MODULE 16: SURVIVAL ANALYSIS FOR CLINICAL TRIALS

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

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OVERVIEW

- Session 1
  - Review basics
  - Cox model for adjustment and interaction
  - Estimating baseline hazards and survival
- Session 2
  - Weighted logrank tests
- Session 3
  - Other two-sample tests based on functionals and metrics
- Session 4
  - Choice of outcome variable
  - Power and sample size
  - Information accrual under sequential monitoring
  - Time-dependent covariates

SESSION 1:
REVIEW, COX MODEL FOR ADJUSTMENT AND INTERACTION, AND ESTIMATION OF BASELINE HAZARDS AND SURVIVAL

Module 16: Survival Analysis in Clincal Trials
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OUTLINE

- Review of censored data, KM estimation, logrank test and Cox model basics
- Covariate adjustment in Cox model
- Precision in Cox model
- Interaction (Effect Modification) in Cox Model
- Stratification adjustment in Cox model
- Estimation of baseline hazards and survival based on Cox model fit

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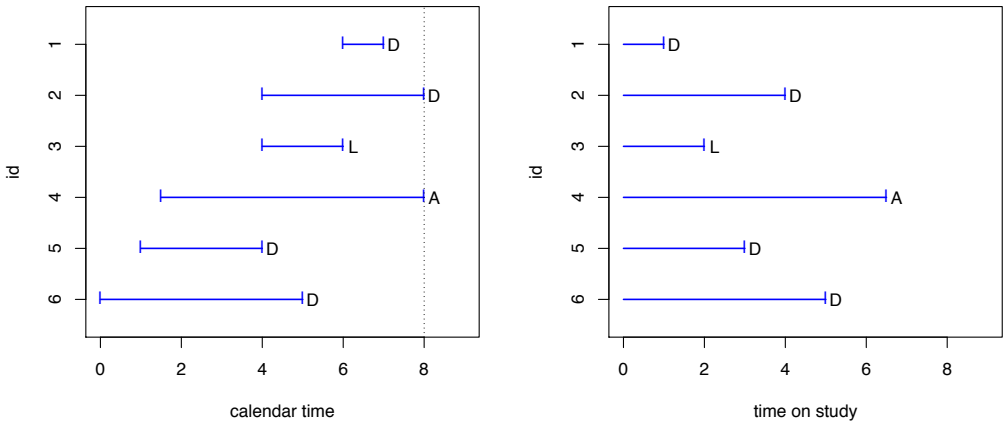
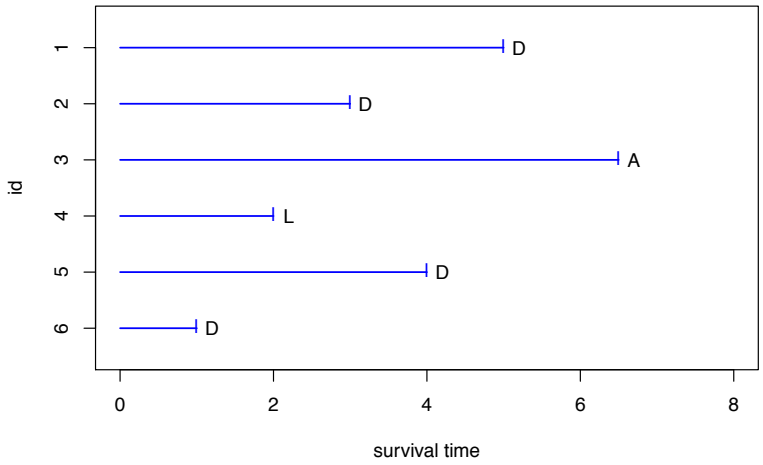
TIME IN A CLINICAL TRIAL



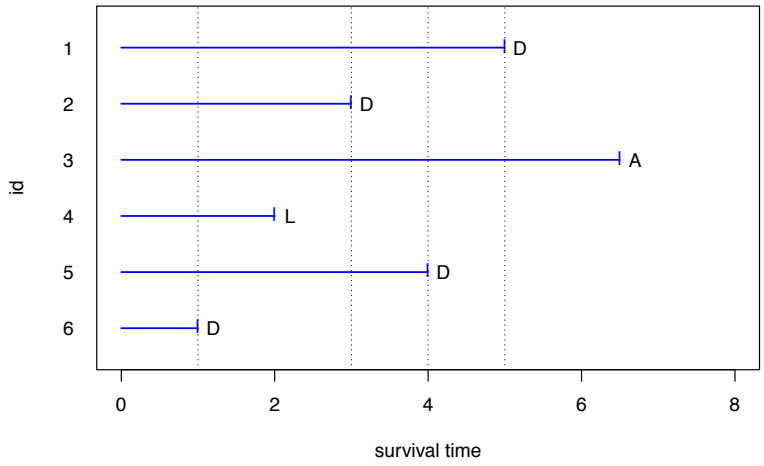
CENSORED DATA



id	Y	δ
1	5	1
2	3	1
3	6.5	0
4	2	0
5	4	1
6	1	1

"Censored" observations give some information about their survival time.

RISK SETS

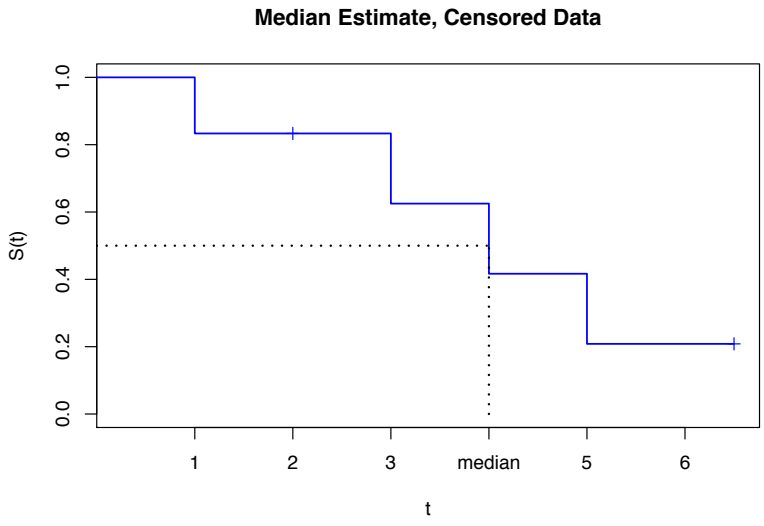


R_1 $\{1,2,3,4,5,6\}$ R_2 $\{1,2,3,5\}$ R_3 $\{1,3,5\}$ R_4 $\{1,3\}$

CENSORED DATA ASSUMPTION

- Important assumption: subjects who are censored at time t are at the same risk of dying at t as those at risk but not censored at time t.

MEDIAN & SURVIVAL CENSORED DATA



EQUIVALENT CHARACTERIZATIONS

- Any one of the density function(f(t)), the survival function(S(t)) or the hazard function(λ(t)) is enough to determine the survival distribution.
- They are each functions of each other:

$$S(t) = \int_t^\infty f(s)ds = e^{-\int_0^t \lambda(s)ds}$$

$$f(t) = -\frac{d}{dt}S(t) = \lambda(t)e^{-\int_0^t \lambda(s)ds}$$

$$\lambda(t) = \frac{f(t)}{S(t)}$$

LOGRANK TEST

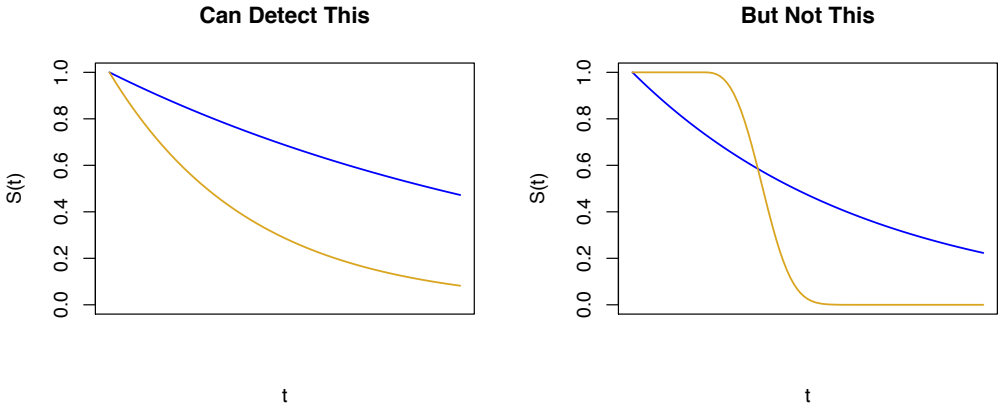
- The test is based on a 2x2 table of group by current status at each observed failure time (ie for each risk set)
- $T_{(j)}$, $j=1,\ldots m$, as shown in the Table below.

Event/Group	1	2	Total
Die	$d_{1(j)}$	$d_{2(j)}$	$D_{(j)}$
Survive	$n_{1(j)}$-$d_{1(j)}$= $s_{1(j)}$	$n_{2(j)}$-$d_{2(j)}$ = $s_{2(j)}$	$N_{(j)}$-$D_{(j)}$ = $S_{(j)}$
At Risk	$n_{1(j)}$	$n_{2(j)}$	$N_{(j)}$

LOGRANK TEST

- Detects consistent differences between survival curves over time.
- Best power when:
  - H_0: $S_1(t) = S_2(t)$ for all t vs H_A: $S_1(t) = [S_2(t)]^c$, or
  - H_0: $\lambda_1(t) = \lambda_2(t)$ for all t vs H_A: $\lambda_1(t) = c\,\lambda_2(t)$
- Good power whenever survival curve difference is in consistent direction

LOGRANK TEST



Other tests (generalized Wilcoxon and others) can give more weight to early or late differences.

COX REGRESSION MODEL

- Usually written in terms of the hazard function
- As a function of independent variables $x_1, x_2, \ldots x_k$,

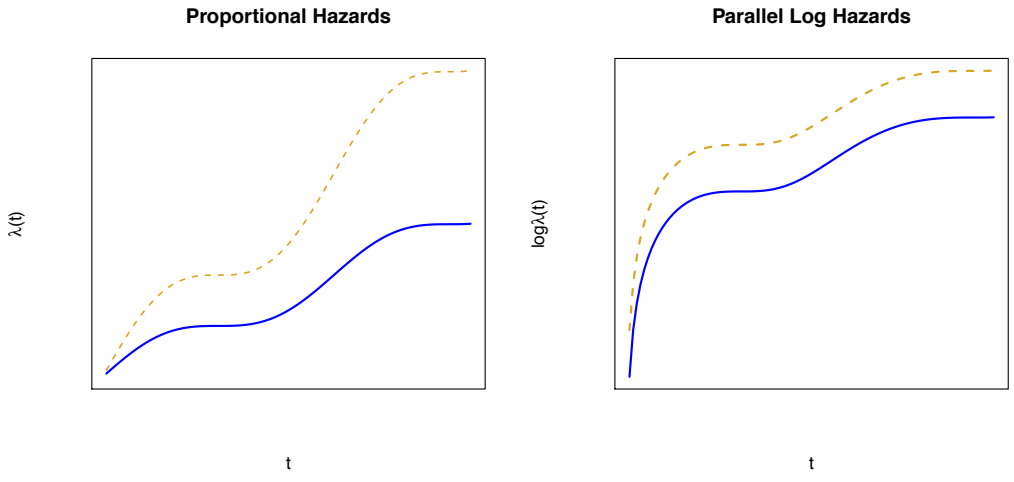
$$\lambda(t) = \lambda_0(t)e^{\beta_1 x_1 + \cdots + \beta_k x_k}$$

↑ relative risk / hazard ratio

$$\log\lambda(t) = \log\lambda_0(t) + \beta_1 x_1 + \cdots + \beta_k x_k$$

↑ intercept

EXAMPLE



RELATIONSHIP TO SURVIVAL FUNCTION

Single binary x:

$$x = \begin{cases} 1 & \text{Test treatment} \\ 0 & \text{Standard treatment} \end{cases}$$

$$\lambda(t) = \lambda_0(t)e^{\beta x} \implies S(t) = [S_0(t)]^{e^{\beta x}}$$

In terms of $S_0(t)$:

$S(t)$ for $x = 1$: $\quad [S_0(t)]^{e^{\beta \cdot 1}} = [S_0(t)]^{e^{\beta}}$

$S(t)$ for $x = 0$: $\quad [S_0(t)]^{e^{\beta \cdot 0}} = [S_0(t)]^{1} = S_0(t)$

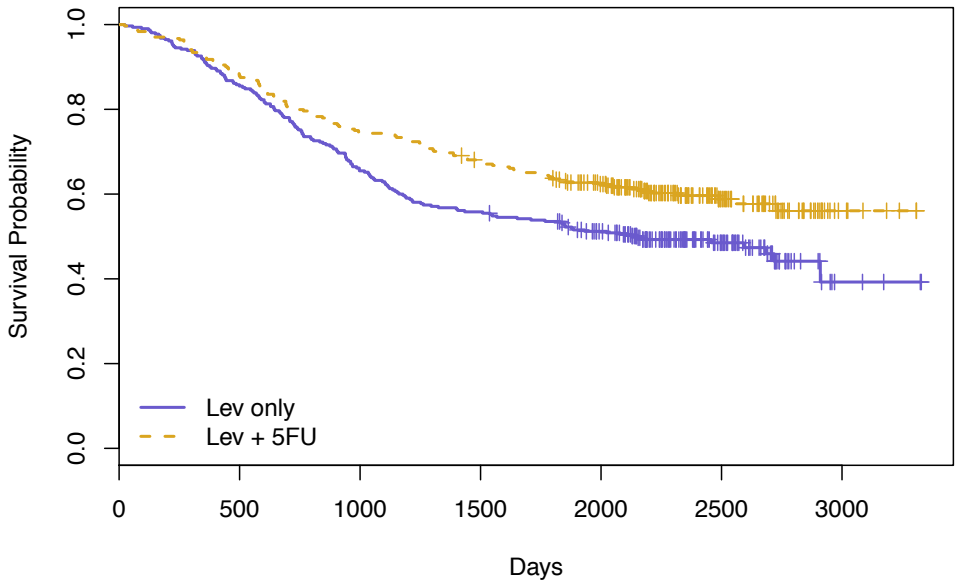
CONFOUNDING/PRECISION

- Because of randomization not truly a problem, but imbalance may be an issue , especially in small trials.
- As in linear regression, regression models for censored survival data allow group comparisons among subjects with similar values of adjustment or "precision" variables (more later).
- Fairer and more powerful comparison as long as adjustment variables are not the result of treatment.

COLON CANCER EXAMPLE

- Levamisole and Fluorouracil for adjuvant therapy of resected colon carcinoma
  - Moertel et al. *New England Journal of Medicine*. 1990;322(6): 352–358.
  - Moertel et al. *Annals of internal medicine*. 1995;122(5):321–326.
- 1296 patients
- Stage B_2 or C
- 3 unblinded treatment groups
  - Observation only
  - Levamisole (oral, 1yr)
  - Levamisole (oral, 1yr) + 5 fluorouracil (intravenous 1yr)
- Will examine two treatment arms in Stage C patients only

COLON CANCER EXAMPLE



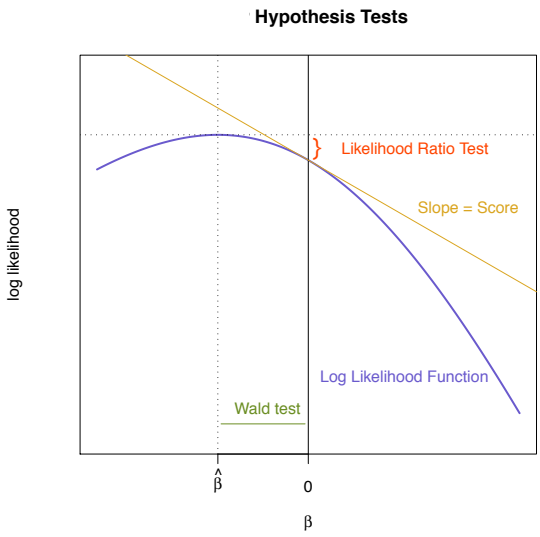
COLON CANCER EXAMPLE

Variable	n	Deaths	Hazard ratio	CI	P-value
Levamisole Only	310	161	1.0 (reference)	--	--
Levamisole + 5FU	304	123	0.71	(0.56, 0.90)	.004

Q: Which group has better survival?

A:

LIKELIHOODS AND TESTS



TEST COMPARISON

Test	Statistic	P-value
Wald's	8.13	.004
Score	8.21	.004
Likelihood Ratio	8.21	.004

Two-sided tests

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STRATIFIED RANDOMIZATION

- For strong predictors: concern about possible randomization imbalance
  - Clinic or center
  - Stage of disease
  - Sex
  - Age
- Adjust for stratification variables in analysis
  - More powerful if predictors are strong
  - Same conditioning as the sampling

ADJUSTMENT AND PRECISION

- In Cox regression, addition of variables to a model that are associated only with the outcome can improve power.
- There is little effect on the coefficient estimate for other variables (eg treatment) or their standard errors, except when the association between outcome and the added variable is very strong.
- When there is an effect of adding a predictive variable, this is what happens to inference for the treatment variable or other variable of interest:
  - The standard error of its coefficient increases
  - The estimate of the coefficient moves farther from zero
  - The test of whether the coefficient is zero has more power.

ANALYSES

- Primary analysis: If randomization was blocked on prognostic variables, adjust for them.
  - Depth of invasion (extent)
  - Interval since surgery
  - Number of positive nodes (≥ 4)

- Secondary analysis: Adjust for additional prognostic variables: Observed at time of randomization and therefore not affected by treatment
  - Obstruction
  - Histologic differentiation

PROGNOSTIC VARIABLE ADJUSTMENT

$$x_1 = \begin{cases} 1 & \text{moderate differentiation} \\ 0 & \text{otherwise} \end{cases} \qquad x_2 = \begin{cases} 1 & \text{poor differentiation} \\ 0 & \text{otherwise} \end{cases}$$

$$x_3 = \begin{cases} 1 & \text{tumor obstructed bowel} \\ 0 & \text{otherwise} \end{cases} \qquad x_4 = \begin{cases} 1 & \text{4+ nodes positive} \\ 0 & \text{otherwise} \end{cases}$$

$$x_5 = \begin{cases} 1 & \text{extent to muscle} \\ 0 & \text{otherwise} \end{cases} \qquad x_6 = \begin{cases} 1 & \text{extent to serosa} \\ 0 & \text{otherwise} \end{cases}$$

$$x_7 = \begin{cases} 1 & \text{extent to contiguous structures} \\ 0 & \text{otherwise} \end{cases} \qquad x_8 = \begin{cases} 1 & \text{Levamisole only} \\ 0 & \text{otherwise} \end{cases}$$

$$x_9 = \begin{cases} 1 & \text{Levamisole + 5FU} \\ 0 & \text{otherwise} \end{cases}$$

$$\lambda(t) = \lambda_0(t) e^{\beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_4 x_4 + \beta_5 x_5 + \beta_6 x_6 + \beta_7 x_7 + \beta_8 x_8 + \beta_9 x_9}$$

PROGNOSTIC VARIABLE ADJUSTMENT

$$\lambda(t) = \lambda_0(t)e^{\beta_1 x_1+\beta_2 x_2+\beta_3 x_3+\beta_4 x_4+\beta_5 x_5+\beta_6 x_6+\beta_7 x_7+\beta_8 x_8+\beta_9 x_9}$$

Interpretation of e^{β_8}:

"Relative risk (or hazard ratio) comparing Levamisole Only to Observation among those with the same values of prognostic variables".

Interpretation of e^{β_9}:

"Relative risk (or hazard ratio) comparing Levamisole + 5FU to Observation among those with the same values of prognostic variables".

PROGNOSTIC VARIABLE ADJUSTMENT

$$\lambda(t) = \lambda_0(t)e^{\beta_1 x_1+\beta_2 x_2+\beta_3 x_3+\beta_4 x_4+\beta_5 x_5+\beta_6 x_6+\beta_7 x_7+\beta_8 x_8+\beta_9 x_9}$$

Interpretation of $e^{\beta_9-\beta_8}$:

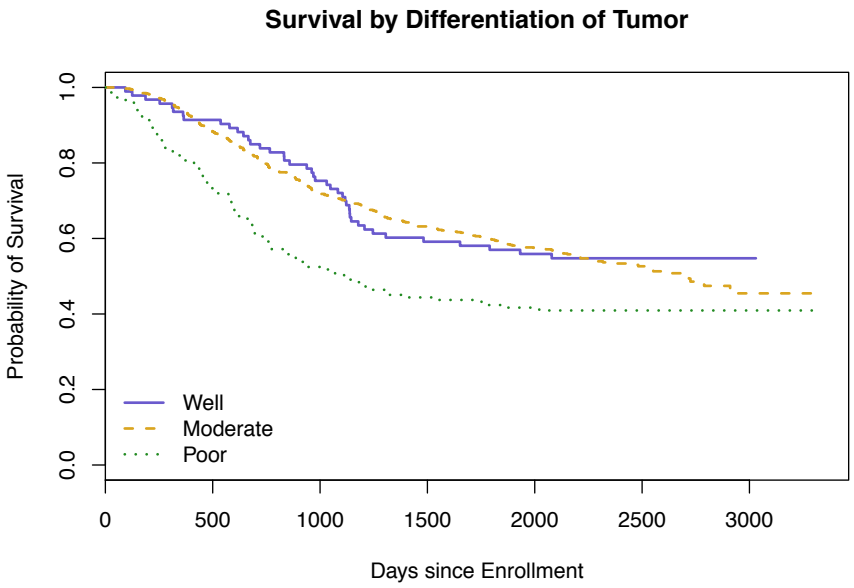
"Relative risk (or hazard ratio) comparing Levamisole + 5FU to Levamisole Only among those with the same values of prognostic variables".

$\lambda(t)$ for $x_1, \ldots, x_7$ and $x_8 = 0$ and $x_9 = 1$: $\lambda_0(t)e^{\beta_1 x_1+\cdots+\beta_7 x_7+\beta_8\cdot 0+\beta_9\cdot 1}$

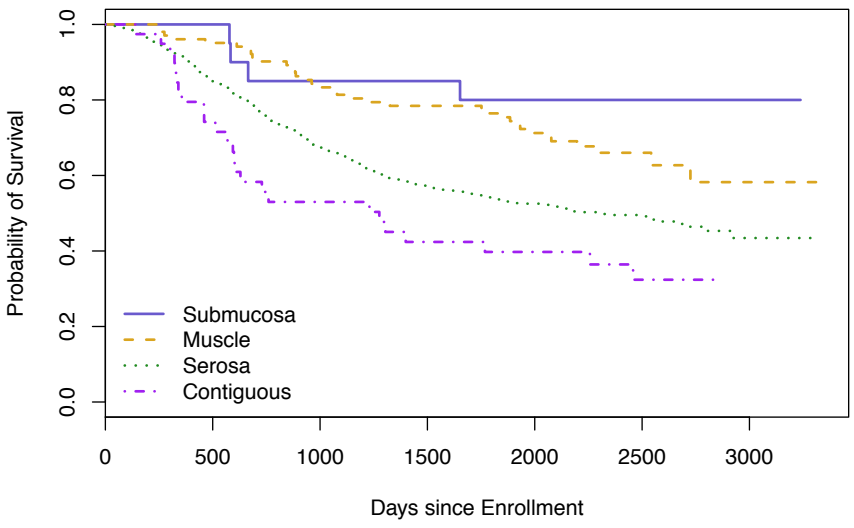
$\lambda(t)$ for $x_1, \ldots, x_7$ and $x_8 = 1$ and $x_9 = 0$: $\lambda_0(t)e^{\beta_1 x_1+\cdots+\beta_7 x_7+\beta_8\cdot 1+\beta_9\cdot 0}$

ratio: $e^{\beta_8(0-1)+\beta_9(1-0)} = e^{\beta_9-\beta_8}$

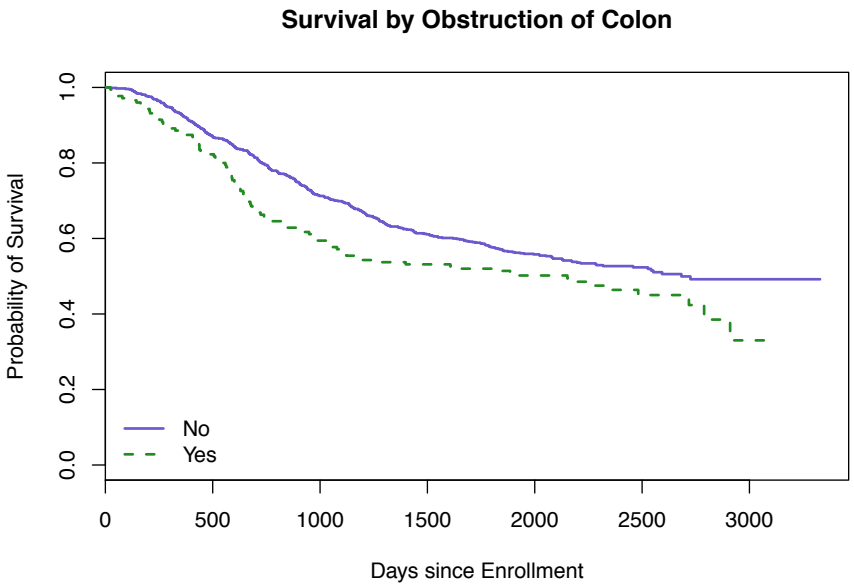
PROGNOSTIC VARIABLES



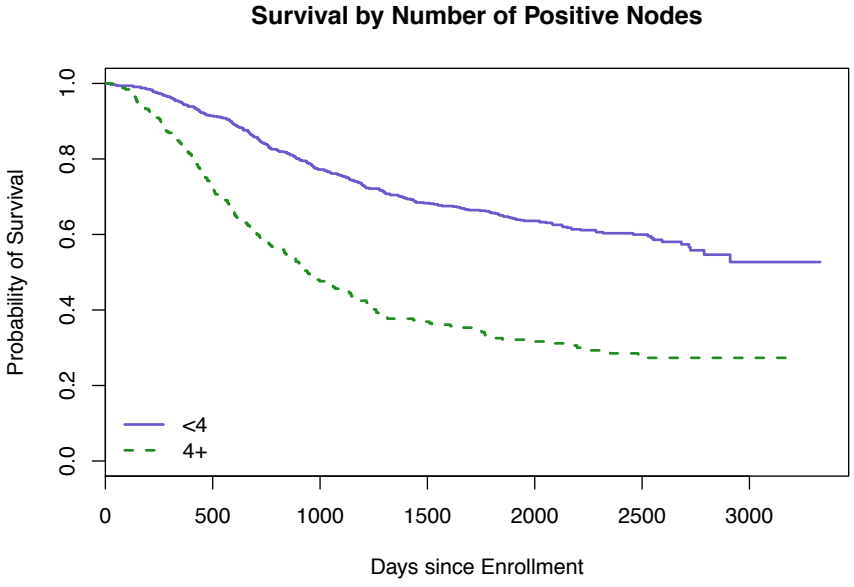
PROGNOSTIC VARIABLES



PROGNOSTIC VARIABLES



PROGNOSTIC VARIABLES



ADJUSTED

Group	Hazard Ratio	95% CI	P-value
Observation Only	1.0 (reference)	--	--
Levamisole Only	0.97	(0.78, 1.21)	0.79
Levamisole + 5FU	0.69	(0.54, 0.87)	0.002

Adjusted for tumor differentiation (well, moderate, poor), colon obstruction (yes, no), < 4 nodes positive, extent (submucosa, muscle, serosa, contiguous tissues)

ADJUSTMENT VARIABLES

Variable	Hazard Ratio	95% CI
Moderate Differentiation	0.94	(0.67, 1.29)
Poor Differentiation	1.38	(0.95, 2.00)
Obstructed bowel	1.30	(1.03, 1.63)
4+ nodes positive	2.45	(2.03, 2.98)
Extent: muscle	1.41	(0.50, 3.99)
Extent: serosa	2/29	(0.85, 6.16)
Extent: contiguous	3.34	(1.15, 9.65)

Usually not presented.

ANOTHER SIMPLER EXAMPLE

Two binary variables, x_1 and x_2 and 2 treatment groups:

$$x_1 = \begin{cases} 1 & \text{Levamisole + 5FU} \\ 0 & \text{Levamisole Only} \end{cases} \qquad x_2 = \begin{cases} 1 & \text{4+ Nodes Positive} \\ 0 & \text{<4 Nodes Positive} \end{cases}$$

$$\lambda(t) = \lambda_0(t)e^{\beta_1 x_1 + \beta_2 x_2}$$

Interpretation of e^{β_1}:

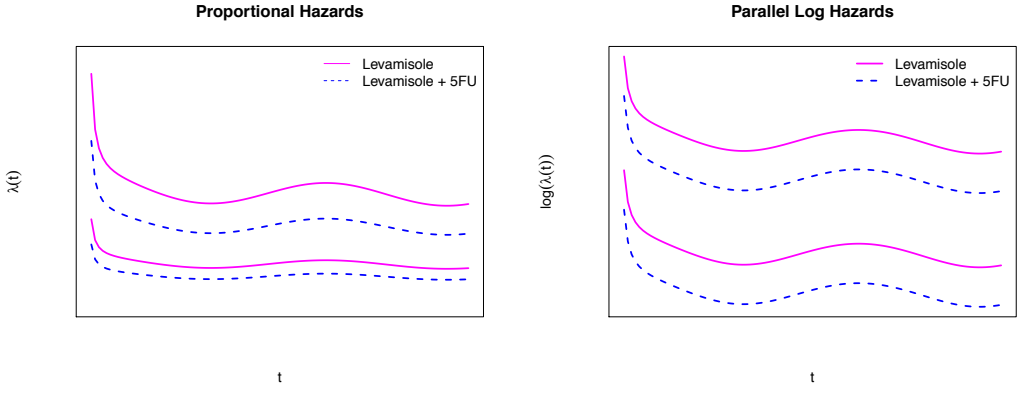
"Relative risk (or hazard ratio) comparing Levamisole + 5FU to Levamisole Only among those with similar numbers of positive nodes".

$\lambda(t)$ for $x_1 = 1$ and x_2: $\lambda_0(t)e^{\beta_1 \cdot 1 + \beta_2 x_2}$

$\lambda(t)$ for $x_1 = 0$ and x_2: $\lambda_0(t)e^{\beta_1 \cdot 0 + \beta_2 x_2}$

ratio: $e^{\beta_1(1-0)+\beta_2(x_2-x_2)} = e^{\beta_1}$

HEURISTIC HAZARDS

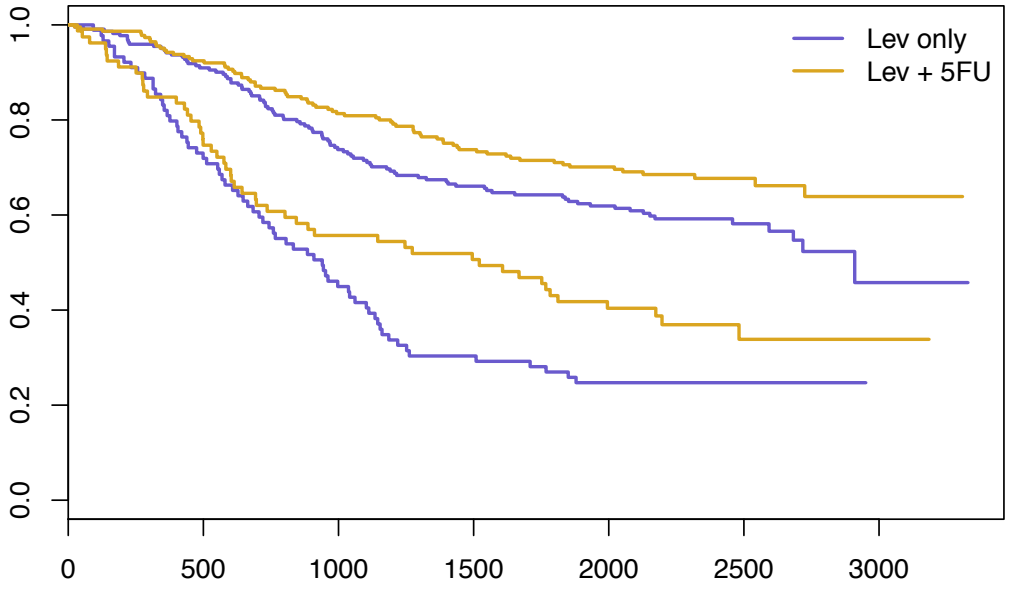


SIMPLER MODEL

Variable	Hazard ratio	95% CI	P-value
Levamisole + FU	0.71	(0.56, 0.90)	0.005
4+ nodes positive	2.67	(2.10, 3.38)	< .0001

Often, second row would not be given, and group sample sizes and numbers of deaths would be presented

COLON CANCER TRIAL DATA



RESULTS

"There was strong evidence that adjuvant treatment with 5FU + Levamisole improves survival in stage C colon cancer patients compared to Levamisole alone. After adjustment for number of positive nodes (<4, 4+) the hazard ratio comparing 5FU + Levamisole to Levamisole was 0.71, (95% CI 0.56 - 0.90, P = .004)."

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MORE SECONDARY ANALYSES

- Often interested in examining a small number of subgroups to determine subjects especially benefitted by treatment.
- Should be specified in advance!
- Should be few in number.
- Test results are usually corrected for multiple comparisons.
- Should test for interaction, not just notice that the estimated hazard ratios look different.

INTERACTION

Two binary variables, x_1 and x_2 with interaction:

$$x_1 = \begin{cases} 1 & \text{5FU + Levamisole} \\ 0 & \text{Levamisole alone} \end{cases} \qquad x_2 = \begin{cases} 1 & \text{4+ nodes positive} \\ 0 & \text{<4 nodes positive} \end{cases}$$

$$\lambda(t) = \lambda_0(t) e^{\beta_1 x_1 + \beta_2 x_2 + \beta_3 x_1 x_2}$$

Interpretation of e^{β_1}:

HR comparing 5FU + Levamisole to Levamisole only among those with fewer than 4 positive nodes.

Interpretation of $e^{\beta_1+\beta_3}$:

HR comparing 5FU + Levamisole to Levamisole only among those with at least 4 positive nodes.

WITH INTERACTION

Two binary variables, x_1 and x_2 with interaction:

$$x_1 = \begin{cases} 1 & \text{5FU + Levamisole} \\ 0 & \text{Levamisole alone} \end{cases} \qquad x_2 = \begin{cases} 1 & \text{4+ nodes positive} \\ 0 & \text{<4 nodes positive} \end{cases}$$

$$\lambda(t) = \lambda_0(t)e^{\beta_1 x_1 + \beta_2 x_2 + \beta_3 x_1 x_2}$$

$\lambda(t)$ for $x_1 = 1$ and $x_2 = 0$: $\lambda_0(t)e^{\beta_1 \cdot 1}$ $\lambda(t)$ for $x_1 = 1$ and $x_2 = 1$: $\lambda_0(t)e^{\beta_1 \cdot 1 + \beta_2 \cdot 1 + \beta_3 \cdot 1}$

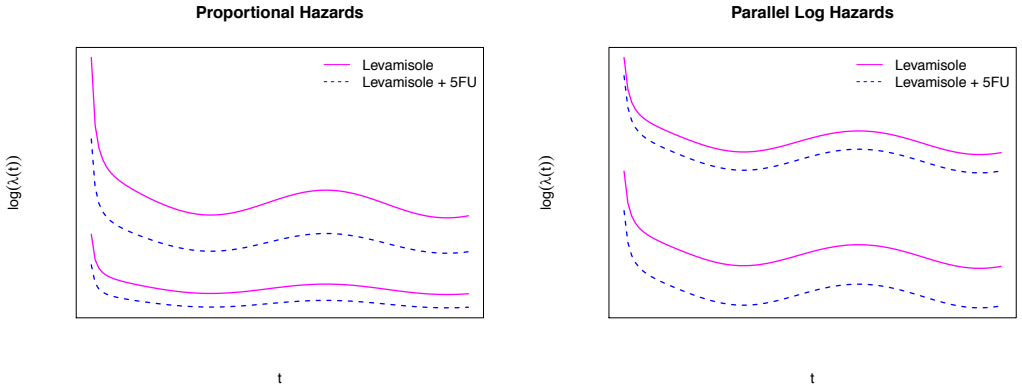
$\lambda(t)$ for $x_1 = 0$ and $x_2 = 0$: $\lambda_0(t)e^{\beta_1 \cdot 0}$ $\lambda(t)$ for $x_1 = 0$ and $x_2 = 1$: $\lambda_0(t)e^{\beta_1 \cdot 0 + \beta_2 \cdot 1 + \beta_3 \cdot 0}$

ratio: $e^{\beta_1(1-0)} = e^{\beta_1}$ ratio: $e^{\beta_1(1-0)+\beta_3(1-0)} = e^{\beta_1+\beta_3}$

PRESENTATION

- Usually we present hazard ratios at different values of the interacting/effect modifying variable with CIs and results of a test for interaction.
- Interaction term coefficient β or e^{β} usually not of primary interest.
- In previous example:
  - Treatment HR when <4 nodes positive: $e^{\beta 1}$
  - Treatment HR when 4+ nodes positive: $e^{\beta 1 + \beta 3}$

HEURISTIC HAZARDS



RESULTS

	HR (5FU + Lev/Lev)	95% CI	P-value
< 4 nodes positive	0.72	(0.53, 0.97)	0.03221
4+ notes positive	0.71	(0.49, 1.02)	0.06368
Test for interaction			0.95726

RESULTS

- "We did not find evidence that the hazard ratio associated with treatment differed depending on whether the patient had four or more positive nodes. (P = .96)."

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RISK SET STRATIFICATION

There are two ways to adjust for a binary (or other categorical) variable:

$$x_1 = \begin{cases} 1 & \text{Levamisole + 5FU} \\ 0 & \text{Levamisole Only} \end{cases} \qquad x_2 = \begin{cases} 1 & \text{4+ Positive Nodes} \\ 0 & \text{<4 Positive Nodes} \end{cases}$$

Dummy variable stratification:

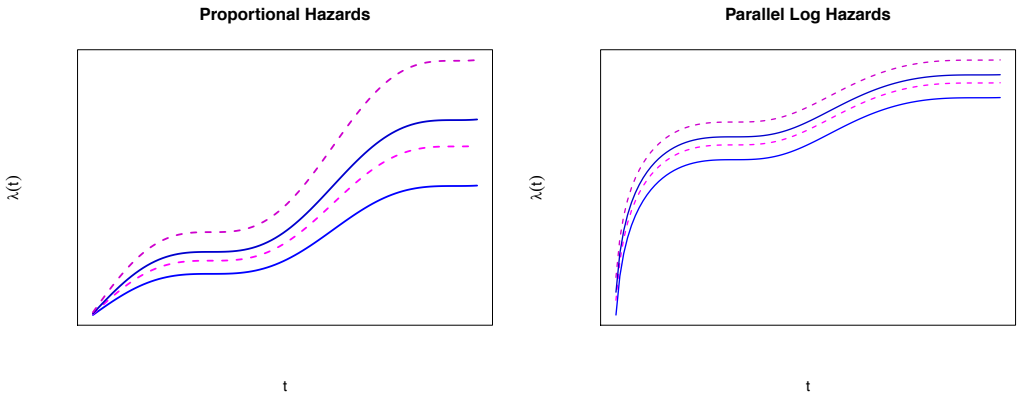
$$\lambda(t) = \lambda_0(t)e^{\beta_1 x_1 + \beta_2 x_2}$$

True stratification:

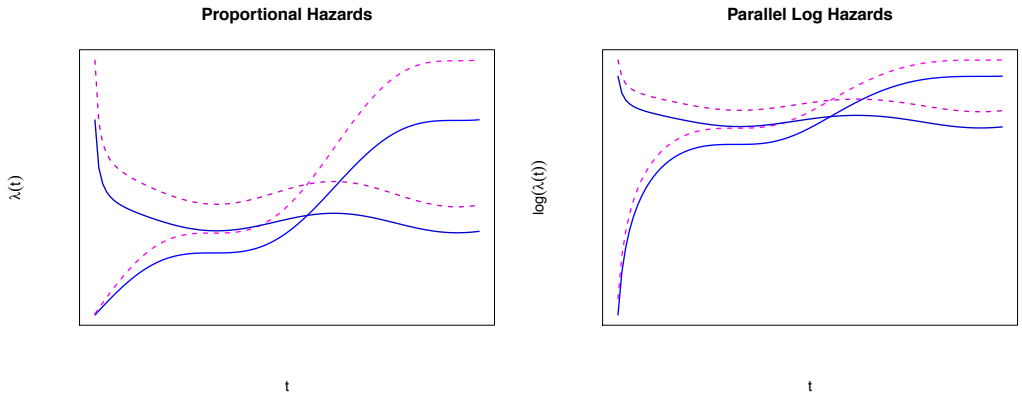
$$\lambda(t) = \lambda_{0x_2}(t)e^{\beta_1 x_1}$$

Stratified logrank test ≈ score test of $H_0 : \beta_1 = 0$ in true stratification model.

DUMMY VARIABLE STRATIFICATION



TRUE STRATIFICATION



RESULTS

"There was strong evidence that adjuvant treatment with 5FU + Levamisole improves survival in stage C colon cancer patients compared to Levamisole alone. After adjustment for number of positive nodes (<4, 4+) the hazard ratio comparing 5FU + Levamisole to Levamisole was 0.72, (95% CI: 0.57 - 0.91) P=0.005."

Very similar to covariate adjustment.

ADDING INTERACTION

Can include interaction for variable with true stratification:

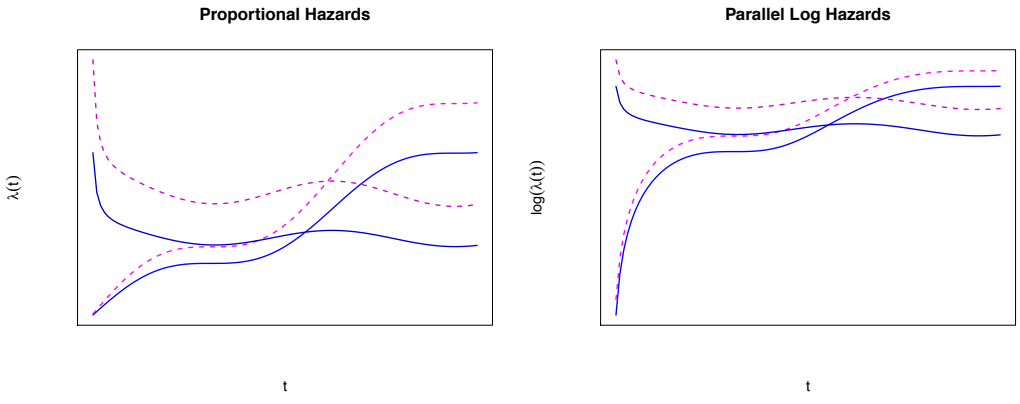
$$x_1 = \begin{cases} 1 & \text{Test treatment} \\ 0 & \text{Standard treatment} \end{cases}$$

$$x_2 = \begin{cases} 1 & \text{Failed prior treatment} \\ 0 & \text{No prior treatment} \end{cases}$$

True stratification with interaction:

$$\lambda(t) = \lambda_{0x_2}(t)e^{\beta_1 x_1 + \beta_2 x_1 x_2}$$

HEURISTIC HAZARDS



INTERACTION AND STRATIFICATION

- The interaction model does not violate rules about including main effects for terms that are part of interactions in a regression model.
- The "main effect" of x_2 is included in the $\lambda_{0x2}(t)$ term.

RESULTS

	HR (5FU + Lev/Lev)	95% CI	P-value
< 4 nodes positive	0.71	(0.53, 0.97)	0.03076
4+ notes positive	0.72	(0.5, 1.04)	0.07969
Test for interaction			0.97371

Very similar to covariate node4 model.

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ESTIMATING THE FUNCTIONS

- After fitting the Cox model,

$$\lambda(t) = \lambda_0(t)e^{\beta x}$$

  we may be interested in estimating

  - hazard: $\lambda(t)$
  - cumulative hazard: $\Lambda(t)$ and
  - survival function: $S(t)$

  at values of x, consistent with the model.

- Can be done by estimating baseline versions of these:

  $\lambda_0(t), \Lambda_0(t)$, and $S_0(t)$,

  and multiplying by $e^{\hat{\beta}x}$.

BASELINE CUMULATIVE HAZARD

$$\hat{\Lambda}_0(t) = \sum_{j:t_{(j)} \le t} \frac{D_j}{\sum_{i \in R_j} e^{\hat{\beta}_1 x_{1i} + \ldots + \hat{\beta}_K x_{Ki}}}$$

↑ observed failure times

↑ risk set

- Estimate depends on $\hat{\beta}_1, \ldots, \hat{\beta}_K$.
- Actually makes sense. Consider special cases.

BASELINE CUMULATIVE HAZARD

$$\hat{\Lambda}_0(t) = \sum_{j:t_{(j)} \le t} \frac{D_j}{\sum_{i \in R_j} e^{\hat{\beta}_1 x_{1i} + \ldots + \hat{\beta}_K x_{Ki}}}$$

1. One group, no covariates ($\hat{\beta}_1 x_{1i} + \ldots + \hat{\beta}_K x_{Ki} = 0$):

$$\hat{\Lambda}_0(t) = \sum_{j:t_{(j)} \le t} \frac{D_j}{\sum_{i \in R_j} 1} = \sum_{j:t_{(j)} \le t} \frac{D_j}{N_j}$$

↑ For the single homogeneous group

↑ Estimator from before

BASELINE CUMULATIVE HAZARD

$$\hat{\Lambda}_0(t) = \sum_{j:t_{(j)} \le t} \frac{D_j}{\sum_{i \in R_j} e^{\hat{\beta}_1 x_{1i} + \ldots + \hat{\beta}_K x_{Ki}}}$$

2. Two groups, one binary covariate:

$$x = \begin{cases} 1 & \text{group 2} \\ 0 & \text{group 1} \end{cases}$$

$$\hat{\Lambda}_0(t) = \sum_{j:t_{(j)} \le t} \frac{D_j}{\sum_{i \in R_j} e^{\hat{\beta} x_i}} = \sum_{j:t_{(j)} \le t} \frac{D_j}{\underbrace{\sum_{i \in R_j} e^{\hat{\beta} x_i}}_{\text{Group 1}} + \underbrace{\sum_{i \in R_j} e^{\hat{\beta} x_i}}_{\text{Group 2}}}$$

↑ For Group 1

$$= \sum_{j:t_{(j)} \le t} \frac{D_j}{\underbrace{n_{1j} + e^{\hat{\beta}} n_{2j}}}$$

Effective risk set size in group 1

BASELINE CUMULATIVE HAZARD

$$\hat{\Lambda}_0(t) = \sum_{j:t_{(j)} \le t} \frac{D_j}{\sum_{i \in R_j} e^{\hat{\beta}_1 x_{1i} + \ldots + \hat{\beta}_K x_{Ki}}}$$

In general:

The denominator $\sum_{i \in R_j} e^{\hat{\beta}_1 x_{1i} + \ldots + \hat{\beta}_K x_{Ki}}$ is

- Bigger than N_j when the average risk for a subject in R_j is bigger than the risk for a subject in R_j with $x_{1i} = x_{2i} = \cdots = x_{Ki} = 0$
- Smaller than N_j when the average risk for a subject in R_j is smaller than the risk for a subject in R_j with $x_{1i} = x_{2i} = \cdots = x_{Ki} = 0$

BASELINE CUMULATIVE HAZARD

$$\hat{\Lambda}_0(t) = \sum_{j:t_{(j)} \le t} \frac{D_j}{n_{1j} + e^{\hat{\beta}} n_{2j}}$$

↑

Group 1

D_j counts deaths in both groups.

$\hat{\beta} > 0 \implies$ More deaths in group 2
Effective risk set size must be increased to estimate risk in group 1.

$\hat{\beta} < 0 \implies$ More deaths in group 1
Effective risk set size must be decreased to estimate risk in group 1.

COLON CANCER TRIAL DATA

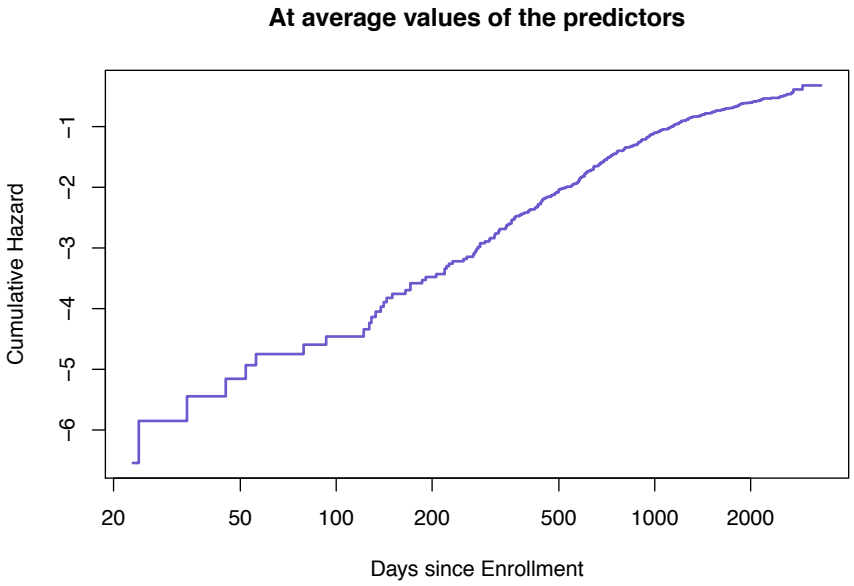
Observation Arm Omitted

	$\hat{\beta}$	exp($\hat{\beta}$)	se($\hat{\beta}$)	z	Pr(>|z|)
5FU + Lev	-0.34	0.71	0.12	-2.83	0.0064
4+ Nodes Pos	0.98	2.67	0.12	8.08	<0.0001

$e^{\beta_{Rx}}$ CI: (0.5629, 0.9008)

LRT: 8.098 on 1 df, P = 0.0044

COLON CANCER TRIAL DATA



BASELINE SURVIVAL AND HAZARD FUNCTION

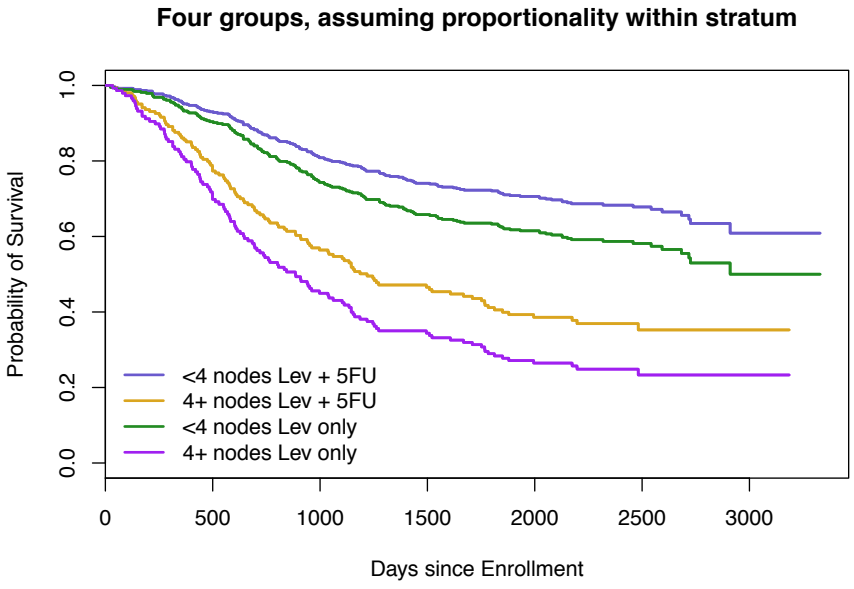
- Baseline survival function: $\hat{S}_0(t) = e^{-\hat{\Lambda}_0(t)}$
  (Since $S(t) = e^{-\Lambda(t)}$).
- As before, kernel smoothed baseline hazard estimator:

$$\hat{\lambda}_0(t) = \frac{1}{b}\sum_{j=1}^{J} K\left(\frac{t - t_j}{b}\right) \frac{D_j}{\sum_{j \in R_j} e^{\hat{\beta}_1 x_{1i} + \ldots + \hat{\beta}_K x_{Ki}}}$$

ESTIMATING AT COVARIATE VALUES

- $\hat{\Lambda}(t|x_1, x_2, \ldots, x_k) = \hat{\Lambda}_0(t)e^{\hat{\beta}_1 x_{1i} + \ldots + \hat{\beta}_K x_{Ki}}$
- $\hat{\lambda}(t|x_1, x_2, \ldots, x_k) = \hat{\lambda}_0(t)e^{\hat{\beta}_1 x_{1i} + \ldots + \hat{\beta}_K x_{Ki}}$
- $\hat{S}(t|x_1, x_2, \ldots, x_k) = \hat{S}_0(t)^{e^{\hat{\beta}_1 x_{1i} + \ldots + \hat{\beta}_K x_{Ki}}}$

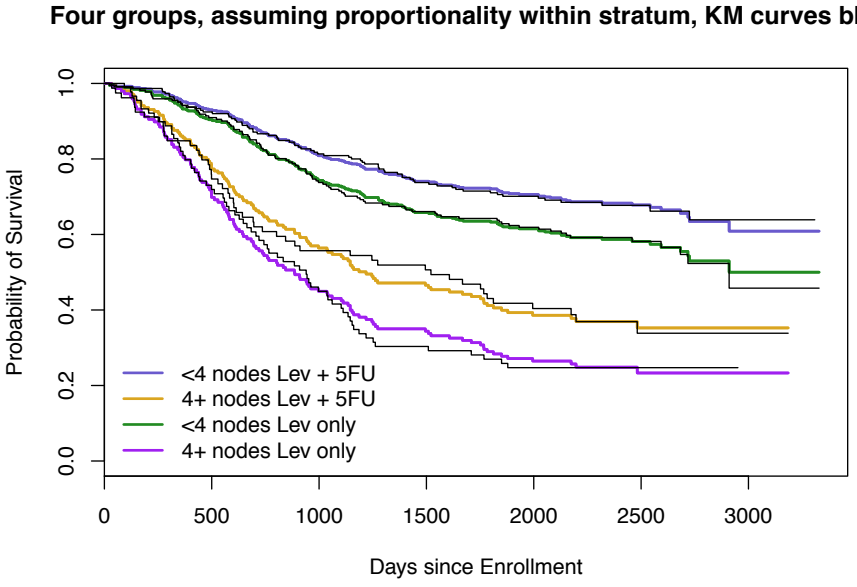
COLON CANCER TRIAL DATA



USES FOR BASELINE AND SPECIFIC-X FUNCTIONS

- To estimate hazard or survival for different covariate combinations, according to the model.
- To examine the shape of the hazard, under the constraints imposed by the model.
- To check the fit of the model, by comparing $\hat{\Lambda}_x(t), \hat{S}_x(t)$, or $\hat{\lambda}_x(t)$ to $\hat{\Lambda}(t), \hat{S}(t)$, or $\hat{\lambda}(t)$ for groups with like values of $\hat{\beta}_1 x_{1i} + \ldots + \hat{\beta}_K x_{Ki}$.
- To check whether hazards in different risk set strata are proportional.

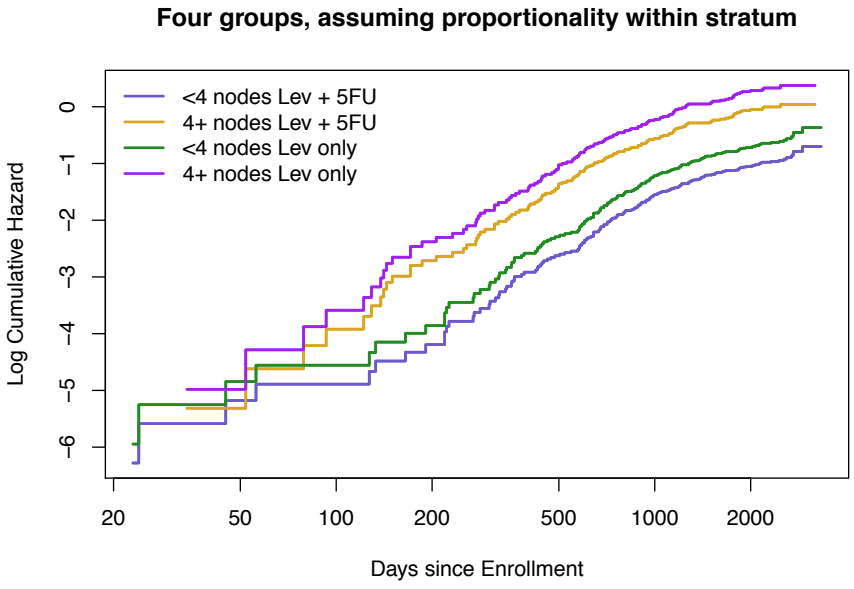
COLON CANCER TRIAL DATA



COLON CANCER TRIAL DATA

- Can examine proportionality of hazards graphically after adjustment for other covariates
  - Fit risk-set stratified Cox model
  - Estimate stratum-specific baseline hazards
  - Plot log(baseline cumulative hazards) and see if they are parallel (cumulative hazards proportional)
- Cox model
  - Covariate: Tx
  - Risk set strata: nodes ≤4, nodes 4+

PROPORTIONAL STRATA



TO WATCH OUT FOR:

- Coefficients in Cox regression are positively associated with risk, not survival.
  - Positive β means large values of x are associated with shorter survival.
- Without certain types of time-dependent covariates (more later), Cox regression does not depend on the actual times, just their order.
  - Can add a constant to all times to remove zeros (which are removed by some software) without changing inference
- For LRT, nested models must be compared based on same subjects.
  - If some values of variables in larger model are missing, these subjects must be removed from fit of smaller model.
- Coefficient interpretation depends on what other variables are in the model and how they are coded (ie. interaction terms, 0/1 vs 1/-1 etc.)
- Hazards may not be proportional