MODULE 12: INTRODUCTION TO SURVIVAL ANALYSIS

Summer Institute in Statistics for Clinical Research
University of Washington
July, 2017

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OVERVIEW

• Session 1
  – Introductory examples
  – The survival function
  – Survival Distributions
  – Mean and Median survival time

• Session 2
  – Censored data
  – Risk sets
  – Censoring Assumptions
  – Kaplan-Meier Estimator and CI
  – Median and CI

• Session 3
  – Two-group comparisons: logrank test
  – Trend and heterogeneity tests for more than two groups

• Session 4
  – Introduction to Cox regression
OVERVIEW – MODULE 16

Module 16: Survival analysis in Clinical Trials

• Quick review of basics
• Estimating survival after Cox model fit
• More two-sample tests
  – Weighted logrank
  – Additional tests based on functionals and metrics
• Adjustment, precision and post-randomization variables
• Power
• Choice of outcome
• Information accrual in sequential monitoring

OVERVIEW – MODULE 20

Module 20: Survival analysis for Observational Data

• More complicated Cox models
  – Adjustment
  – Interaction
• Hazard function Estimation
• Competing Risks: Cox and Fine-Gray models
• Choice of time variable
• Left Entry/Truncation
• Immortal time bias
• Index event bias
• Time-dependent covariates
SESSION 1:
SURVIVAL DATA: EXAMPLES

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PRELIMINARIES

• No prior knowledge of survival analysis techniques assumed
• Familiarity with standard one- and two-sample statistical methods (estimation and testing) is assumed
• Emphasis on application rather than mathematical details
• Examples
SECTIONS/BREAKS

• 8:30 – 10:00
  – Break until 10:30
• 10:30 – 12:00
  – Break until 1:30
• 1:30 – 3:00
  – Break until 3:30
• 3:30 – 5:00

WHAT IS SURVIVAL ANALYSIS ABOUT?

• Studies the occurrence of an event over time
  – Time from randomization to death (cancer RCT)
  – Time from acceptance into a heart transplant program to death
  – Time from randomization to diagnosis of Alzheimer’s Disease in a prevention trial
  – Time from randomization to ovarian cancer death in a randomized screening trial
  – Time from birth to removal of supplementary oxygen therapy
  – Time from first VTE diagnosis to recurrent VTE
WHAT IS SURVIVAL ANALYSIS ABOUT?

• Explores factors that are thought to influence the chance that the event occurs
  – Treatment
  – Age
  – Gender
  – Body Mass Index
  – Diet

  – Etc.
EXAMPLE 1

- Levamisole and Fluorouracil for adjuvant therapy of resected colon carcinoma
  Moertel et al., 1990, 1995
- 1296 patients, enrolled 1 – 5 weeks after surgery
- Stage B_2 or C
- 3 unblinded treatment groups in stage C (2:1:1 ratio)
  - Observation only
  - Levamisole (oral, 1yr)
  - Levamisole (oral, 1yr) + fluorouracil (intravenous 1yr)


EXAMPLE 1

- Randomization
  - Dynamic method based on accrued:
  - For B_2, extent of invasion, time since surgery
  - For C, extent of invasion, time since surgery, number of lymph nodes involved
EXAMPLE 1

- Statistical analysis
  - Survival primary outcome (recurrence secondary)
  - Kaplan-Meier survival curves
  - Log-rank statistic
  - Cox proportional-hazards model for all multivariable analysis
  - Backward regression, maximal partial-likelihood estimate statistic
  - O’Brien-Fleming boundary for sequential monitoring; stopped early for stage C

Figure 1: Recurrence-free interval according to treatment arm. Patients who died without recurrence have been censored. 5-FU = fluorouracil.
EXAMPLE 1

• **Results** (stage C) after 2nd interim analysis
  • Fluorouracil + Levamisole reduced the
    – Recurrence rate by 41% (95% CI 23% - 54%) (p<0.0001)
    – Death rate by 33% (95% CI 10% - 50%) (p<0.006)
  • Levamisole reduced the
    – Recurrence rate by 2%
    – Death rate by 6%
• Toxicity was mild (with few exceptions)
• Patient compliance excellent

EXAMPLE 1

• R survival package data “colon”
  – 929 eligible stage C patients (971 randomized – 42 ineligible)
  – Treatment groups (rx)
  – Sex, age
  – Obstruction of colon by tumor (obstruct)
  – Perforation of colon (perfor)
  – Adherence to nearby organs (adhere)
  – Number of lymph nodes with detectable cancer (nodes)
  – Days until event or censoring (time)
  – Censoring status (status)
EXAMPLE 1

- Multivariable analysis:
  - Proportional hazards model
  - “we kept the variable of treatment in the model and used backward regression for other covariates”
  - Other covariates (P < 0.01)
    - Depth of primary tumor invasion,
    - Invasion of adjacent structures
    - Regional implants
    - Number of metastatic lymph nodes
    - Histological differentiation
    - Preoperative carcinoembryonic antigen level

EXAMPLE 1

- Multivariable results: “After correction for the influence of prognostic factors through the use of a proportional hazards model, patients receiving fluorouracil plus levamisole were again found to have a significant survival advantage when compared with patients assigned to observation only; they had a 33% reduction in mortality rate (95% CI, 16% to 47%; P = 0.0007). Therapy with levamisole alone showed essentially no effect (6% reduction in death rate; P = 0.57.”

EXAMPLE 2 – ALZHEIMER’S

- Petersen et al. 2005, NEJM
- Subjects with amnestic subtype of mild cognitive impairment
- Adaptive randomization based on MMSE score, age, Apo ε4 genotype
- Three arms: Vitamin E, Donepezil, and Placebo
- Primary outcome: Time from randomization to possible or probable AD diagnosis
- Length of double-blind treatment: 3 years


EXAMPLE 2 – ALZHEIMER’S

- Primary analysis: Cox regression adjusted for randomization influencing variables MMSE score, age and Apo E genotype
- 769 enrolled: 253 donepezil, 257 vitamin E, 259 placebo
- 230 dropped out: 92 donepezil, 74 vitamin E, 66 placebo
  – Treatment related toxicity: GI complaints, muscle aches, insomnia
- Dropout was observed to be related to MMSE score
EXAMPLE 2 – ALZHEIMER’S

• 212 developed possible or probable AD
• “There were no significant differences ... during the three years of treatment”
• Vitamin E vs Placebo
  – Hazard Ratio 1.02 (95% CI, 0.74, 1.41), p-value 0.91
• Donepezil vs Placebo
  – Hazard Ratio 0.80 (95% CI, 0.57, 1.13), p-value 0.42

EXAMPLE 2 – ALZHEIMER’S

• Prespecified analyses
• At 6 months intervals
  – Donepezil vs Placebo significantly reduced likelihood of progression to AD during the first 12 months (p-value 0.04)
  – Finding supported by secondary outcome measures
  – Subgroup ≥ 1 apolipoprotein E ε4 alleles significantly reduced likelihood of progression to AD over 3 years
  – Vitamin E vs Placebo: no significant differences
  – Vitamin E vs Placebo: also no significance for above subgroup
• Simulations assuming informative treatment-related dropout did not change primary conclusions
EXAMPLE 2 – RESULTS

• Overall and at 6 and 12 months

![Graphs showing progression to AD over months for different groups.]

EXAMPLE 2 – RESULTS

• APOE ε4 results

![Graphs showing progression to AD over months for APOE ε4 and non-ε4 groups.]

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EDITORIAL

• “long-awaited results”
• Donepezil standard therapy for AD
• “Implications .... Enormous”
  – Clear-cut negative findings for Vitamin E
  – Especially noteworthy
  – Despite dearth of evidence of its efficacy

  – Findings for donepezil “much less clear”
  – “not quite as disappointing”

EDITORIAL COMMENTS

• “rate of progression ... somewhat lower in the treatment group during the first year of the study”
• “by two years, even this small effect had worn off”
• Possible explanation: “Reduced statistical power later in the study as the number of subjects at risk declined owing to death, withdrawal and development of AD
• Secondary analyses suggest... benefits wore off
EXAMPLE 2 – RESULTS

• Interesting steps.....

SCREENING TRIAL

• 202,546 women 50-72 years of age, England, Wales, Northern Ireland
• Randomized to one of three arms in 1:1:2 ratio between June 1, 2001 and Oct 21, 2005.
  – Annual multimodal screening (serun CA 125 + algorithm)
  – Annual transvaginal ultrasound
  – No screening
• Screening ended Dec 31, 2011.
• Not blinded
• Primary outcome: death from ovarian cancer (by end of 2014)

OVARIAN CANCER SCREENING TRIAL

- Primary analysis: Cox regression (proportional hazards)
  - MMS vs. no screening: Mortality reduction = 
    \[(1 - HR)100 = 15\%\ (95\% CI: -1\% - 33\%)\ P = .10\]
  - USS vs. no screening: Mortality reduction = 
    \[(1 - HR)100 = 11\%\ (95\% CI: -7\% - 27\%)\ P = .21\]
OVARIAN CANCER SCREENING TRIAL

- Why the delayed difference?

OVARIAN CANCER SCREENING TRIAL

- Secondary analyses, excluding prevalent cases:
- Post-hoc Weighted* logrank test:
  - MMS mortality reduction = 22% (3-38%) P = .023
  - USS mortality reduction = 20% (0 – 35%) P = .049

* by pooled cumulative mortality
“COUNTER” EXAMPLE

• Resuscitation Outcomes Consortium
  – Out-of-hospital cardiac arrest
  – Traumatic injury
• Prehospital interventions
• Exception from informed consent
• 10 Regional Centers
  – 7 US
  – 3 Canada

• Times
  – Event (cardiac arrest, traumatic injury)
  – 911 call
  – Arrival of EMS
  – Treatment start
  – Potential outcomes
    • Return of spontaneous circulation (Cardiac arrest)
    • ED admission
    • Survival to hospital discharge
    • Neurologically intact survival
    • 28-day survival
    • 6-month neurological outcomes
“COUNTER” EXAMPLE

- Time of injury/cardiac arrest (ordinarily unknown)
- 911 call
- Cardiac arrest: Many deaths before admission to hospital
- Trauma: Many deaths within the first 24 – 48 hours

SURVIVAL DATA AND FUNCTION

- Original applications in biometry were to survival times in cancer clinical trials
- Many other applications in biometry: eg. disease onset ages
- Interest centers not only on average or median survival time but also on probability of surviving beyond 2 years, 5 years, 10 years, etc.
- Best described with the entire survival function $S(t)$.
  - For $T =$ a subject’s survival time, $S(t) = P[T > t]$.
  - Characterizes the entire distribution of survival times $T$.
  - Gives useful information for each $t$. 
SURVIVAL FUNCTION

Survival Function

\[ S(t) = \Pr[T > t] \]

SURVIVAL DISTRIBUTION

- Continuous probability distribution of times \( T \)
- Only non-negative \( T \)'s are possible: \( \Pr(T<0)=0 \)
- Density function \[ f(t) = \lim_{\Delta t \to 0} \frac{1}{\Delta t} \Pr(t \leq T < t + \Delta t) \]
- Area under the \( f(t) \) curve between two points is the probability \( T \) is between the two points.
DENSITY AND SURVIVAL FUNCTIONS

Density Function

Survival Function

MEDIAN SURVIVAL TIME

Median Survival Time

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MEDIAN SURVIVAL TIME

Density Function

ILLUSTRATIVE DATA

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SURVIVAL FUNCTION ESTIMATE

- Nonparametric Estimate: reduce estimate by $1/n$ every time there is an event (death): Empirical survival function estimate

![Survival Function Estimate](image)

MEDIAN ESTIMATE

By convention: median is earliest time where survival estimate $\leq 0.5$
OTHER WAYS TO DESCRIBE A SURVIVAL DISTRIBUTION

• So far we have looked at the density function and survival function $S(t)$.
• Also of interest: “hazard” function $\lambda(t)$

$$\lambda(t) = \lim_{\Delta t \to 0} \frac{1}{\Delta t} \Pr[t \leq T < t + \Delta t | T \geq t]$$

• Instantaneous rate at which death occurs at $t$ in those who are alive at $t$
• Examples:
  – Age-specific death rate
  – Age-specific disease incidence rate

HAZARD FUNCTION FOR HUMANS

[Graph of Human Mortality]

$\lambda(t)$ vs. age in years
EQUIVALENT CHARACTERIZATIONS

- Any one of the density function \( f(t) \), the survival function \( S(t) \) or the hazard function \( \lambda(t) \) is enough to determine the survival distribution.

- They are each functions of each other:
  
  \[ S(t) = \int_t^\infty f(s)ds = e^{-\int_0^t \lambda(s)ds} \]
  
  \[ f(t) = -\frac{d}{dt}S(t) = \lambda(t)e^{-\int_0^t \lambda(s)ds} \]
  
  \[ \lambda(t) = \frac{f(t)}{S(t)} \]
EQUIVALENT CHARACTERIZATIONS

Hazard Function

Survival Function

Density Function

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