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of two survival curves under  
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Technical Report 29

February 1998

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# CONFIDENCE BANDS FOR THE DIFFERENCE OF TWO SURVIVAL CURVES UNDER PROPORTIONAL HAZARDS MODEL

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## **Abstract.**

A common approach to testing for differences between the survival rates of two therapies is to use a proportional hazards regression model which allows for an adjustment of the two survival functions for any imbalance in prognostic factors in the comparison. An alternative approach to this problem is to plot the difference between the two predicted survival functions with a confidence band that provides information about when these two treatments differ. Such a band will depend on the covariate values of a given patient. In this paper we show how to construct a confidence band for the difference of two survival functions based on the proportional hazards model. A simulation approach is used to generate the bands. This approach is used to compare the survival probabilities of chemotherapy and allogeneic bone marrow transplants for chronic leukemia.

## **1. Introduction**

A common problem encountered in biomedical applications is the comparison of the survival rates of two treatments. In this comparison one tests whether the two treatments have the same survival function or equivalently the same hazard function over a given time period. When there are additional covariates associated with survival then this testing is typically performed in the framework of a Cox (1972) proportional hazards model.

When the testing results indicate that two survival functions are different, patients and physicians often want to know “at what times are these two treatments different?”. This is particularly important when one treatment has a higher early survival but lower long term survival. This question is of particular interest in comparing the survival rates of bone marrow transplantation (BMT) and conventional chemotherapy patients. Here, bone marrow transplantation patients may have a higher early mortality rate, due to treatment toxicity, and a lower late death rate, due to a reduced relapse risk.

To answer this question, it is useful to plot the estimate of the difference between the two survival functions along with a confidence band for the difference. Visually examining these

plots and comparing the confidence bands with the zero line summarizes how the difference between the two survival functions change with time. Recently, Parzen *et al* (1997) used the Kaplan-Meier (1958) estimators of the two survival functions,  $\hat{F}_1(\cdot)$  and  $\hat{F}_2(\cdot)$ , to estimate the difference between the survival functions and they proposed a simulation method to construct a confidence band for this difference.

In many applications there is a need, when comparing two treatments, to make adjustments for other covariates that may affect outcome. When the two treatments are found to have different survival rates then patients and physicians want to know “for a given patient with a certain set of covariates, when are the two treatments different?”. In the sequel, we attempt to answer this question by comparing the estimated survival functions for the two treatments using a stratified Cox(1972) proportional hazards model. That is, we estimate the difference between the two conditional survival functions for a particular set of covariate values,  $D(\cdot; z_0) = F_2(\cdot; z_0) - F_1(\cdot; z_0)$ , by  $\hat{D}(\cdot; z_0) = e^{-\hat{\Lambda}_2(\cdot; z_0)} - e^{-\hat{\Lambda}_1(\cdot; z_0)}$  where  $\hat{\Lambda}_i(\cdot; z_0), i = 1, 2$  are the Breslow (1975) type estimate for the cumulative hazard functions.

To find a confidence band for  $D(\cdot; z_0)$ , using the martingale central limit theory one can show that  $\hat{D}(\cdot; z_0)$  converges weakly to a zero mean Gaussian process. It is well known that this limiting Gaussian process does not have independent increments, hence, it is difficult to evaluate this limiting distribution analytically. In the one sample cases, Lin *et al* (1994) proposed a simulation method to construct the confidence bands for  $F(\cdot; z_0)$ . In this paper we propose to use a similar simulation method to construct a confidence band for  $D(\cdot; z_0)$ .

In Section 2, we present the estimates and simulation method used to construct a confidence band for the difference of two survival functions based on a stratified Cox proportional hazards model. In Section 3, we present an example of this technique using chronic leukemia data from The International Bone Marrow Transplant Registry and German CML Study Group.

## 2. Confidence bands for the difference of two survival functions

Let the observations on subject  $j$  of treatment group  $i$  be  $\{X_{ij}, T_{ij}, D_{ij}, Z_{ij}\}$  where  $X_{ij}$  is the left-truncation time,  $D_{ij} = 0$  if subject  $(i, j)$  is censored,  $D_{ij} = 1$  otherwise,  $T_{ij}$  is the observation time of subject  $(i, j)$  which is observed only if  $T_{ij} \geq X_{ij}$ , and  $Z_{ij}$  are the covariates, for  $i = 1, 2$  and  $j = 1, \dots, n_i$ . So the data considered here are left-truncated and right censored. Note that if  $X_{ij} = 0$  for all  $i, j$  then the data is right censored only. We fit a Cox (1972) model stratified on treatment. That is for a patient given treatment  $i, i = 1, 2$ , the hazard function is

$$\lambda_i(t; z) = \lambda_{i0}(t)e^{\beta'z},$$

where  $\lambda_{i0}(t)$  is the baseline hazard functions for treatment  $i$ ,  $z$  is a  $p$ -vector of covariates that influence survival, and  $\beta$  is a  $p$ -vector of unknown regression coefficients.

Here,  $\beta$  can be estimated by maximizing the stratified Cox partial log likelihood function

$$C(\beta, t) = \sum_{i=1}^2 \sum_{j=1}^{n_i} \int_0^t \beta' Z_{ij} dN_{ij}(u) - \sum_{i=1}^2 \int_0^t \log \left( \sum_{j=1}^{n_i} Y_{ij}(u) e^{\beta' Z_{ij}} \right) d\bar{N}_i(u),$$

where  $N_{ij}(u) = I\{X_{ij} \leq T_{ij} \leq u, D_{ij} = 1\}$ ,  $\bar{N}_i = \sum_i N_{ij}$ , and  $Y_{ij}(u) = I\{X_{ij} \leq u \leq T_{ij}\}$  is the indicator of whether the  $j$ th individual is at risk at time  $u$  and is in the  $i$ th treatment group. Note that an individual is at risk only since his or her truncation time, so that the size of the risk set is initially increasing and then decreases.

To compare two predicted survival curves, we estimate the conditional survival functions for the two treatments for a patient with a particular set of covariates  $z_0$ ,

$$F_i(t; z_0) = P(T > t | z_0, \text{ Treatment } i) = e^{-\Lambda_i(t; z_0)},$$

where  $\Lambda_i(t | z_0) = e^{\beta' z_0} \int_0^t \lambda_{i0}(u) du$ . An estimator of the cumulative baseline hazard rate for treatment  $i$ ,  $i = 1, 2$  is given by Breslow's (1975) estimator

$$\hat{\Lambda}_{i0}(t) = \int_0^t \frac{d\bar{N}_i(u)}{\sum_{j=1}^{n_i} Y_{ij}(u) \exp(\hat{\beta}' Z_{ij})}.$$

For convenience we introduce the notations

$$\begin{aligned} S_i^{(k)}(\beta, t) &= \frac{1}{n_i} \sum_{j=1}^{n_i} Y_{ij}(t) Z_{ij}^{\otimes k} e^{\beta' Z_{ij}}, \\ E_i(\beta, t) &= S_i^{(1)}(\beta, t) / S_i^{(0)}(\beta, t), \\ V_i(\beta, t) &= S_i^{(2)}(\beta, t) / S_i^{(0)}(\beta, t) - E_i(\beta, t), \\ s_i^{(k)}(\beta, t) &= E\{S_i^{(k)}(\beta, t)\}, \\ e_i(\beta, t) &= s_i^{(1)}(\beta, t) / s_i^{(0)}(\beta, t), \\ v_i(\beta, t) &= s_i^{(2)}(\beta, t) / s_i^{(0)}(\beta, t) - e_i(\beta, t), \end{aligned}$$

for  $i = 1, 2$ , and  $k = 0, 1, 2$ , where for a column vector  $a$ ,  $a^{\otimes 0} = 1$ ,  $a^{\otimes 1} = a$ , and  $a^{\otimes 2} = aa'$ .

For simplicity of presentation, we assume  $\{X_{ij}, T_{ij}, D_{ij}, Z_{ij}\}$ , ( $j = 1, \dots, n_i$ ) are independent and identically distributed,  $P(T_{ij} \geq X_{ij}) > 0$ , and  $\{Z_{ij}\}$  is bounded. Left-truncated and right-censored survival data has been studied extensively. The more general conditions required to obtain large sample results for this type of data can be found in Woodroffe (1985), Lai and Ying (1991) and Andersen *et al* (1993). Andersen *et al* (1993) argued that the martingale central limit theory can be applied to the left-truncated data, so that the asymptotic results based on right censored data can be extended to the left-truncated and right censored data. Also we assume that two samples are independent. Let  $n = n_1 + n_2$ . Then, if  $n_i/n \rightarrow p_i > 0$ , for  $i = 1, 2$ ,  $\hat{\beta}$  is a consistent estimate of  $\beta$ , and

$$\sqrt{n}(\hat{\beta} - \beta) \xrightarrow{\mathcal{D}} N(0, \Sigma^{-1}),$$

where

$$\Sigma = \sum_{i=1}^2 p_i \int_0^\infty v_i(\beta, t) s^{(0)}(\beta, t) \lambda_{i0}(t) dt,$$

which is assumed to be positive definite and can be consistently estimated by the observed information matrix

$$\hat{\Sigma} = \frac{1}{n} \sum_{i=1}^2 \int_0^\infty V_i(\hat{\beta}, t) d\bar{N}_i(t).$$

To find the limiting distribution of

$$W(t; z_0) = \sqrt{n} \{ [\hat{F}_2(t; z_0) - \hat{F}_1(t; z_0)] - [F_2(t; z_0) - F_1(t; z_0)] \},$$

the delta-method can be used to show that this process behaves asymptotically like

$$W_1(t; z_0) = \sqrt{n} \{ F_1(t; z_0) [\hat{\Lambda}_1(t; z_0) - \Lambda_1(t; z_0)] - F_2(t; z_0) [\hat{\Lambda}_2(t; z_0) - \Lambda_2(t; z_0)] \}.$$

Let  $N_{ij}$  be the observed counting process and define the martingales

$$M_{ij}(t) = N_{ij}(t) - \int_0^t Y_{ij}(u) e^{\beta' Z_{ij}} \lambda_{i0}(u) du, \quad (1)$$

for  $i = 1, 2$  and  $j = 1, \dots, n_i$ . Let  $\bar{M}_i = \sum_{j=1}^{n_i} M_{ij}$ , Andersen and Gill (1982) showed that  $W_1(t; z_0)$  is asymptotically equivalent to

$$\begin{aligned} \widetilde{W}(t; z_0) &= \sqrt{n} F_1(t; z_0) \int_0^t \frac{e^{\beta' z_0} d\bar{M}_1(u)}{n_1 S_1^{(0)}(\beta, u)} - \sqrt{n} F_2(t; z_0) \int_0^t \frac{e^{\beta' z_0} d\bar{M}_2(u)}{n_2 S_2^{(0)}(\beta, u)} \\ &+ \left( F_1(t; z_0) h_1(t; z_0) - F_2(t; z_0) h_2(t; z_0) \right)' \Sigma^{-1} \left\{ \frac{1}{\sqrt{n}} \sum_{i=1}^2 \sum_{j=1}^{n_i} \int_0^\infty [Z_{ij} - E_i(\beta, u)] dM_{ij}(u) \right\}, \quad (2) \end{aligned}$$

where  $h_i(t; z_0) = \int_0^t e^{\beta' z_0} [z_0 - e_i(\beta, u)] \lambda_{i0}(u) du$ , which can be estimated by

$$\hat{h}_i(t; z_0) = \int_0^t e^{\hat{\beta}' z_0(u)} [z_0 - E_i(\beta, u)] \frac{d\bar{N}_i(u)}{n_i S_i^{(0)}(\hat{\beta}, u)}.$$

By Rebolledo's martingale central limit theorem we can show that  $\widetilde{W}(t; z_0)$  converges weakly to a zero mean Gaussian martingale on  $[0, \tau]$ , where  $\tau < \inf\{t : EY_{ij}(t) = 0\}$ , with covariate function

$$\begin{aligned} \xi(t, v; z_0) &= \sum_{i=1}^2 \frac{1}{p_i} F_i(t; z_0) F_i(v, z_0) \int_0^{t \wedge v} \frac{e^{2\beta' z_0} \lambda_{i0}(u) du}{s_i^{(0)}(\beta, u)} \\ &+ \left( F_1(t; z_0) h_1(t; z_0) - F_2(t; z_0) h_2(t; z_0) \right)' \Sigma^{-1} \left( F_1(v; z_0) h_1(v; z_0) - F_2(v; z_0) h_2(v; z_0) \right). \end{aligned}$$

It follows that the variance of  $W(t; z_0)$  can be consistently estimated by

$$\begin{aligned} \hat{\sigma}^2(t; z_0) &= \sum_{i=1}^2 \frac{n}{n_i^2} \hat{F}_i^2(t; z_0) \int_0^t \frac{e^{2\hat{\beta}'z_0} d\bar{N}_i(u)}{[S_i^{(0)}(\hat{\beta}, u)]^2} \\ &+ \left( \hat{F}_1(t; z_0) \hat{h}_1(t; z_0) - \hat{F}_2(t; z_0) \hat{h}_2(t; z_0) \right)' \hat{\Sigma}^{-1} \left( \hat{F}_1(t; z_0) \hat{h}_1(t; z_0) - \hat{F}_2(t; z_0) \hat{h}_2(t; z_0) \right). \end{aligned}$$

The limiting Gaussian process for  $W(t; z_0)$  does not have independent increments, which makes the computation of the distribution of limiting functionals of  $W(t; z_0)$  difficult. To approximate these limiting distributions we shall use a modification of a Monte Carlo technique proposed recently by Parzen *et al* (1997) and Lin *et al* (1994). First, note that the martingales  $\{M_{ij}(u)\}$  in (1) have mean zero and variance  $\{N_{ij}(u)\}$ . By the results in Lin *et al* (1994), if one replaces  $\{M_{ij}(u)\}$  with  $\{G_{ij}N_{ij}(u)\}$ , in (2), where  $G_{ij}$  are independent standard normal random variables, then the limiting distribution of  $\widetilde{W}$ , evaluated using the estimated regression coefficients and covariance matrix is the same as that of  $W$ . In particular, to construct the confidence band for  $D(t; z_0) = F_2(t; z_0) - F_1(t; z_0)$ ,  $t \in [t_1, t_2]$ , we simulate  $N$  realizations of

$$\hat{B}(t; z_0) = \widehat{W}(t; z_0) / \hat{\sigma}(t; z_0),$$

with

$$\begin{aligned} \widehat{W}(t; z_0) &= \sqrt{n} \hat{F}_1(t; z_0) \sum_{j=1}^{n_1} \int_0^t \frac{e^{\hat{\beta}'z_0} G_{1j} dN_{1j}(u)}{n_1 S_1^{(0)}(\hat{\beta}, u)} - \sqrt{n} \hat{F}_2(t; z_0) \sum_{j=1}^{n_2} \int_0^t \frac{e^{\hat{\beta}'z_0} G_{2j} dN_{2j}(u)}{n_2 S_2^{(0)}(\hat{\beta}, u)} \\ &+ \left( \hat{F}_1(t; z_0) \hat{h}_1(t; z_0) - \hat{F}_2(t; z_0) \hat{h}_2(t; z_0) \right)' \hat{\Sigma}^{-1} \left\{ \frac{1}{\sqrt{n}} \sum_{i=1}^2 \sum_{j=1}^{n_i} \int_0^\infty [Z_{ij} - E_i(\hat{\beta}_0, u)] G_{ij} dN_{ij}(u) \right\}. \quad (3) \end{aligned}$$

A  $(1 - \alpha) \times 100\%$  confidence band for  $D(t; z_0)$  over the interval  $[t_1, t_2]$  is given by

$$[\hat{F}_2(t; z_0) - \hat{F}_1(t; z_0)] \pm n^{-1/2} C_\alpha \hat{\sigma}(t; z_0),$$

where  $C_\alpha$  is the  $(1 - \alpha) \times 100th$  percentile of the sample  $\bar{B}^{(k)} = \text{Sup}_{t \in [t_1, t_2]} |\hat{W}^{(k)}(t; z_0) / \hat{\sigma}(t; z_0)|$ , for  $k = 1, \dots, N$ , simulated from (3).

### 3. Example

To illustrate this approach we compare the survival probabilities of chronic phase chronic myelogenous leukemia (CML) patients treated with conventional chemotherapy against patients treated by an allogeneic bone marrow transplants. Patients treated with conventional chemotherapy were from a multicenter trial conducted by the German CML study group. Of the 196 patients in that study, 75 recieved primary treatment with interferon and 121 with hydroxyurea. Patients in this study arm were followed from the time of diagnosis to death or until the end of the study.

The transplant cohort included 548 patients receiving hydroxyurea or interferon pre-treatment and a HLA-identical sibling bone marrow transplant (BMT). All patients were reported to the International Bone Marrow Transplant Registry (IBMTR). IBMTR is a voluntary working group of over 300 transplant centers worldwide that contribute data on their allogeneic bone marrow transplants to a Statistical Center at the Medical College of Wisconsin. Patients in this arm were diagnosed between 1983 and 1991, and were between 15 and 55 years of age. For detailed patient characteristics see Gale *et al* (1998).

The IBMTR only records data on consecutive transplants from member institutions and does not provide data on patients who died while waiting for a transplant. Thus the transplant data is left truncated at the time of transplant. This left truncation can lead to a time-to-treatment bias (See Klein and Zhang (1996)) unless a proper adjustment is made to the risk set. Hence, at each time point, the risk set in the non-transplant cohort consists of all patients still under study while the risk set in the transplant cohort includes only those with a waiting time to transplant less than the current time point who are still under study.

For the CML data, the following covariates were associated with survival: sex (1–female, 0–male), spleen size (1– $\geq 10$  cm, 0–otherwise), year of diagnosis (1– $\geq 1998$ , 0–otherwise), and age at diagnosis (1– $\geq 35$  years, 0–otherwise). A test of interaction indicated that year of diagnosis had a different effect for the two treatments. We fit it separately for the two treatments. Also, the proportionality assumption did not hold for treatment effect, indicating that the relationship between treatment and outcome differed over time. We fit a Cox model stratified on treatment to the time from diagnosis to death. The regression coefficient estimates are given in Table 1.

**Table 1.** Regression coefficient estimates.

Variable	Coefficient Estimate	Standard Error
Sex	-0.434	0.139
Spleen size	0.461	0.146
Age	0.198	0.139
Year of diagnosis:		
Chemotherapy	0.120	0.216
Transplant	-0.553	0.182

When comparing two survival curves based on left-truncated data additional care is required in choosing the comparison interval,  $[t_1, t_2]$ . It is important to choose  $t_1$  such that the risk sets at  $t_1$  consists of a sufficient number of patients for both cohorts in order to make a stable comparison. We choose the comparison interval as  $[6.4, 100.4]$  months since diagnosis. At 6.4 month, the sizes of the risk sets were 189 and 117 for non-transplant and transplant cohort respectively, and at 100.4 month both cohort had at least 10 patients still at risk.

We plot the predicted survival curves and the estimated differences for a particular set of covariates values. The critical value  $C_\alpha$  was approximated based on 5,000 realizations of (3).

Figure 1a shows the estimated survival curves for a recently diagnosed ( $\geq 1988$ ) older ( $\geq 35$  years) male patient with large spleen size  $\geq 10$  cm. Figure 1b shows the estimated difference (BMT-Chemotherapy) between the two survival curves with a 95% pointwise confidence interval and 95% confidence band for such a patient. A similar plot for a patient diagnosed prior to 1988 with the same characteristics is given in Figure 2.

These confidence band plots indicated that the chemotherapy treatment has an early survival advantage due, perhaps, to the toxicity of the bone marrow transplant. There is a significant late survival advantage for transplant patient due to a lower relapse rate. Also for the recently treated cases (Figure 1) BMT had a survival advantage (95% confidence band is  $> 0$ ) starting at 5.50 years after diagnosis. This is in contrast to patients treated prior to 1988 (Figure 2) where BMT started to show an advantage only after 8.29 years since diagnosis. This may be due to the improvement of bone marrow transplant techniques over the years.

In this example, there are 16 sets of possible covariates values. The time points since diagnosis where BMT starts to have a survival advantage are presented in Table 2. These time points ranged from 5.50 years to 8.29 years since diagnosis depending on the given patient characteristics. By contrast to the comparison of two Kaplan-Meier survival curves, this comparison of two predicted survival curves based on the Cox model provides more information to both the physicians and patients.

**Table 2.** Time points  $t_0$  since diagnosis (DX) in years where BMT starts to have survival advantage.

Covariate Values				$C_\alpha$	$t_0$
Sex	Spleen Size	Age	Year of DX		
M	< 10 cm	< 35	< 88	2.96	7.84
M	< 10 cm	< 35	$\geq 88$	2.97	5.97
M	$\geq 10$ cm	< 35	< 88	2.96	7.84
M	$\geq 10$ cm	< 35	$\geq 88$	2.99	5.88
M	< 10 cm	$\geq 35$	< 88	2.99	7.84
M	< 10 cm	$\geq 35$	$\geq 88$	2.95	5.88
M	$\geq 10$ cm	$\geq 35$	< 88	2.96	8.29
M	$\geq 10$ cm	$\geq 35$	$\geq 88$	2.94	5.50
F	< 10 cm	< 35	< 88	2.96	8.29
F	< 10 cm	< 35	$\geq 88$	2.93	5.97
F	$\geq 10$ cm	< 35	< 88	2.99	7.84
F	$\geq 10$ cm	< 35	$\geq 88$	2.98	6.24
F	< 10 cm	$\geq 35$	< 88	2.92	7.84
F	< 10 cm	$\geq 35$	$\geq 88$	2.89	5.97
F	$\geq 10$ cm	$\geq 35$	< 88	2.90	7.84
F	$\geq 10$ cm	$\geq 35$	$\geq 88$	2.92	5.88



## 4. Remarks

Plotting the confidence band for the difference of two predicted survival functions provides a valuable decision making tool for physicians and patients. The proposed simulation method is easy to program, and offers a flexible way to construct such confidence bands, particularly when the limiting distributions cannot be evaluated analytically. The proposed simulation method can be extended to compare the difference of two survival curves based on other models, such as Aalen's (1989) additive model or other more general models.

The estimated critical value,  $C_\alpha$ , depends on the number of realizations  $N$ . It is important to know what is the appropriate  $N$ . In our example for an early diagnosed young ( $< 35$  yr) male patient with small spleen size ( $< 10$  cm), the estimated  $C'_\alpha$ 's were 3.01, 2.98, 2.97, 3.01, 2.97, and 3.01 for  $N = 500, 1500, 3000, 5000, 8000$  and  $10000$ , respectively. It appears that the estimate of  $C_\alpha$  is reasonably stable after only 500 replications.

## ACKNOWLEDGMENTS

This research was supported by Grant 2 RO1 CA54706-06 from the National Cancer Institute, and PO1-CA-40053 from the National Cancer Institute, the National Institute of Allergy and Infectious Diseases and The National Heart, Lung and Blood Institute. We thank the IBMTR and the German CML Study Group for providing us the CML data

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Figure 1(a). Predicted Probability of Survival for Recently Diagnosed, Older, Male Patient with Large Spleen Size

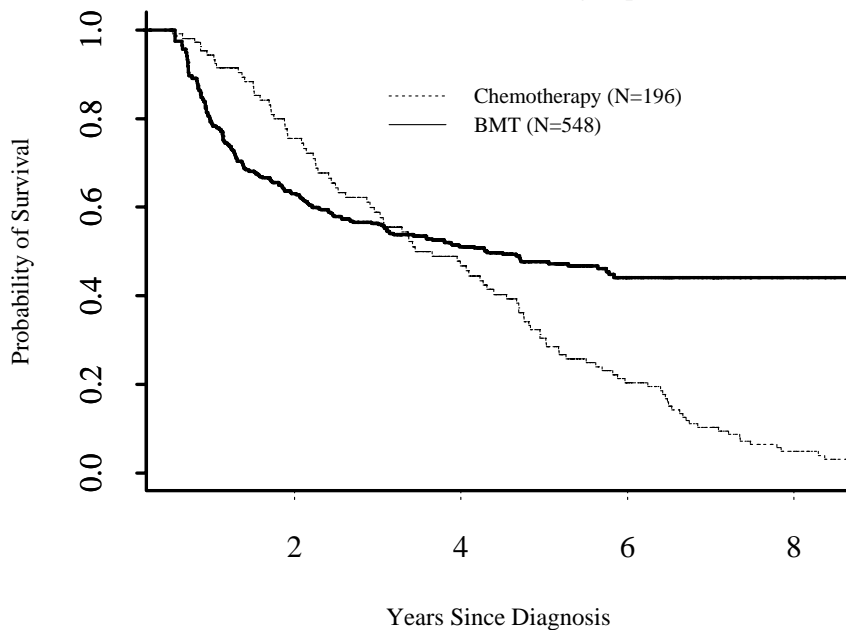


Figure 1(b). Difference of Survival Probabilities (BMT - Chemotherapy) for Recently Diagnosed, Older, Male Patient with Large Spleen Size

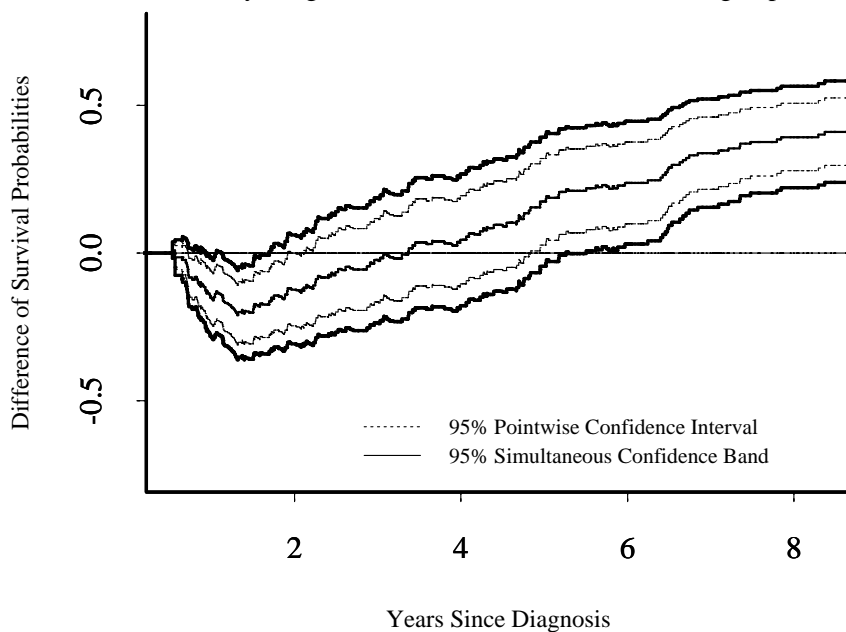


Figure 2(a). Predicted Probability of Survival for Early Diagnosed, Older, Male Patient with Large Spleen Size

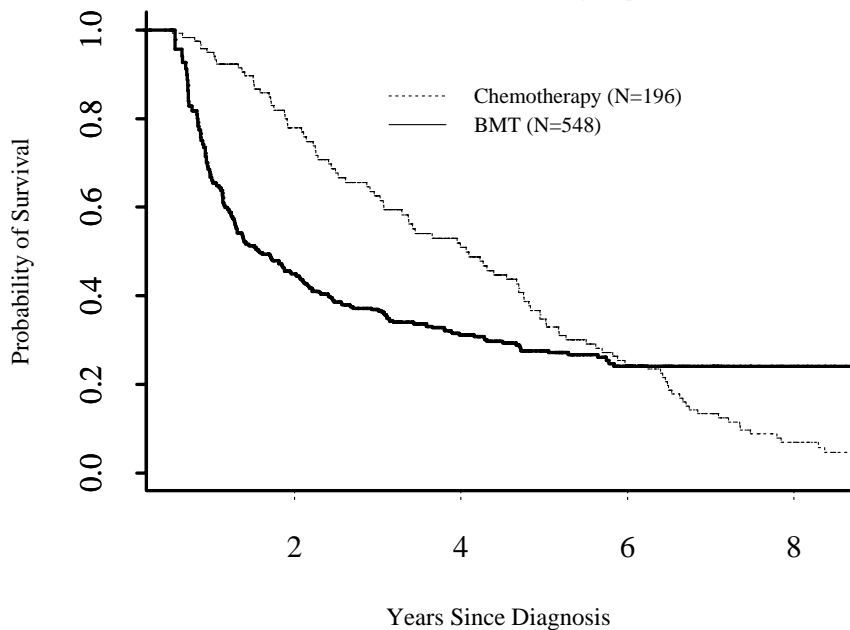


Figure 2(b). Difference of Survival Probabilities (BMT - Chemotherapy) for Early Diagnosed, Older, Male Patient with Large Spleen Size

