

Determining When One Treatment is Different From

The results of these analyses tell the investigator whether the two treatments have the same survival rates or not. When the results of the test indicate that the survival curves are different the natural question posed by most clinicians is "at what times are these two treatments different?" The answer to this question is crucial to a patient and physician in deciding which

the first several months after transplant. It is well known, however, that graft-versus-host disease has some protective effect against the reoccurrence of the leukemia, so allogeneic patients who survive the initial period tend to have lower leukemia relapse rates, offsetting their higher early treatment related mortality. For a patient there is thus a trade off between early high mortality with allogeneic transplants and lower reoccurrence rates. To help in the decision between these two competing treatment modalities a confidence set for the times at which the survival probabilities of the two treatments are the same is of interest. Also, since autologous transplants are easier to perform as no donor is needed, a confidence set for those times where the survival probability for an autologous transplant patient is not smaller than the corresponding survival probability for an allogeneic transplant patient is also of interest.

## 2 Confidence Set Based On Cox's Proportional Hazards Model

Often there are other risk factors that need to be adjusted for prior to making the main comparison between the two treatments in many experiments. In this section we construct the confidence set based on the proportional hazards model which has become one of the most commonly used model in the analysis of failure time observations.

### 2.1 Adjustment For Covariates Not Confounded With Outcome

Let  $\mathbf{Z} = (Z_1, \dots, Z_p)$  be a vector of fixed time covariates that influence survival. In this section we assume that there is no significant interaction between the comparison of interest (treatment) and any of these covariates. Here we fit a proportional hazards model for the explanatory covariates stratifying on the treatment of interest. That is we fit the model

$$\lambda(t|\mathbf{Z}, \text{Treatment}) = \begin{cases} \lambda_{10}(t) e^{-\beta^T \mathbf{Z}}, & \text{for treatment 1,} \\ \lambda_{20}(t) e^{-\beta^T \mathbf{Z}}, & \text{for treatment 2.} \end{cases} \quad (2.1)$$

Let  $\hat{\beta}$  and  $I(\hat{\beta})$  be the partial maximum likelihood estimate and its variance-covariance matrix, respectively.

For an individual with a covariate vector  $\mathbf{Z}_0$ , the two treatments will have the same survival rate at time  $t_0$  if  $\Lambda(t|\mathbf{Z}_0, \text{Treatment 1}) = \Lambda(t|\mathbf{Z}_0, \text{Treatment 2})$ , which from (2.1) is equivalent to having  $\Lambda_{10}(t_0) = \Lambda_{20}(t_0)$  or  $\Delta(t_0) = \Lambda_{20}(t_0) - \Lambda_{10}(t_0) = 0$ . Note that this comparison is independent of the value of  $\mathbf{Z}_0$ . The test statistic for this hypothesis is

$$\hat{\Delta}(t_0) = \text{that}$$

addition to type of transplant, on each patient includes remission status (1st or second complete remission), age (dichotomized as  $\leq 30$  or  $> 30$ ) and Karnofsky score (dichotomized as  $< 90$  or  $\geq 90$ ) at transplant. For patients in second complete remission the duration of the first complete remission (dichotomized as  $\leq 1$  yr or  $> 1$  yr) is also available.

The confidence set is based on the results

Here

$$\mathbf{W}_j(\hat{\beta}, t_0) = e^{-\mathbf{p}\{\hat{\gamma}_j^T \mathbf{Z}_{10}\}} \int_0^{t_0} [\tilde{\mathbf{Z}}_j(\hat{\beta}, \cdot) - \mathbf{Z}_{(j)}] d\hat{\Lambda}_{j0}(\cdot), \quad j = 1, 2$$

with  $\tilde{\mathbf{Z}}_j(\hat{\beta}, \cdot)$ , defined by (2.6) and  $\mathbf{Z}_{(1)} = (\mathbf{0}^T, \mathbf{Z}_{10}^T, \mathbf{0}^T)$  and  $\mathbf{Z}_{(2)} = (\mathbf{0}^T, \mathbf{0}^T, \mathbf{Z}_{10}^T)$ .

Since at  $t_0$  an  $\alpha$  level test of the equality of the two survival functions for a fixed value of  $\mathbf{Z}$  is accepted when  $\hat{\Delta}(t_0|\mathbf{Z}_{10})/[\text{Var}(\hat{\Delta}(t_0|\mathbf{Z}_{10}))]^{1/2}$  is in the interval  $[-z_{\alpha/2}, z_{\alpha/2}]$ , a  $(1 - \alpha) \times 100\%$  confidence set for those times at which the two treatments are not different is given by

$$\{t : -z_{\alpha/2} \leq \hat{\Delta}(t_0|\mathbf{Z}_{10})/[\text{Var}(\hat{\Delta}(t_0|\mathbf{Z}_{10}))]^{1/2} \leq z_{\alpha/2}\}$$

Similarly a confidence set for those points in time where treatment 2 is at least as good as treatment 1 is given by

$$\{t : \hat{\Delta}(t_0|\mathbf{Z}_{10})/[\text{Var}(\hat{\Delta}(t_0|\mathbf{Z}_{10}))]^{1/2} \leq z_{\alpha}\}$$

To illustrate this approach we again use the data comparing autologous and allogeneic transplants. Here, based on a standard semi-parametric regression analysis, it appears that age has a differential effect on the two types of transplants. To adjust for this confounding factor a proportional hazards model stratified on type of transplant is fit to the covariates remission status, Karnofsky score ( $< 90$  or  $\geq 90$ ), duration of first complete remission (dichotomized as  $\leq 1$  yr or  $> 1$  yr) and two interaction covariates. The interaction covariates are  $Z_{11} = 1$  if age  $> 30$  and allo transplant and  $Z_{12} = 1$  if age  $> 30$  and auto transplant. Note that here the estimate of  $\Delta$  for a patient under age 30 is the difference of the baseline cumulative hazards from the stratified Cox model, while for patients over 30 each of the baseline hazards is multiplied by the factor  $e^{-\mathbf{p}[\gamma_j]}$  before differencing.

The 95% confidence sets for the times (in years) where the two treatments have the same survival probability are

$$C2_{\leq 30} = \{t_0 | t_0 \in [0, 1.242) \cup [2.349, 2.418)\}$$

for patients age 30 or less and

$$C2_{> 30} = \{t_0 | t_0 \in [0, 0.115) \cup [0.118, 0.129) \cup [0.1590, 5.891)\}$$

for patients over age 30. This suggests that for older patients there is no advantage in survival for either type of transplant but for younger patients the two survival rates are different after the first 15 months or so.

95% confidence set for those times where patients given an auto transplant have a survival probability at least as high as patients given an allo transplant is given by

$$C1_{\leq 30} = \{t_0 | t_0 \in [0, 0.858) \cup [0.885, 1.162)\}$$

or patients age 30 or less and

$$C1_{> 30} = \{t_0 | t_0 \in [0, 5.891)\}$$

for patients over age 30. Note that this suggests that the auto transplant survival rate is at least as good as the allo transplant rate for patients over age 30, but for patients under 30 the survival rate is only as good for a little over a year after transplant.

## 3 Confidence Sets Based On The Additive Hazards Model

### 3.1 Estimation In The Additive Model

An alternative to the proportional hazards model is the additive hazards model first suggested by Kalbfleisch (1980). This model allows for covariate effects which vary over time since the regression coefficients are functions of time as opposed to the Cox model where they are constants. This approach uses a linear model for the conditional hazard rate and estimates regression coefficient functions by a least squares technique.

To define the model suppose we have an individual with covariates  $Z_1(t), \dots, Z_p(t)$ 's

$X(t)$  is a generalized inverse of  $Y(t)$ , and  $I_k$  is the  $n$ -vector of whose  $i$ th element is 1 if subject  $i$  experiences the event at time  $T_k$  and is 0 if they don't. The estimator (3.2) is only defined over the range where the matrix  $Y(t)$  is of full rank. Let  $\tau$  be the random point in time where  $Y(t)$  loses its full rank.

Any generalized inverse can be used in computing the estimator (3.1). By analogy to the usual linear models analysis we shall use the generalized inverse suggested by Kalbfleisch (1980), Huffer and McKeague (1991), McKeague (1988), namely

$$X(t) = (Y(t)^T Y(t))^{-1} Y(t)^T \quad (3.3)$$

an alternative choice of the



variable. Inverting this test yields a  $100 \times (1 - \alpha)$  confidence set for the times at which  $S_1(t) = S_2(t)$  as

$$\begin{aligned} & \left\{ t_0 : -z_{\alpha/2} \leq \hat{\Delta}(t_0)/[\text{Var}(\hat{\Delta}(t_0))]^{1/2} \leq z_{\alpha/2} \right\} \\ = & \left\{ t_0 : \hat{\Delta}(t_0) - z_{\alpha/2}\sqrt{\text{Var}(\hat{\Delta}(t_0))} \leq 0 \leq \hat{\Delta}(t_0) + z_{\alpha/2}\sqrt{\text{Var}(\hat{\Delta}(t_0))} \right\} \quad (3.10) \end{aligned}$$

To find sets of time where we are  $(1 - \alpha) \times 100\%$  confident that  $S_1(t) \leq S_2(t)$  consider testing the hypothesis  $H_0 : \Lambda_1(t_0) \geq \Lambda_2(t_0)$  versus  $H_A : \Lambda_1(t_0) < \Lambda_2(t_0)$ . This is equivalent

## 4 Example

To illustrate these calculations we consider data from a retrospective study of the effectiveness of bone marrow transplantation for patients with acute myelocytic leukemia (AML). Of interest is the comparison of survival rates between patients given either an autologous (auto) or allogeneic (allo) transplant. The data set consists of data on 1,325 patients reported over a four year period to either the International Bone Marrow Transplant Registry (allo transplants) or the Autologous Blood and Marrow Registry (auto transplants). 381 patients received an autologous transplant and 944 a HL-identical sibling allogeneic transplant.

The comparison of interest is between the leukemia free survival times (LFS) of the two groups. A patient is considered as an event if they die or their leukemia returns. The event time is the smaller of the time of relapse or death. Figure 1 shows the unadjusted Kaplan-Meier estimators for the two treatment groups. The log-rank test of equality of the survival functions

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