A case study on competing risks: Follicular cell lymphoma study

Guanlin Zhang

Department of Biostatsitics
University of Kansas Medical Center

07 May 2018

Overview

Introduction
Follicular cell lymphoma data
Methods and Results
Estimates and tests without covariates
Covariate effects via cox models
Accelerated failure time models
Conditional processes
Cumulative incidence function
Discussion

Introduction: Background and Concepts

In general, a competing risk situation arises when an individual can experience more than one type of event and the occurrence of one type of event hinders the occurrence of other types of events[**pintilie06**].

different ways to express

1. some described competing risks as the situation in which an individual can experience more than one type of event.
2. some explained it as the failure to achieve independence between the time to an event and the censoring mechanism.
3. some defined the concept of competing risks as the situation where one type of event 'either precludes the occurrence of another event under investigation or fundamentally alters the probability of occurrence of this other event'.

Introduction: Backgroud and Concepts

examples

1. bone marrow transplantation for leukemia: death in remission is competing with relapse.
2. cardiovascular studies: death due to other causes such as cancer are competing with death via cardiovascular disease.
3. follicular cell lyphoma study: death before relapse is computing with relapse or no response to treatment (our study case).
4. Incidence of Involuntary pregnancy: Other types of discontinuation of IUD are competing with involuntary pregnancy.

Introduction: Concepts

Formal definition: two approaches.

latent variable format

1. $T = \min\{T_1, T_2, \ldots, T_p\}$, $C \in \{0, 1, 2, \ldots, p\}$
2. multivariate joint survival function: $S(t_1, t_2, \ldots, t_p) = P(T_1 > t_1, T_2 > t_2, \ldots, T_p > t_p)$
3. subdensity for event type j: $f_j(t) = \left(-\frac{\partial S(t_1, t_2, \ldots, t_p)}{\partial t_j} \right)_{t_1 = t_2 = \ldots = t_p = t}$
4. The marginal survivor function for event type j: $S_j(t) = S(t_1 = 0, t_2 = 0, \ldots, t_j = t, \ldots, t_p = 0)$
5. subdistribution function: $F_j(t) = \int_0^t f_j(s)ds$
6. marginal hazard: $h_j(t) = -\frac{\partial \log(S_j(t))}{\partial t}$

Introduction: Concepts

Cause(Type)-Specific hazard:

$\tilde{h}_j(t) = \lim_{\delta \to 0} \left\{ \frac{P(t<T\leq t+\delta, C=j | T>t)}{\delta} \right\}$

about cause-specific hazard:

1. $\tilde{h}_j(t) = \left(- \frac{\partial \log \left(S(t_1, t_2, \ldots, t_p) \right)}{\partial t_j} \right)_{t_1=t_2=\ldots=t_p=t}$
2. $h(t) = \sum_{j=1}^{p} \tilde{h}_j(t)$

Under the assumption of independence for different events, there is $\tilde{h}_j(t) = h_j(t)$

Introduction: Concepts

another approach:

bivariate random variable

1. record the outcome of competing risks as a bivariate random variable (T, C), $C \in \{0, 1, 2, \ldots, p\}$
2. Under this approach we could define CIF: $F_j(t) = P(T \leq t, C = j)$
3. the subdensity function defined in the previous approach follows $f_j(t) = \frac{\partial F_j(t)}{\partial t}$
4. $\lim_{t \to \infty} F_j(t) = P(C = j) < 1$ that is why sometimes it is also called sub distribution.

Introduction: Concepts

Discussion regaring different approaches:

discussion:

1. For latent failure time approach, we rely on the assumptino of independence between event types. Otherwise marginal distributions could not identify the joint distribution.
2. However independence is not testable in application when one only observes the first event (examples...).
3. So people will only consider cause-specific hazard under the bivariate definition.
4. assumig independence, we can just treat event of interest as our event and all the other event types as censoring. Then the Cox model and parametric AFT model could all come into play.

Data Description:

about the data

1. A hospital database of lymphoma patient data was created at the Princess Margaret Hospital, Toronto, with records dating from 1967.
2. A subset of 541 patients from the data will be used in our case study, all of them identified as having follicular type lymphoma, registered for treatment at the hospital between 1967 and 1996, with early stage disease (I or II) and treated with radiation alone (RT) or with radiation and chemotherapy(CMT).
3. The goal of this study was to report the long-term outcome in this group of patients.
4. The response to treatment is given here in a simplified version: CR is complete response and NR is no response.

Data Description:

Tabel: Follicular cell lymphoma data

Variable name	Description
stnum	Patient ID
Variables assessed at the time of diagnosis	
age	Age (years)
hgb	Haemoglobin (g/l)
clinstg	Clinical stage: 1 = stage I, 2 = stage II
ch	Chemotherapy: Y = Yes, blank = No
rt	Radiotherapy: Y = Yes, blank = No
Outcome variables	
resp	Response after treatment: CR = Complete response, NR = No response
relsite	Site of relapse: L = Local, D = Distant, B = Local and Distant, blank = No relapse
survtime	Time from diagnosis to death or last follow-up
stat	Status: 1 = Dead, 0 = Alive
dftime	Time from diagnosis to first failure (no response, relapse or death) or last follow-up
dfcens	Censoring variable: 1 = Failure, 0 = Censored

Data Description:

In our study, the event of interest is failure from the disease: either no response to treatment or relapse at any location(coded as 1), and there is one competing risk that is death without relapse(coded as 2). The rest of the events falling out of these two categories are considered as censored(coded as 0).

1. We aim to explore a series of goals, including compare the cause-specific hazard functions for different event types, identify significant covariates for each event type along with proper interpretation, compare the regression coefficients for significant covariates across event types, both globally and individually, identify the most recommended parametric AFT models for each event type by running goodness of fit test, and observing the plot of cumulative incidence function and so on.

Methods:

(1) estimates and tests without covariates
(2) covariate effects via cox models
(3) accelerated failure time(AFT) models
(4) conditional processes
(5) using cumulative incidence functions(CIFs)

Estimates and tests without covariates

$H_0 : h_j(t) = h(t)$ for all j

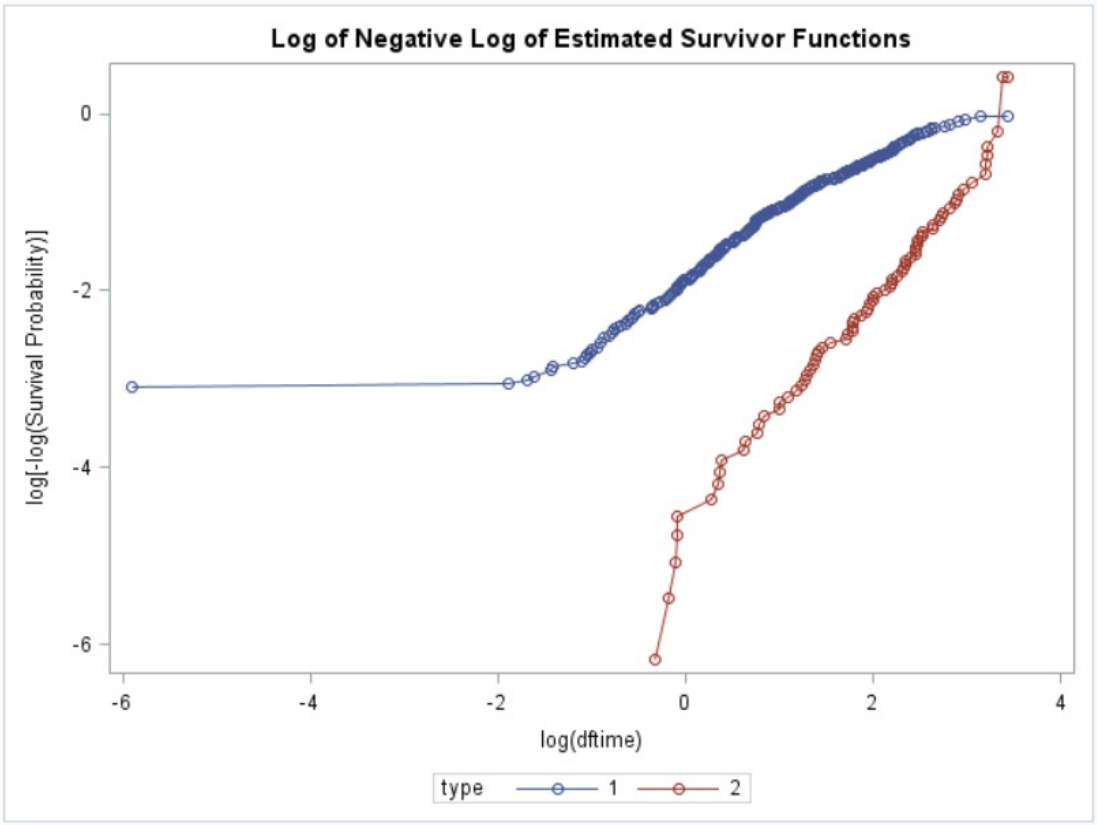
1. a quick check on frequency: 272 event, 76 competing risk, 193 censoring
2. formal chi-square test: $\chi^2_1 = 55.2, p < 0.0001$

$H_0 : h_j(t) = \omega_j h(t), j = 1, 2$

1. log-log survival plot (parallel if proportional)
2. parametric model by Cox and Oakes(1984): $\log h_j(t) = \alpha_0(t) + \alpha_j + \beta_j t$, implies a binary logistic model. Coefficient for time is 0 if proportional. We fit proc logistic and get $\beta = -0.1817, p < 0.0001$, indicating a rejection of the proportionality hypothesis.
3. $\beta = -0.1817$ tells us that the hazard for event of interest increases more slowly with time than the hazard for competing risk. Specifically the ratio decrease by about $100 \times (1 - \exp(-0.1817)) = 16.7\%$ each year.

Estimates and tests without covariates

Figur: log-log survival plot



Covariate effects via cox models

We fit the data into cox semi-parametric models (PH model):

1. $h(t) = h_0(t) \cdot \exp(\beta_1 \text{age\_group} + \beta_2 \text{hgb} + \beta_3 \text{clinstg} + \beta_4 \text{chemo})$
2. $h_1(t) = h_{1,0}(t) \cdot \exp(\beta_{1,1} \text{age\_group} + \beta_{1,2} \text{hgb} + \beta_{1,3} \text{clinstg} + \beta_{1,4} \text{chemo})$
3. $h_2(t) = h_{2,0}(t) \cdot \exp(\beta_{2,1} \text{age\_group} + \beta_{2,2} \text{hgb} + \beta_{2,3} \text{clinstg} + \beta_{2,4} \text{chemo})$
4. age is grouped here;
5. baseline hazards are different.

Covariate effects via cox models

The goal here:

1. finding significant covariates
2. test on $H_0 : \boldsymbol{\beta} = \boldsymbol{\beta}_j, j = 1, 2$ with likelihood ratio.
3. test on $H_0 : \beta_{1,i} = \beta_{2,i}, i = 1, 2, 3, 4$ with
   $T = \frac{(\hat{\beta}_{1,i} - \hat{\beta}_{2,i})^2}{\hat{\mathrm{Var}}(\beta_{1,i}) + \hat{\mathrm{Var}}(\beta_{2,i})}$

Covariate effects via cox models

covariates effect via cox model: combined events:

Analysis of Maximum Likelihood Estimates								
Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Label
a	1	1	0.71530	0.11783	36.8549	<.0000001	2.045	a 1
hgb		1	0.00211	0.00361	0.3403	0.5596407	1.002	
clinstg	2	1	0.41717	0.11844	12.4050	0.0004282	1.518	clinstg 2
chemo	1	1	-0.28951	0.15076	3.6879	0.0548080	0.749	chemo 1

also $H_0 : \boldsymbol{\beta} = \mathbf{0}$ has a p value around 0.001.

Covariate effects via cox models

covariates effect via cox model: event of interest

Analysis of Maximum Likelihood Estimates								
Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Label
a	1	1	0.41908	0.13567	9.5420	0.0020082	1.521	a 1
hgb		1	0.00230	0.00406	0.3196	0.5718767	1.002	
clinstg	2	1	0.48191	0.13095	13.5429	0.0002332	1.619	clinstg 2
chemo	1	1	-0.32457	0.16639	3.8049	0.0511018	0.723	chemo 1

also $H_0 : \boldsymbol{\beta}_1 = \mathbf{0}$ has a p value < 0.001.

Covariate effects via cox models

covariates effect via cox model: competing risk

Analysis of Maximum Likelihood Estimates								
Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Label
a	1	1	1.87145	0.26520	49.7997	<.0000001	6.498	a 1
hgb		1	0.00162	0.00812	0.0399	0.8416812	1.002	
clinstg	2	1	0.21985	0.28336	0.6020	0.4378132	1.246	clinstg 2
chemo	1	1	-0.09558	0.35714	0.0716	0.7889872	0.909	chemo 1

also $H_0 : \boldsymbol{\beta}_2 = \mathbf{0}$ has a p value < 0.001.

Covariate effects via cox models

To test $H_0 : \boldsymbol{\beta} = \boldsymbol{\beta}_j, j = 1, 2$, we have:

model	-2log-likelihood	df
combined events	3888.993	4
event of interest	3140.689	4
competing risk	719.480	4

The test statistic is

$$T = 3140.689 + 719.480 - 3888.993 = 28.824$$

with p value:

$$p = P(\chi^2_4 \geq 28.824) =< 0.0001$$

so we reject H_0 and conclude that the regression coefficients across different models are different.

Covariate effects via cox models

To test $H_0 : \beta_{1,i} = \beta_{2,i}, i = 1, 2, 3, 4$, we got:

		test statistic	p value
age_group	$\beta_{1,1}$ vs $\beta_{2,1}$	23.77102	< 0.0001
hgb	$\beta_{1,2}$ vs $\beta_{2,2}$	0.0056	0.94
clinstg	$\beta_{1,3}$ vs $\beta_{2,3}$	0.7048	0.40
chemo	$\beta_{1,4}$ vs $\beta_{2,4}$	0.3378	0.56

We have significant statistical justification to conclude that the coefficient for age group are different between the model for event of interest and the model for competing risk.

Covariate effects via cox models

For the other three covariates, we want to further test whether the three covariates are equal to 0.

covariate	null hypothesis	test statistic	p value
hgb	$\beta_{1,2} + \beta_{2,2} = 0$	0.3595	0.84
clinstg	$\beta_{1,3} + \beta_{2,3} = 0$	14.1449	< 0.01
chemo	$\beta_{1,4} + \beta_{2,4} = 0$	3.8765	0.14

So for the rest of the study, we only keep age group and clinical stage in the model.

Accelerated failure time models

1. we fit AFT model to the data, taking age group and clinical stage as covariates.
2. for nested models, we use likelihood ratio test
3. for other models, we look at AIC and BIC.
4. for exponential model, SAS gives lagrange multiplier test for scale parameter: $H_0 : \sigma = 1$.
5. we can also look at output for weibull mode, point estimate and confidence interval for scale parameter.
6. $\log \frac{P(J=1|T=t)}{P(J=2|T=t)} = (\alpha_1 - \alpha_2) \log t + (\beta_{1,0} - \beta_{2,0}) + (\beta_{1,1} - \beta_{2,1})\text{Age\_group} + (\beta_{1,2} - \beta_{2,2})\text{clinstg}$

Accelerated failure time models

-2log-likelihood	event of interest	competing risk
exponential	1825.207	436.588
weibull	1673.698	415.013
gamma	1673.695	413.606
log-normal	1700.212	425.910
log-logistic	1673.949	419.122

AIC	event of interest	competing risk
exponential	1831.207	442.588
weibull	1681.698	423.013
gamma	1683.695	423.606
log-normal	1708.212	433.910
log-logistic	1681.949	427.122

Accelerated failure time models

BIC	event of interest	competing risk
exponential	1844.087	455.468
weibull	1698.872	440.187
gamma	1705.162	445.073
log-normal	1725.386	451.083
log-logistic	1699.122	444.296

Accelerated failure time models

test on scale parameter of exponential

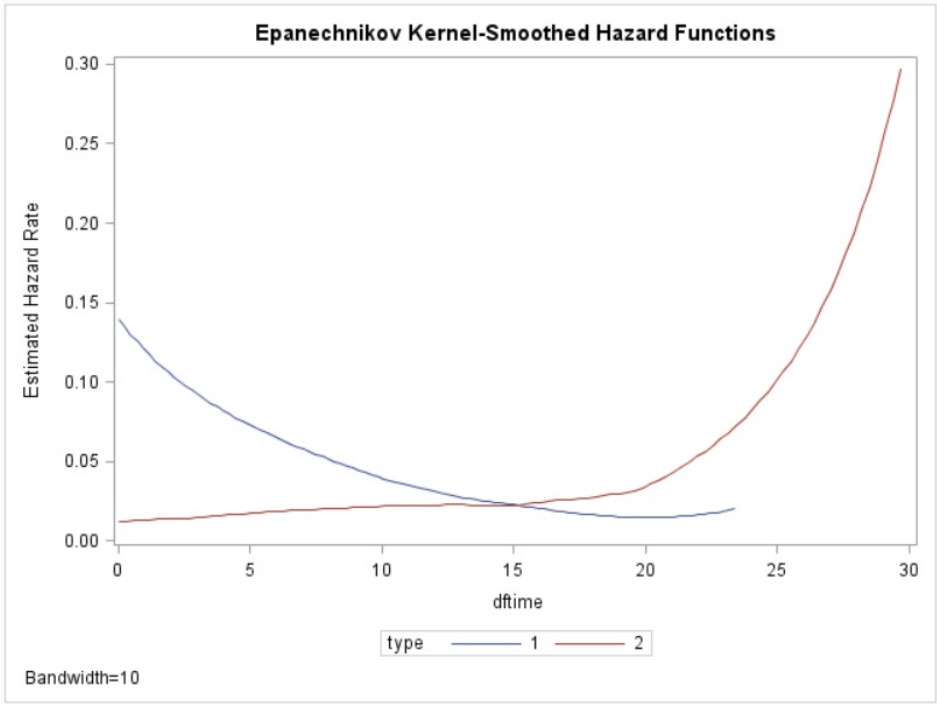
scale parameter	p value	point estiate	confidence interval
event of interest	< 0.0001	1.7955	$(1.6147, 1.9965)$
competing risk	< 0.0001	0.6445	$(0.5451, 0.7621)$

goodness of fit between weibull and generalized gamma:

	χ^2 statistic	p value
event of interest	0.003	0.96
competing risk	1.407	0.24

Accelerated failure time models

$1/(1.796) - 1 = -0.44$: hazard of relapse or no response decrease with time; $1/(0.6445) - 1 = 0.55$: hazard of death before relapse increase with time.



Accelerated failure time models

$$H_0 : (\beta_{1,1}, \beta_{1,2}) = (\beta_{2,1}, \beta_{2,2})$$

Tabel: output for $H_0 : (\beta_{1,1}, \beta_{1,2}) = (\beta_{2,1}, \beta_{2,2})$

Testing Global Null Hypothesis: BETA=0			
Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	81.0824	3	<.0000001
Score	50.1237	3	<.0000001
Wald	47.9694	3	<.0000001

Analysis of Maximum Likelihood Estimates						
Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept		1	3.3636	0.5945	32.0094	<.0000001
ldftime		1	-1.1028	0.1719	41.1723	<.0000001
a	1	1	-1.3661	0.3151	18.7993	0.0000145
a	0	0	0	.	.	.
clinstg		1	-0.0638	0.3227	0.0391	0.8433157

Conditional processes

$$P(T = t, J = j) = P(T = t)P(J = j|T = t)$$

Given the event time $T = t$, what is the chance that this is a specific type $J = j$? For the conditional probability, we could use the output of the logistic regreesion to tell us the odds of the event belonging to a specific type. Then for $T = t$ alone, we could just use a cox model for the combined events type.

Conditional processes

The logistic model from equation says that the given that there is a treatment failure(no response, relapse, or death before relapse), patients over age of 65 only hae about 25% odds of experiencing event of interest(no response, or relapse).

The cox model tells that patients who are above age 65 have about twice as much risk of experiencing failure(by means of either no response or relapse, or death before relapse) . Also patients who are at clinical stage 2 have about 50% more risk of experiencing treatment failure.

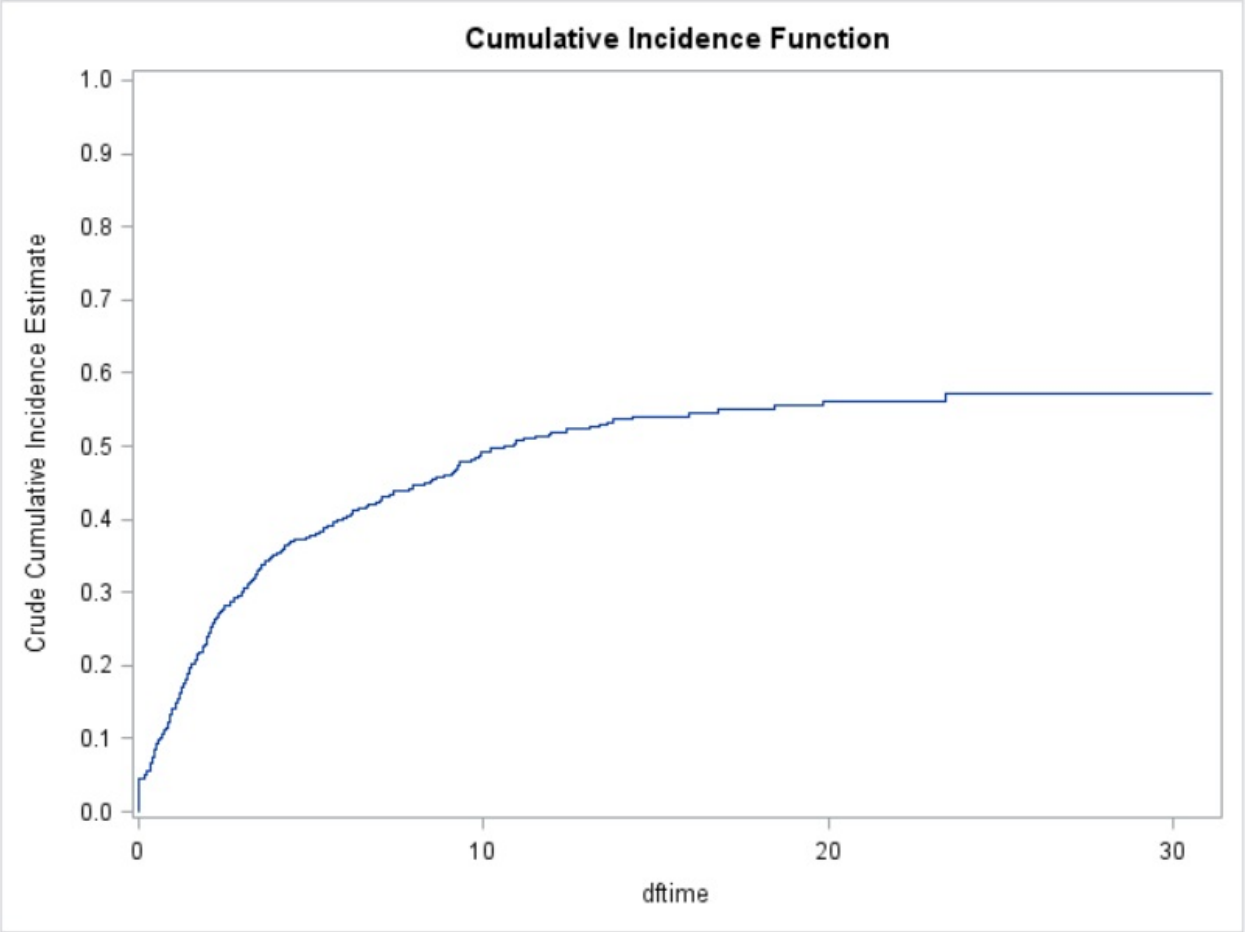
Cumulative incidence function

$$F_j(t) = P(T \leq t, C = j)$$

1. a consistent estimate of the cumulative incidence function is given by $\hat{F}_j(t) = \sum_{k|t_k \leq t} \hat{S}(t_k) \frac{d_k}{n_k}$
2. $\hat{S}(t) + \sum_j \hat{F}_j(t) \xrightarrow{p} S(t) + \sum_j F_j(t) = 1$

Cumulative incidence function

Figur: cumulative incidence function



Discussion

we have reached the following major conclusion:

1. the hazard rate for relapse or no response is different than the hazard rate for death before relapse
2. among all the covariates in the data, only age group and clinical stage have significant effect on either of the event type (or combined together)
3. the most recommended AFT model for either event type is weibull.

Discussion

We did not spend much space to discuss the methods assuming dependence between different event types. There are opinions that it may not be all that exciting to assume dependence after all. For any model that incorporates dependence among event types, there is an independence model that does an equally good job of fitting the data. To keep an open mind though, we are aware that there are regression methods based on cumulative incidence functions (Fine and Gray, 1999; Scheike and Zhang, 2008) and might need to explore in the future study.

References I

- Allison, Paul D. (2010) *Survival Analysis Using SAS: A Practical Guide, 2nd Edition*. SAS Institute Inc., Cary, NC, USA.
- Caplan, R.J., Pajak, T.F. and Cox, J.D. (1994). Analysis of probability and risk of cause-specific failure. *International Journal of Radiation Oncology. Biology, Physics.* **29**, 1183-1186.
- Cox, D.R. and Oakes, D.(1984) *Analysis of Survival Data.* London: Chapman& Hall.
- Fine, Jason P., and Gray, Robert J., (1999) A proportional Hazards Model for the Subdistribution of a Competing Risk. *Journal of the American Statistical Association* Vol. 94, No. 446, 496-509.

References II

- Gelman, R., Gelber, R., Henderson, I.C., Coleman, C.N. and Harris, J.R.(1990). Improved methodology for analyzing local and distant recurrence. *Journal of Clinical Oncology*. **8**, 548-555.
- T. A., Leisenring, W., Crowley, J. and Storer, B. E. (1999). Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. *Statistics in Medicine,* **18**, 695-706.
- Kalbfleisch, J.D. and Prentice, R.L. *The Statistical Analysis of Failure Time Data.* Hoboken, NJ: John Wiley & Sons, Inc.
- Klein, John P. and Moeschberger, Melvin L . *Survival Analysis Techniques for Censored and Truncated Data* Springer. 1997.

References III

- P.M., Gospodarowicz, M., Tsang, R., Pintilie, M., Wells, W., Hodgson, D., Sun, A., Crump, M., Patterson, B. and Bailey, D. (2004). Long-term outcome in stage I and II follicular lymphoma following treatment with involved field radiation therapy alone. *Journal of Clinical Oncology*, **22**, 563S.
- Pintilie, Melania. *Competing Risks: A practical Perspective* John Wiley & Sons, Ltd. 2006.
- Scheike, T.H., Zhang, M., and Gerds, T.A., Predicting Cumulative Incidence Probability by Direct Binomial Regression, *Biometrika*, **95**, 205-220.

Thank You!