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Comparison of restricted mean survival times between treatments based on a stratified Cox model

Abstract: Causal inference in survival analysis has been centered on treatment effect assessment with adjustment of covariates. The direct adjustment method is usually employed to find the survival function of a treatment. A Cox model that stratifies the cumulative hazard by treatment is an ideal choice for performing direct adjustment because the treatment effects are allowed to vary over time. A SAS macro was developed to implement comparison of direct adjusted survivals between treatments at a selected time point. The restricted mean survival time can be derived from a direct adjusted survival function. This statistic summarizes the survival outcome of a treatment. Comparison of restricted means provides assessment of treatment effect over a time interval. The first aim of this article was to provide an overview of the restricted mean survival time. The second aim was to introduce a SAS macro that computes the restricted mean survival times from direct adjusted survivals based on a stratified Cox model. Data preparation and macro invocation are illustrated in an analysis of survival data involving three types of stem cell transplants.

Keywords: direct adjusted survival; restricted mean survival time; stratified Cox model.

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Introduction

A central problem in medical studies is comparing the survival outcomes of different treatments. The exploratory investigation on this matter is to plot the Kaplan-Meier survival curves of all treatment groups. The p value of the log-rank test is often added to the figure to indicate whether any significant differences exist between the treatments. The Kaplan-Meier curves of treatments are usually biased because in observational studies, the distribution of confounding variables is imbalanced between treatment groups. A proper regression model needs to be selected and constructed to adjust for the effects of confounding variables. The treatment-specific survivals will be predicted based on the selected regression model. The Cox model [1] is commonly utilized in analysis of survival data. In a Cox model, the effect of a covariate will be interpreted as a constant hazard ratio. This type of interpretation is easily understood by patients and researchers. When the primary goal is to assess treatment effects, one can consider a stratified Cox model that allows the hazard functions of treatments to vary over time:

$$\lambda_k(t|z)=\lambda_{0k}(t)\exp(\beta^T z), \quad (1)$$

where $\lambda_{0k}(t)$ is the baseline hazard rate function for the kth treatment, β is the vector of regression coefficients, and z is the vector of covariates.

Let $\Lambda_{0k}(t)$ be the cumulative baseline hazard function where $\Lambda_{0k}(t)=\int_0^t \lambda_{0k}(u)\,du$. Prediction of survival of treatment k, given covariate z, can be obtained by the formula $S_k(t|z)=\exp\{-\Lambda_{0k}(t)\exp(\beta^T z)\}$. It is practically important to have the overall survival of treatment k with adjustment of covariates. Direct adjustment, a common epidemiological method, can be employed to define the needed quantity. One may consider the survival functions for all patients in the sample, given that they would have all received treatment k. The average of these survival functions represents the overall survival outcome for treatment k and is known as the direct adjusted survival of treatment k. Suppose that patient characteristics in the sample of K treatment groups can be summarized as Z_{ij} for $i=1, \ldots, K$, $j=1, \ldots, n_i$. Let n be the sample size, where $n=\sum_{i=1}^{K} n_i$. The direct adjusted survival function of treatment k can be defined as $\bar{S}_k(t)=n^{-1}\sum_{i=1}^{K}\sum_{j=1}^{n_i} S(t|Z_{ij})$, where the survival functions for individual patients rely on the underlying regression model. Chang et al. [2], Makuch [3], and Gail and Byar [4] studied the inferences of the direct adjusted survival function by considering a regular Cox model. Zhang et al. [5] developed a SAS macro implementing the inferences of the function based on the stratified Cox model given in Eq. (1).

When the survival functions of treatments cross each other, the results for comparing the survivals at different time points may not be consistent. It is very helpful if we can obtain the summary statistics of a survival function such as the mean or median survival time. The mean survival time is mathematically defined as the total area between a survival function and the *x*-axis. When the largest observed time of a sample is a censoring time, the survival function beyond the largest time is unestimable. This brings complexity in estimating the mean survival time because one has to guess the tail pattern of the survival function. The restricted mean survival time is more appealing because it is a well-defined quantity as long as the reference time τ is smaller than the largest time of the sample. This quantity can be interpreted as the expected survival time restricted to the common follow-up time τ among patients. Let $S(t)$ be a general survival function. The mathematical definition of restricted mean survival time is given by $\mu^{\tau}=\int_0^{\tau} S(t)\,dt$. The restricted mean associated with a direct adjusted survival function has been studied by Zucker [6] and Chen and Tsiatis [7]. Comparison between treatments is the main objective for constructing direct adjusted survival functions. Zucker [6] and Chen and Tsiatis [7] developed the inferences for comparing restricted mean survival times between two treatments based on slightly different underlying regression models. Zucker considered a stratified Cox model in which treatment effects can vary over time and levels of covariates have constant hazard ratios. Chen and Tsiatis assumed individual Cox models for the subsamples belonging to each treatment. Both methods offer a sufficient amount of flexibility for modeling the treatment effects. The method of Chen and Tsiatis even takes care of the interaction between covariates and treatments. However, the power for detecting treatment and covariate effects is reduced because of inclusion of too many regression parameters.

One important application of restricted mean survival time is to evaluate treatment efficacy. Comparison of restricted mean survival times of different treatments is especially meaningful when treatment effects dramatically change over time. The restricted mean survival times summarize the survival outcome of different treatments over the interval $[0, \tau]$. Zucker [6] developed the inference for comparing restricted mean survival times between two treatments based on a stratified Cox model. We developed a SAS macro that implemented Zucker's method. This article focused on presenting this SAS macro and introducing its application through a real example.

The remainder of the article is organized as follows. The Methods section centers on the restricted mean of direct adjusted survival based on a stratified Cox model. This section first introduces the restricted mean survival for the univariate survival data, followed by the restricted mean of direct adjusted survival using a stratified Cox model as the underlying regression model. It also presents the inference for comparing restricted mean survivals of different treatments. The third component of this section is a description of a SAS macro that implements the relevant inferences for the restricted mean survival. The Results section presents the analytical results of one real example to illustrate usage of the SAS macro. The final discussions are given in the Discussion section.

Methods

The mean is a parameter about the central tendency of a distribution. Whether the underlying populations have the same mean has been a central statistical problem. If censoring is present, mean survival time may not be estimable. For censored survival data, the restricted mean survival time is a more appealing parameter. In this section, we introduce the concept of the restricted mean survival time with univariate survival data. Next, we discuss the restricted mean survival times of different treatments when multiple covariates are associated with the survival. Finally, we present a SAS macro that computes restricted mean survival times and implements comparison between treatments.

The restricted mean survival for univariate survival data

Suppose that we observe the survival times on everyone in the sample; the mean survival time can be found by obtaining the average of all observed times. In real applications, censoring is the main feature of survival data that the survival time may be censored due to loss to follow-up or end of study. The average of all observed times is a biased estimator of the mean because the actual survival times are longer than the observed censoring times. Estimation of the mean with censored survival data relies on the relation that the mean is the area between the survival function and the *x*-axis. Let $S(t)$ be the survival function and μ be the mean survival time. The relation between the mean and the survival function can be mathematically described by the equation $\mu=\int_0^{\infty} S(t)\,dt$. The well-known Kaplan-Meier estimator can be evaluated to estimate the survival function. One can find the area between the

Kaplan-Meier curve and the *x*-axis and use this area as the estimate of the mean survival time.

When the largest observed time of a sample is a censoring time, the estimated survival curve will not reach the *x*-axis. Estimation of the mean survival time involves projecting the tail of the survival curve, which introduces a large degree of uncertainty into the mean estimate. An alternative parameter, the mean survival time restricted to a reference time point τ, is practically more meaningful. Its mathematical definition is given by $\mu^\tau=\int_0^\tau S(t)\,dt$, the area up to time τ. Suppose that $\hat{S}(t)$ is the Kaplan-Meier estimate of the survival function. A plug-in estimator of μ^τ is given by $\hat{\mu}^\tau=\int_0^\tau \hat{S}(t)\,dt$. The asymptotic properties of $\hat{\mu}^\tau$ can be established through the convergence results of the Kaplan-Meier estimator, and the details can be found in Andersen et al. [8]. Klein and Moeschberger [9] provide the formula for estimating the variance of $\hat{\mu}^\tau$. Let $\hat{\text{var}}(\hat{\mu}^\tau)$ be the variance estimator given in Klein and Moeschberger. In practice, the reference time point τ can be a landmark time point for survival, such as 1 year or 5 years. When survival data are collected from multiple treatment groups, the general rule for selecting τ is to consider some time point no larger than the smallest observed time across the groups. In this way, the restricted mean survival times of all treatments can be properly estimated and comparison between treatments is feasible. Let $\hat{\mu}_k^\tau$ and $\hat{\mu}_l^\tau$ be the restricted means for the *k*th and *l*th treatment, respectively. Comparison of the restricted mean survival times between treatment groups can be performed by evaluating the following test statistic

$$\tilde{Z}_{k\_l}=\frac{\hat{\mu}_k^\tau-\hat{\mu}_l^\tau}{\sqrt{\hat{\text{var}}(\hat{\mu}_k^\tau)+\hat{\text{var}}(\hat{\mu}_l^\tau)}}. \tag{2}$$

One can find the critical value from the standard normal distribution. If the evaluated test statistic is more extreme than the critical value, one should draw the conclusion of rejecting the null hypothesis of equal restricted means.

The restricted means of direct adjusted survivals based on a stratified Cox model

Direct adjustment is a common technique in epidemiology to calculate and compare the event rates between populations of different characteristics. Usage of direct adjustment in analysis of survival data involves selecting a regression model and estimating the survival functions of treatments. The Cox mode is the most popular regression model for analyzing multivariate survival data. The covariate effects based on a Cox model are specified as constant hazard ratios. An important modification on the Cox model for modeling treatment effects is not to assume constant hazard ratios between treatments. Instead, one should let each treatment have its own baseline hazard function, leading to the stratified Cox model given in Eq. (1).

The survival function of the *k*th treatment, given *z*, can be predicted by $S_k(t|z)=\exp\{-\Lambda_{0k}(t)\exp(\beta^T z)\}$. Direct adjusted survival of the *k*th treatment requires averaging the survival functions of all patients in a sample. Suppose that Z_{ij} ($i=1,\ldots,K, j=1,\ldots,n_i$) summarizes patients' characteristics in a sample of *K* treatment groups. Direct adjusted survival of the *k*th treatment is given by

$$\bar{S}_k(t)=n^{-1}\sum_{i=1}^{K}\sum_{j=1}^{n_i}S(t|Z_{ij})=n^{-1}\sum_{i=1}^{K}\sum_{j=1}^{n_i}\exp\{-\Lambda_{0k}(t)\exp(\beta^T Z_{ij})\}. \tag{3}$$

Let $\hat{\beta}$ be the maximum likelihood estimate of the vector of regression coefficients and $\hat{\Lambda}_{0k}$ be the Breslow estimator of the cumulative baseline hazard function. An estimator of direct adjusted survival can be obtained by plugging $\hat{\beta}$ and $\hat{\Lambda}_{0k}$ in the above formula,

$$\hat{\bar{S}}_k(t)=n^{-1}\sum_{i=1}^{K}\sum_{j=1}^{n_i}\hat{S}(t|Z_{ij})=n^{-1}\sum_{i=1}^{K}\sum_{j=1}^{n_i}\exp\{-\hat{\Lambda}_{0k}(t)\exp(\hat{\beta}^T Z_{ij})\}. \tag{4}$$

Zhang et al. provided a SAS macro that computes the direct adjusted survivals of *K* treatments given in Eq. (4). It also implements pointwise comparison of the survivals. It often happens that the survival curves of treatments cross each other and comparison results at different time points may be inconsistent. It is very useful to have a statistic that summarizes the survival outcome in an interval. The restricted mean survival time derived from a direct adjusted survival function will serve this purpose. Treatment effect assessment is straightforward by comparing the restricted mean survival times of different treatments. Based on the direct adjusted survival function of the *k*th treatment, we can define the mean survival time restricted to τ as $\bar{\mu}_k^\tau=\int_0^\tau \bar{S}_k(t)\,dt$. Integrating the estimated direct adjusted survival over *x*-axis, we will get the estimator $\hat{\bar{\mu}}_k^\tau=\int_0^\tau \hat{\bar{S}}_k(t)\,dt$. Zucker [6] studied the asymptotic

properties of this estimator and developed the inference for the difference in the restricted mean survival time between two treatments, $\hat{\bar{\mu}}_k^\tau - \hat{\bar{\mu}}_l^\tau$. Let $\hat{\text{var}}[\hat{\bar{\mu}}_k^\tau - \hat{\bar{\mu}}_l^\tau]$ be the estimator of the variance of $\hat{\bar{\mu}}_k^\tau - \hat{\bar{\mu}}_l^\tau$. Zucker provided the explicated expression of this variance estimator and the proposed test statistic, $Z_{k\_l} = (\hat{\bar{\mu}}_k^\tau - \hat{\bar{\mu}}_l^\tau) / \hat{\text{var}}[\hat{\bar{\mu}}_k^\tau - \hat{\bar{\mu}}_l^\tau]$, that follows the standard normal distribution.

A global test for the restricted mean survival times can be mathematically expressed as $H_0 : \bar{\mu}_1^\tau = \cdots = \bar{\mu}_K^\tau$. A test can be developed by extending Zucker's result. Consider the vector of estimated restricted means, $\hat{\bar{\mu}}^\tau = [\hat{\bar{\mu}}_1^\tau \cdots \hat{\bar{\mu}}_K^\tau]^T$. Let $\hat{\Omega}$ be the estimated variance-covariance matrix for $\hat{\bar{\mu}}^\tau$. The matrix has $\hat{\sigma}_{ii}$ in diagonal positions and $\hat{\sigma}_{ij}$ in off-diagonal positions, where $\hat{\sigma}_{ii}$ is the estimated variance for $\hat{\bar{\mu}}_i^\tau$ and $\hat{\sigma}_{ij}$ is the estimated covariance between $\hat{\bar{\mu}}_i^\tau$ and $\hat{\bar{\mu}}_j^\tau$. In Zucker's paper [6], the formula for $\hat{\sigma}_{ii}$ is given in Section 2.2 and $\hat{\sigma}_{ij} = n^{-1}(\tilde{\Psi}_i)^T \hat{\Sigma}^{-1} \tilde{\Psi}_j$. Define the $(K-1)\times K$ matrix D with explicit expression

$$D = \begin{bmatrix} 1 & -1 & 0 & \cdots & 0 \\ 0 & 1 & -1 & & 0 \\ & & \cdots\cdots & & \end{bmatrix}.$$

The test statistic for the null hypothesis is given by $T = (\hat{\bar{\mu}}^\tau)^T D^T (D \hat{\Omega} D^T)^{-1} D \hat{\bar{\mu}}^\tau$. The approximate distribution of T under the null hypothesis is χ^2 with $K-1$ degrees of freedom.

The SAS macro

A SAS macro was developed by Zhang et al. [5] to compute the direct adjusted survivals of treatments based on the stratified Cox model. We have revised the macro by adding the restricted mean survival time. The user will need to specify the reference time point τ. The new macro will produce the restricted mean survival times of each treatment, the estimated standard error, and all pairwise comparison results. Data preparation and macro invocation are introduced in this section.

A SAS data set should be prepared to include the variables for time, vital status, treatment, and covariates. The variable of vital status has to take a value of 1 if the survival time is observed and a value of 0 if the censoring time is observed. The variable of treatment takes the values 1, …, K to distinguish K treatment groups.

The macro name is %RESMEAN and saved in the text file "RESMEAN.txt". Suppose that the text file is stored under the root directory of the flash drive G:. The first step is to load the macro from the flash drive into the current SAS session by the statement

%INCLUDE "G:/RESMEAN.txt";

One should write the following statement to invoke the macro:

%RESMEAN(indata, time, event, treatment, covlist, tau, outdata);

One needs to specify seven parameters in order to run this macro: "indata" is the name of the input data set, which contains the aforementioned variables; "time", "event", and "treatment" are the variables for time, vital status, and treatment, respectively; "covlist" is a list of covariates separated by spaces; "tau" is the reference time point for the restricted mean; and "outdata" is the name of the output data set, which contains the direct adjusted survival estimates as well as the estimated standard errors. The output of the macro consists of two parts; the first part is the direct adjust survival estimates and the second one shows restricted mean survival times.

Results

The analytical results of one retrospective study of 904 follicular lymphoma patients are presented in this section. The objective of the study was to assess the efficacy of three types of stem cell transplants. The data set was used as an illustrative example for estimating direct adjusted survival and comparison of direct adjusted survivals at the selected time point [5]. In this section, this example was revisited to illustrate the application of restricted mean survival times of treatments. Using this statistic, we were able to evaluate the overall treatment effects over a time interval.

Besien et al. [10] conducted a retrospective study to assess the efficacy of three types of transplants on follicular lymphoma patients, and the data source was the Center of International Bone Marrow Transplant Registry (CIBMTR). The CIBMTR is a repository of results of blood and bone marrow transplants at more than 450 centers worldwide. The patient population of this study consisted of 904 follicular lymphoma patients receiving unpurged autologous, purged autologous, or allogeneic transplants in the time frame 1990 to 1998. A total of 354 deaths were observed, with a median follow-up time of 41 months. Table 1 shows patient characteristics in the

Table 1 Patient characteristics in the three transplantation groups.

	Unpurged autologous	Purged autologous	Allogeneic	p-Value
Age				
≤40 years	100 (17%)	22 (17%)	77 (44%)	<0.001
>40 years	497 (83%)	109 (83%)	99 (56%)	
Disease stage				
Early	350 (59%)	69 (53%)	85 (48%)	0.039
Advanced	247 (41%)	62 (47%)	91 (52%)	
Karnofsky score				
≤80%	183 (31%)	17 (13%)	60 (34%)	<0.001
90%–100%	414 (69%)	114 (87%)	116 (66%)	
Serum LDH				
Normal	389 (65%)	55 (42%)	117 (66%)	<0.001
Abnormal	174 (29%)	27 (21%)	44 (25%)	
Unknown	34 (6%)	49 (37%)	15 (9%)	
Chemosensitivity				
Sensitive	488 (82%)	111 (84%)	118 (67%)	<0.001
Resistant	66 (11%)	14 (11%)	31 (18%)	
Untreated	43 (7%)	6 (5%)	27 (15%)	
Time from diagnosis to transplant				
<1 year	115 (19%)	27 (21%)	26 (15%)	0.425
1–2 years	156 (26%)	32 (24%)	56 (32%)	
>2 years	326 (55%)	72 (55%)	94 (53%)	
Year of transplant				
1990–1993	181 (30%)	70 (53%)	50 (28%)	<0.001
1994–1996	269 (45%)	41 (31%)	64 (36%)	
1997–1998	147 (25%)	20 (15%)	62 (35%)	

three transplantation groups. Patients in the allogeneic group were associated with worse health status as more patients in this group had advanced disease, low Karnofsky performance score, and resistant or untreated chemosensitivity.

We prepared a SAS data set "Transplant" that included the variables "Time", "Event", and "Group", used for the observed time, vital status, and type of transplant, respectively. Values in "Group" were 1 for unpurged autologous transplant, 2 for purged autologous transplant, and 3 for allogeneic transplant. Quite a few factors were identified to be significant predictors of survival, including disease stage, chemosensitivity status, serum lactate dehydrogenase (LDH), Karnofsky score, time from diagnosis to transplant, age, and year of transplant. All these factors were categorical, and for the purpose of regression analysis, we created the following binary variables: "Stage", "Chemo1", "Chemo2", "LDH1", "LDH2", "Kscore", "DX2T1", "DX2T2", "Age40", "Year1", and "Year2". We first set the value 0 to all the variables. These variables were then set to value 1 when the data entry was related to advanced disease, resistant chemosensitivity, untreated chemosensitivity, Karnofsky score ≤80, abnormal LDH, unknown LDH, 1–2 years of waiting before transplant, >2 years waiting before transplant, age >40 years, transplant in 1994–1996, and transplant in 1997–1998, respectively.

We performed Cox analysis and let three transplants have their own baseline hazard functions. The previous study [5] showed that, compared with autologous transplants, the allogeneic transplant had much higher mortality rate within 1 year of transplant but tended to have lower mortality rates afterward. It was of great interest to find the restricted mean survival times of these three transplants. Comparison of the restricted mean survival times would provide important evidence for drawing conclusions about the transplants. We chose 5 years as the reference time point and wrote the following statement to invoke the macro:

%RESMEAN(Transplant, Time, Event, Group, Stage Chemo1 Chemo2 LDH1 LDH2 Kscore DX2T1 DX2T2 Age40 Year1 Year2, 5, Survout);

The direct adjusted survival estimates were provided in the output data set "Survout". We depicted the survival curves in Figure 1 together with the vertical line corresponding to the reference time point. The curve of allogeneic transplant shows a rapid decline in survivorship

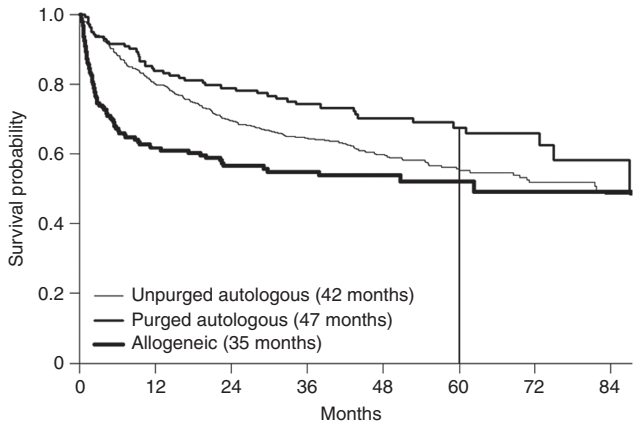

Figure 1 Direct adjusted survival curves of unpurged autologous, purged autologous, and allogeneic transplants.
The restricted mean survival time can be visualized as the area bounded by the survival function, *x*-axis, and the reference line corresponding to the selected time point. Restricted to 5 years, the estimated mean survival times of unpurged autologous, purged autologous, and allogeneic transplants are 42, 47, and 35 months, respectively.

within 12 months after transplant. Meanwhile, two autologous transplants are associated with better short-term survival.

Restricted mean survival times and comparison results were printed in the output window. The output is provided in the remainder of this section, interspersed with interpretation of the results. It was printed in the output that, restricted to 5 years, the estimated mean survival times for unpurged autologous, purged autologous and allogeneic transplants were 42, 47, and 35 months, respectively. Also included in the output were 95% confidence intervals (CIs), 41.6 to 42.6, 45.6 to 48.3, and 33.6 to 36.7 months for these three transplants, respectively.

Mean survival times and 95% CI of different treatments restricted to time 60

Treatment	ResMean	SE	Lower limit	Upper limit
1	42.076	0.257	41.572	42.580
2	46.968	0.677	45.640	48.296
3	35.150	0.766	33.649	36.651

The global comparison of restricted mean survival times was implemented by the χ^2-test given in the section "The restricted means of direct adjusted survivals based on a stratified Cox model". For the transplant example, the test statistic for global comparison followed χ^2 distribution with 2 degrees of freedom. There existed significant differences among the three restricted mean survival times ($p<0.001$).

Comparison of restricted mean survival among all treatments

Res Mean1	Res Mean2	Res Mean3	Chi-stat	p-Value
42.076	46.968	35.150	97.465	0.000

The final part of the output was pairwise comparison of restricted mean survival times. The purged autologous transplant had a significantly longer restricted mean survival time than unpurged autologous and allogeneic transplants did ($p<0.001$ for each comparison). The restricted mean comparison between purged autologous and allogeneic transplants also reached significance ($p<0.001$).

Comparison of restricted mean survival between treatments 1 and 2

Res Mean1	Res Mean2	Difference	SE	Z-stat	p-Value
42.076	46.968	−4.892	0.768	−6.367	0.000

Comparison of restricted mean survival between treatments 1 and 3

Res Mean1	Res Mean3	Difference	SE	Z-stat	p-Value
42.076	35.150	6.926	0.830	8.344	0.000

Comparison of restricted mean survival between treatments 2 and 3

Res Mean2	Res Mean3	Difference	SE	z-stat	p-Value
46.968	35.150	11.818	1.206	9.802	0.000

Discussion

The evaluation of treatment effects based on observational data is a central problem of statistics and causal inference. Within the score of survival analysis, the method of direct adjustment was employed to produce the survival functions of treatments. This article studied the restricted mean survival time of a direct adjusted survival function based on a stratified Cox model. The statistic summarizes the overall survival outcome of a treatment up to a selected time point and is useful in assessing treatment effects. We wrote a SAS macro that implements the inferences of the restricted mean survival time including confidence interval, *K*-sample test, and pairwise comparison. Readers can contact the author to get the macro and sample program.

It should be noted that the results for comparing restricted mean survival times may vary for different

reference time points. It is advisable to choose a time point clinically meaningful and closer to the end of the study so that the majority of survival outcomes will be covered by the time interval. The issue of multiple testing arises in the context of pairwise comparison. We did not implement any multiple adjustment method in the macro because the users may be interested in one comparison only. When more than one comparison is of study interest, one should choose and implement adjustment method to deal with multiplicity.

Inferences of the restricted mean survival times of treatments were also studied by Chen and Tsiatis [7] by considering individual Cox models for each treatment group. Although the power for detecting treatment and covariate effects becomes lower, the method of Chen and Tsiatis provides a feasible solution for possible interactions between treatment and covariate effects. The users can revise the macro to implement this method.

Acknowledgments: The author thanks Ms. Mary Manuel for reading the manuscript. Her valuable comments helped the author to improve the manuscript.

Received June 23, 2013; accepted October 22, 2013

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