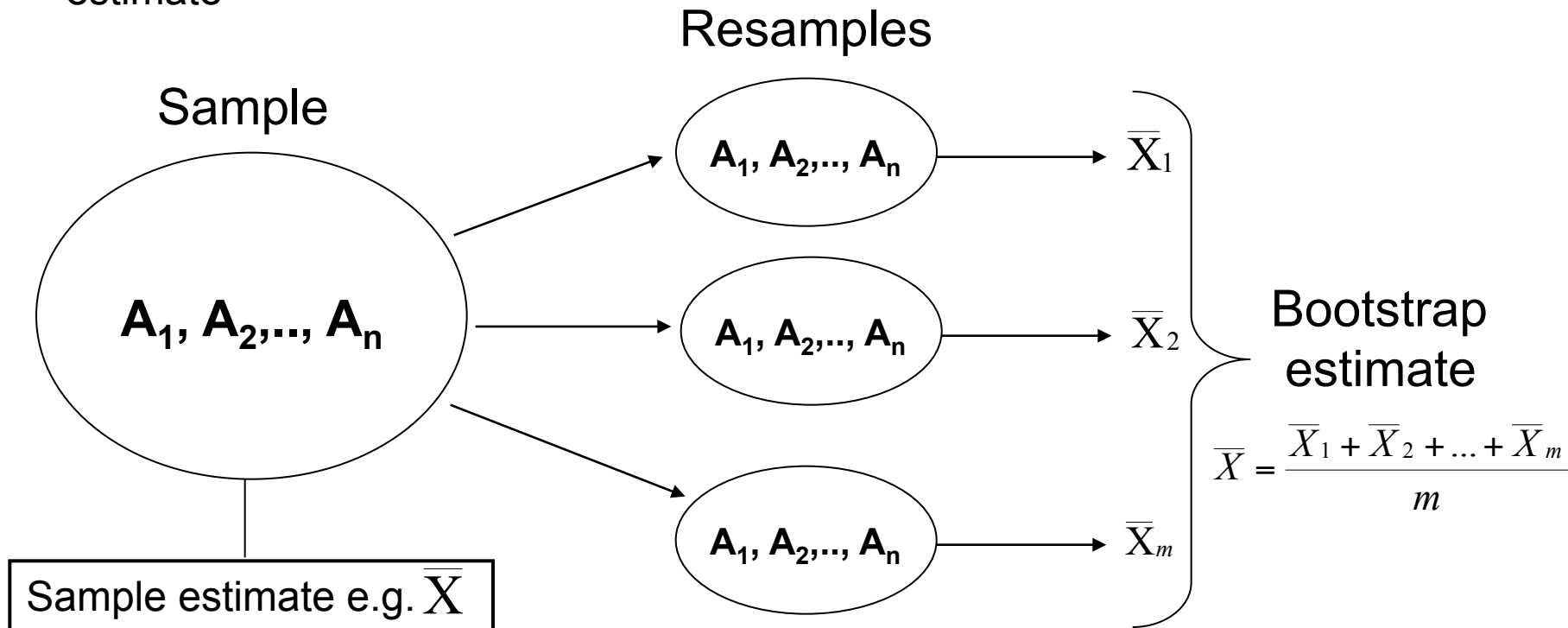
- Direct head-to-head is the most common way to compare
 - Validity is limited by differences in the distribution of prognostic baseline characteristics
- Imagine standard treatment values according literature
 - Median OS is 70 weeks
 - Distribution of the most relevant covariate “cell type”, was 40% squamous, 10% adenocarcinoma and 50% others
- A frequency table was then created to find distribution imbalances that might have an effect on the median OS estimate

Frequency Table

Cell type	Hypothetical Scenario N (%)	Literature (%)
Adenocarcinoma	27 (19.7%)	10%
Squamous	35 (25.5%)	40%
Others	75 (54.7%)	50%

Bootstrapping

- Introduced by Professor Bradley Efron, multiple resampling with replacement of a collected sample to study uncertainty in the statistical estimate



Fitting our Data

- Trial data will be replicated using control distribution
- 10,000 resamplings (n=137):
 - “squamous” subsets size 55 (40% literature)
 - “adenocarcinoma” subsets size 14 (10% literature)
 - “others” subsets size 68 (50% literature)

```
Data SampleSizes;  
INPUT @1 Cell $15. @16 SampleSize @19 Proportion;  
DATALINES;  
Adenocarcinoma 14 0.10  
Other 68 0.50  
Squamous 55 0.40  
;  
run;
```

```
proc surveyselect data=lung method=urs n=SampleSizes  
out=boots rep=10000 OUTHITS;  
strata Cell;  
id SurvTime censor Cell;  
run;
```

- Here resamplings contains 40/10/50% but if some uncertainty is added then review whether resamplings are in the range

Median OS (Bootstrap)

- The next step was to calculate the median OS for every sample and the obtained bootstrap estimate as the mean of the medians

```
PROC LIFETEST DATA=boots OUTSURV = boot2;  
ods output Quartiles=Quartiles;  
time SurvTime*censor(1);  
by Replicate;  
run;
```

```
PROC TABULATE DATA=Quartiles format=comma5.0  
missing;  
var Estimate;  
table Estimate*(n mean p5 p95)/box=' '  
condense indent=1;  
title 'Bootstrap median OS estimation';  
where Percent=50;  
RUN;
```

N	Point estimate	p5%	p95%
10000	90 weeks	59 weeks	111 weeks

Survival Plots

- Whole bootstrap survival curve plot to check the whole data (not only the particular case of the median estimate)

Control estimate data

```
Proc sort data=boot2; by SurvTime;run;
Proc means data=boot2 mean;
var survival;
by SurvTime;
output out=boot3 mean=mean;
run;
```

```
Data boot3b;
retain mean_b 1;
set boot3;
/*To avoid increasing steps*/
If mean<mean_b then mean_b=mean;
run;
```

```
Proc format;
value group
0='Bootstrap'
1='Original';
run;
```

```
Data boot4;
set boot3b;
group=0;
format group group.;
keep group SurvTime mean_b;
rename mean_b=survival;
run;
```

Real data

```
Data lung3;
set lung2;
group=1;
format group group.;
keep group SurvTime survival;
run;
```

```
Data plotdata;
set boot4 lung3;
run;
```

```
*Plot of both data;
```

```
AXIS1 COLOR=BLACK WIDTH=3
LABEL=(FONT='Arial' HEIGHT=20pt
JUSTIFY=
```

```
CENTER
'Time (weeks)' )
```

```
ORDER= 0 TO 200 BY 20
```

```
MAJOR=(COLOR=BLACK NUMBER=21)
```

```
MINOR=(NUMBER=1);
```

```
AXIS2 COLOR=BLACK WIDTH=3
```

```
LABEL=(FONT='Arial' HEIGHT=20pt
```

```
JUSTIFY=
```

```
CENTER
ANGLE=90 'Cumulative probability')
```

```
ORDER= 0 TO 1 BY 0.1;
```

```
symbol1 interpol=join i=stepj ci=red cv=blue
l=1 width=3;
```

```
symbol2 interpol=join i=stepj ci=blue cv=blue
l=1 width=3;
```

```
legend1 label=none
```

```
value=(h=2.1 j=1)
```

```
shape=symbol(5,3)
```

```
across=1
```

```
position=(TOP RIGHT INSIDE)
```

```
mode=share
```

```
offset=(-1 pct,-1 pct)
```

```
;
```

```
proc gplot data=plotdata;
```

```
plot survival*SurvTime=group / vaxis=axis2
```

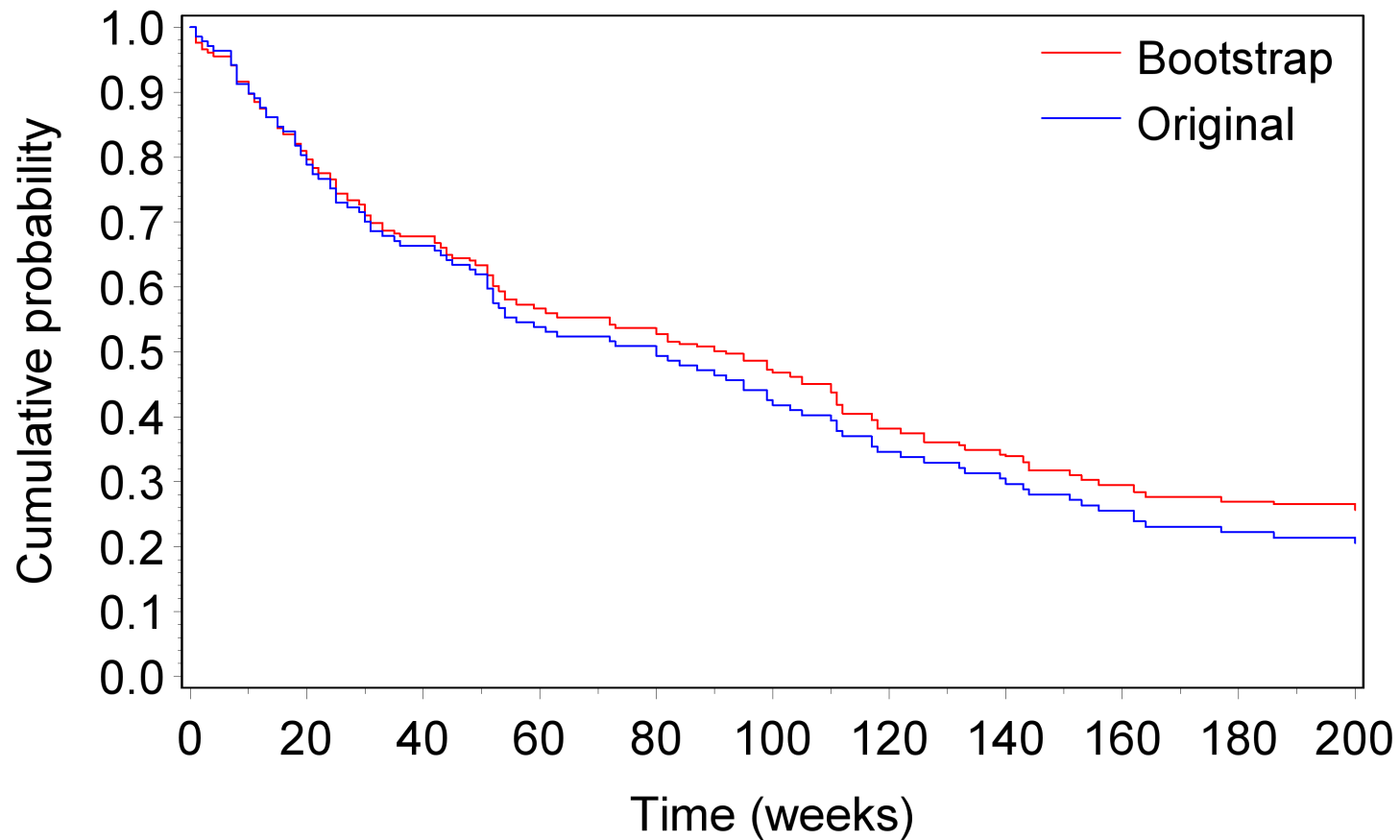
```
haxis=axis1 legend=legend1;
```

```
run;
```

```
RUN;
```

Survival Plots

- Whole bootstrap survival curve plot to check the whole data (not only the particular case of the median estimate)



Process Summary

- Conventional Kaplan-Meier estimate
- Control treatment estimate
 - i.e. bibliographic search
- Baseline covariate frequencies for trial and control
- Bootstrap replications applying control frequencies
 - Review of the distribution
- Proc lifetest of all bootstrap replications
- Median point bootstrap estimate
- Whole survival curve for original and bootstrap

Conclusion

- Comparison of results from different studies is often hampered by the different distribution of prognostic baseline characteristics
- SAS® program to obtain a bootstrap estimation balancing it with the historical distribution was shown
- The code might help to obtain more accurate comparison estimate

Questions

