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# A REVIEW OF INFERENTIAL PROCEDURES FOR SURVIVAL ANALYSIS IN TWO-STAGE RANDOMIZATION DESIGNS

**WENTAO FENG and ABDUS S. WAHED**

Department of Biostatistics
Graduate School of Public Health
University of Pittsburgh
Pittsburgh, PA 15261, U. S. A.
e-mail: wahed@pitt.edu

## Abstract

Two-stage randomization designs are becoming popular in cancer, AIDS and psychiatric clinical trials. In this article we review available methods for statistical inference for survival data from a two-stage randomization design. We present a simulation study comparing all available methods. Directions on future research are also presented in the discussion.



## 1. Introduction

Two-stage randomization designs are special cases of sequential randomization schemes in dynamic treatment regimes. Dynamic treatment regimes, consisting of two or more stages of therapies are used for treating patients with complex diseases such as cancer, AIDS, hepatitis and depression. In most cases, administration of a therapy in

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one stage depends on the intermediate outcome observed as a result of therapies received in prior stages. The goal is to achieve the largest benefit with the treatment strategy at the individual level. An example might be the case where patients are treated according to one of several available treatments (or different doses of same drug) for a fixed period of time and then based on

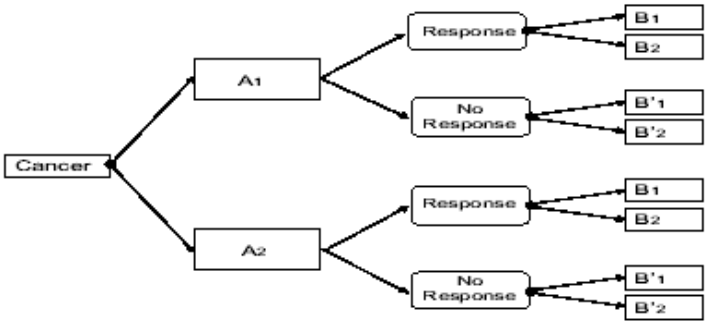


**Figure 1.** A typical two-stage randomization design: full circles, rectangles and arched rectangles represent, respectively, the time of randomization, available treatment arms and the intermediate outcome.

the intermediate response are switched to a different treatment (see, for instance, Rush et al. [12]). Randomized clinical trials comparing treatment strategies with randomization being done upfront to all possible strategies require large number of patients, even when the number of stages and the number of treatment choices at each stage are small. For instance, a clinical trial comparing treatment strategies with three stages and two possible treatment options at each stage requires randomization to $2^3 = 8$ possible regimes. By considering the natural course of treatment, one could randomize patients at the beginning of each stage once they become eligible. For example, to compare treatment strategies for a dynamic treatment regime with two stages and two treatment options at each stage, patients are randomized to one of two possible therapies and depending on the intermediate response, are randomized to further therapies at stage two. A pictorial representation of a standard two-stage design is given in Figure 1. The treatment options $B_j$ and $B'_j$, $j = 1, 2$ may be same or different depending on specific clinical trials. Unlike the situation described in Figure 1, where every

patient receives some sort of therapy at each stage, there may be cases where therapy may be stopped after the first stage if certain clinical conditions are not met. In CALGB clinical trial described below, the non-responding patients did not receive any further treatment in the second stage. Most of the methods discussed in this article are based on a two-stage design where therapy is stopped for patients not responding to the initial treatment. For such designs, the branches involving $B'_j,\ j = 1, 2$ in Figure 1 will not exist.

Clinical trials employing two-stage randomization designs are commonly implemented in biomedical research. We describe two such clinical trials that motivated the methodologies described in this article.

### 1.1. CALGB 8923 trial

Cancer and Leukemia Group B (CALGB) conducted a two-stage clinical trial (Protocol 8923) to investigate the combination of different induction and maintenance therapies. As reported by Stone et al. [13], 388 AML (acute myelogenous leukemia) patients 60 years of age or older participated in this double-blind, placebo controlled trial. Following standard chemotherapy, in the first stage, 195 of these patients were randomly assigned to receive placebo and 193 receive granulocyte-macrophage colony-stimulating factor (GM-CSF). 79 in the GM-CSF group and 90 in the placebo group achieved complete remission and consented to further treatment. In the second stage, 37 GM-CSF and 45 placebo patients were randomly assigned to receive intensification therapy I, and the rest 42 GM-CSF patients and 45 placebo patients to intensification therapy II. The purpose of the trial was to examine the effects of infusions of GM-CSF after initial chemotherapy for elderly patients with AML.

### 1.2. E4494 clinical trial

The E4494 clinical trial conducted by the Eastern Cooperative Oncology Group (ECOG), CALGB and the Southwest Oncology Group (SWOG) and reported by Habermann et al. [3] is another example of TSRD. This study was aimed to address the impact of the addition of rituximab to standard cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) therapy during induction with a second

randomization to maintenance rituximab (MR) or observation on early and late treatment failures in diffuse large *B*-cell lymphoma (DLBCL) in elderly patients. Among the 632 previously untreated patients 60 years of age or older with DLBCL, 318 were randomized to the induction treatment with addition of rituximab (R) to CHOP, and 314 to standard CHOP. In the second stage, out of 415 responding patients, 207 were then randomized to MR and 208 to observation. After ineligibility exclusion, there were 267 R-CHOP and 279 CHOP patents in the induction stage, 174 MR and 178 observation patients in maintenance stage. The goal of the study was to compare the risk of treatment failure, time-to-treatment failure and overall survival among different treatment policies.

## 2. Motivation and Purpose

Traditional methods for analyzing data from two-stage trials separate the two stages, for example, first estimate and compare the survival distributions between two induction treatments for all patients in the study, ignoring the maintenance therapy, then for all responding patents, estimate and compare their survival distributions between two maintenance therapies conditioning on the response, regardless of the induction therapy they had received. The outcome of interest in the second stage is usually taken as the length of time from receiving the maintenance therapy to death or failure. Contrary to implementing intention-to-treat analysis which will be addressed in this article, such methods discard information from the patients who could have potentially received the therapy and consequently reduces the effective sample size and makes the analysis inefficient. More importantly, such methods of analysis are limited to comparing different induction treatments or maintenance treatments, without being able to address the question of finding the best combination of induction and maintenance therapies.

Thall et al. [14] discussed a statistical framework including a family of generalized logistic regression models and an approximate Bayesian method to evaluate each combination of two-stage treatment and select the best strategy. The trial that motivated their methodology involved AML patients who previously achieved a complete remission (CR) but

then relapsed in less than 24 months. At the first stage, all patients were randomized to either the standard chemotherapy: idarubicin + high-dose cytosine arabinoside (IDA), or one of the two experimental treatments: IDA + mylotarg (M) and IDA + topotecan (T). At the second stage, the patients who failed in the IDA group in the first stage were randomly assigned to either IDA + M or IDA + T, while the ones who failed in the IDA + M or IDA + T groups in the first stage were all assigned to receive IDA. For each stage, there were three possible outcomes: CR, death and failure (patient survived without responding). A real-valued objective function was constructed to quantify the trade-off between the probability of response and the risk of death. In the duration of any therapy, interim looks were made to drop the treatment if it was inferior to the others within a subgroup, which made this conduct outcome-adaptive. On the completion of the trial, selection of the best treatment strategy might also be based on the posterior probabilities of the objective function of the two treatment strategies. In this article we focus mainly on estimating survival distributions for specific treatment policies and hence do not elaborate on this study any further.

For the cases where the outcome of the study is survival time, Lunceford et al. [7] proposed a class of consistent, asymptotically normal estimators for the survival distribution of treatment policies. Their framework allowed consistent estimation of survival distributions under intent-to-treat treatment policies. However, these estimators were not efficient and failed to use the auxiliary information collected in the form of covariates. Wahed and Tsiatis [15] obtained the most efficient semi-parametric regular asymptotically linear estimators for survival distribution and related quantities borrowing the idea of semi-parametric theory from Robins et al. [9]. The estimators proposed incorporated auxiliary time independent and time dependent covariates to gain efficiency. The cases of where the data may be right censored, were incorporated in Wahed and Tsiatis [16]. Considering the impractical nature of the most efficient estimator, they also proposed estimators that are easy to compute but are more efficient than Lunceford et al. estimators. Lokhnygina and Helterbrand [6] employed Cox's proportional hazard model to derive a consistent estimator and score test for the log hazard ratio. Guo and Tsiatis [2] proposed a weighted risk set estimator

(WRSE) for the survival distribution with right censoring using the concepts of counting process and risk sets described by Fleming and Harrington [1].

The goal of this article is to provide an exhaustive and comparative review of analytical approaches available for the two-stage randomization designs with survival time as the primary outcome. The aim also is to familiarize the reader with these methods and to point to areas of further methodological research area in this field. We introduce the notations of a typical two-stage randomized design in Section 3. In Section 4, we review some recently developed inferential procedures for estimating the survival distributions of treatment policies in two-stage designs. We compare the performance of different estimators in Section 5 and finish with a conclusion and possible future work in Section 6.

## 3. Model Framework and Notation

Let us consider a two-stage clinical trial similar to the CALGB 8923 study, where the induction treatment is $A$, with levels $A_1$ and $A_2$, and the maintenance treatment is $B$, with levels $B_1$ and $B_2$. The objective is to compare the survival distributions for different treatment policies $A_jB_k$, $j, k = 1, 2$, where $A_jB_k$ stands for "treat with $A_j$ followed by $B_k$ if the patient is eligible and consents to subsequent maintenance therapy." Since the data from patients receiving induction treatment $A_1$ are independent of those from patients with induction treatment $A_2$, in line with most of the papers reviewed here, we focus only on the data from patients who received $A_1$, that is, patients with treatment policies $A_1B_1$ and $A_1B_2$. The methods for policies $A_2B_1$ and $A_2B_2$ follow analogously.

Let us assume that each patient $i$ has an associated set of random variables, also referred to as potential outcomes, $\{R_i, (1 - R_i)T_{0i}, R_iT_i^R, R_iT_{1i}^*, R_iT_{2i}^*, V_i\}$, where $R_i$ is the indicator of the eligible/consent status of patient $i$ on treatment $A_1$, $R_i = 1$ if patient $i$ was eligible and would consent to subsequent maintenance treatment, $R_i = 0$ otherwise; $T_{0i}$ is

the survival time of patient $i$ if s/he was not eligible or refused subsequent maintenance treatment; $T_i^R$ is the time from initial randomization to the time s/he receives maintenance therapy; $T_{1i}^*(T_{2i}^*)$ is the survival time of patient $i$ if s/he was eligible and consented to receive maintenance treatment and received $B_1(B_2)$; $V_i$ is a vector of auxiliary covariates including relevant baseline characteristics for patient $i$. From the definition above, we can see that $T_i^R$ is defined only for those with $R_i = 1$, and all of the three variables $T_{0i}$, $T_{1i}^*$ and $T_{2i}^*$ cannot be observed for the same patient since a patient cannot respond and not respond at the same time and can receive only one of the two maintenance treatments if s/he responds in the 1st stage. These variables, for such reason, are referred to as counterfactuals (Rubin [10] and Holland [4]) or potential random variables.

With the above notations, the survival time for patient $i$ who received treatment policy $A_1B_k$ would be $T_{ki} = (1 - R_i)T_{0i} + R_iT_{ki}^*$. Notice that when $R_i = 1$, $T_{ki}$, $k = 1, 2$ are also potential outcomes since only one of them can be observed based upon the maintenance treatment the patient actually received. Due to the fact that some patients eligible for maintenance therapy $B_k$ may not consent to further treatment or may be randomized to the maintenance therapy $B_{3-k}$, $k = 1, 2$, the inference on features of these distributions addresses directly the "intent-to-treat" question of interest. With the above conceptualization, the primary goal is to estimate parameters and draw inference on the distribution of $T_k$, $k = 1, 2$. Specifically, we consider the problem of estimating $S_k(t) = \Pr(T_k > t) = E\{I(T_k > t)\}$, the survival probability beyond time $t$ for treatment policy $A_1B_k$. In other cases, possible parameters of interest can be the mean or median restricted survival time.

Since in most clinical trials total follow-up time is limited, only restricted survival time up to time $L$ can be considered, where $L$ is some value less than the maximum follow-up time for all patients in the sample, in such cases, $T_k$ will actually represent $\min(T_k, L)$.

If there is no censoring, the observed data can be represented as a set of i.i.d random vectors $\{R_i, R_i T_i^R, V_i, R_i X_{1i}, T_i\}$, $i = 1, ..., n$, where $R_i$, $T_i^R$, $V_i$ are as defined before, and $X_{1i}$ denotes the $B$ treatment assignment indicator, defined only if $R_i = 1$, where $X_{1i} = 1$ if assigned to treatment $B_1$, $X_{1i} = 0$ if assigned to treatment $B_2$, and $T_i$ is the observed survival time for patient $i$. Following stable unit treatment value assumption (Rubin [11]), we assume that the observed survival time for patient $i$ is related to the potential outcomes through the relation

$$T_i = (1 - R_i)T_{0i} + R_i\{Z_i T_{1i}^* + (1 - Z_i)T_{2i}^*\}, \tag{1}$$

that is, if a patient is observed to be a non-responder, then his/her observed survival time $T_i$ is equal to the corresponding potential survival time $T_{0i}$; on the other hand if the patient is observed to be a responder and received treatment $B_1(B_2)$, then his/her observed survival time $T_i$ is equal to the corresponding counterfactual survival time $T_{1i}^*$ $(T_{2i}^*)$. In the presence of right censoring, the observed data can be summarized as the collection of i.i.d random vectors $\{U_i, \Delta_i, G_i^H(U_i)\}$, $i = 1, ..., n$, where $U_i = \min(T_i, C_i)$, $\Delta_i = I(T_i \le C_i)$, $C_i$ is the censoring time and $G_i^H(U_i) = \{R_i I(T_i \le x), X_{1i} R_i I(T_i \le x), V_i(x), x \le u\}$, where $V_i(x)$, similar to the $V_i$ defined before, is a vector of auxiliary variables that may additionally be collected on patient $i$ at time $x$. Thus $G_i^H(U_i)$ represents data-history collected on individual $i$ prior to time $u$, which contains the information of the eligibility/consent status, the time of response if responded, the assignment of maintenance treatment and other auxiliary variables of interest of patient $i$.

## 4. Inferences

### 4.1. Naïve estimator

To estimate $S_k(t)$ for the policy $A_1 B_k$, a naïve method is to construct an estimator only using the data from those patients who are consistent with that policy. If there was no censoring, this would mean that one

could average the indicator function $I(T_i > t)$ over all the patients in the set: $\{i : 1 - R_i + R_i X_{ki} = 1\}$, to get

$$\hat{S}_k^{NAÏVE}(t) = \left\{ \sum_{i=1}^{n} (1 - R_i + R_i X_{ki}) \right\}^{-1} \times \sum_{i=1}^{n} (1 - R_i + R_i X_{ki}) I(T_i > t). \quad (2)$$

This naïve estimator takes into account the patients who did not respond and those who were assigned to maintenance treatment $B_k$. However, it neglects those patients who responded and were randomized to treatment $B_{3-k}, k = 1, 2$, as a result, the naïve estimator is expected to underestimate $S_k(t)$ by overestimating the contribution of the non-responders to the survival distribution. Besides, the group of patients that has been used is no longer a random sample from those who could potentially follow the policy $A_1 B_k$. In the cases where their data is censored, Kaplan-Meier estimator for the survival distribution from the group $\{i : 1 - R_i + R_i X_{ki} = 1\}$ could be used to calculate the naïve estimator.

### 4.2. Consistent and asymptotically normal estimators

In order to make more efficient use of the information from patients who are inconsistent with the policy $A_1 B_k$, Lunceford et al. [7] proposed three forms of consistent and asymptotically normal estimators. Assume that the assignment of $B$ treatment is conditionally independent of the potential survival time given the induction treatment and the data collected prior to observing the response. Let the probability of randomization to the $B_1$ -treatment be denoted by $\pi_1 = P(X_{1i} = 1 | R_i = 1)$. Then this assumption could be interpreted as $X_{1i} \perp T_{1i}^*, T_{2i}^* | G_i^H(T_i^R)$, $R_i = 1$. This, in turn, implies that $\Pr(X_{1i} = 1 | T_{1i}^*, T_{2i}^*, G_i^H(T_i^R), R_i = 1) = \Pr(X_{1i} = 1 | R_i = 1) = \pi_1$. This assumption is the "sequential randomization assumption" or the assumption of "no unmeasured confounders" as

discussed in Robins [9]. The probability $\pi_k$ can be allowed to depend on the data-history prior to the randomization including the induction treatment, but for simplicity, we avoid discussing it here. To be consistent with the examples in the Section 1, we take $\pi_1$ to be known by design. Let us define $\pi_2 = 1 - \pi_1 = \Pr(X_{1i} = 0 | R_i = 1) = \Pr(X_{2i} = 1 | R_i = 1)$, where $X_{2i} = 1 - X_{1i}$. Let $K(u) = \Pr(C_i > u)$ denote the survival distribution for the censoring time $C_i$. Assume also that the censoring time is independent of the observed data and counterfactuals.

The first estimator in the sequel of three is defined as the weighted average of the patients who are consistent with the treatment policy. Since by definition, non-responders are consistent to the policy $A_1 B_k$, they were given unit weight in the construction. Responders who were assigned to $B_k$ with randomization probability $\pi_k$ are also consistent with the policy. But, due to the fact that some of the responders were randomized to the other $B$ treatment, each patient receiving $B_k$ represents $\frac{1}{\pi_k} - 1$ other similar patients who could have potentially be assigned to $B_1$ treatment, and thus received the weight $\frac{1}{\pi_k}$. Combining both, the weight function takes the form $Q_{ki} = 1 - R_i + \frac{R_i X_{ki}}{\pi_k}$, $k = 1, 2$. Additionally, since patients may be censored at any time, a second form of weighting was applied to account for the censored patients. Each uncensored patient with survival time $U_i$ represents $\frac{1}{K(U_i)} - 1$ prognostically similar patients who survived beyond time $U_i$ and thus receives a weight of $\frac{1}{K(U_i)}$. Thus the combined weight for a patient with complete survival time $U_i$ becomes $\frac{\Delta_i Q_{ki}}{K(U_i)}$. Since $K(u)$ is unknown, it is usually estimated by the Kaplan-Meier estimator of the censoring survival curve $\hat{K}(U) = \prod_{u \le t} \{1 - \mathrm{d}N^c(u)/Y(u)\}$, with $N^c(u) = \sum_{i=1}^{n} I(U_i \le u,$

$\Delta_i = 0)$ and $Y(u) = \sum_{i=1}^{n} I(U_i \geq u)$, resulting in an estimated weight function $\Delta_i Q_{ki}/\hat{K}(U_i)$. The estimator for the survival function $S_k(t)$ is then defined as

$$\hat{S}_k^{IPMW}(t) = 1 - n^{-1}\sum_{i=1}^{n} \frac{\Delta_i Q_{ki}}{\hat{K}(U_i)} I(U_i \leq t), \quad k = 1, 2. \tag{3}$$

It was shown that if the true $K(\cdot)$ is substituted in the above equation, then $\hat{S}_k^{IPMW}(t)$ is unbiased for $S_k(t)$. $\hat{S}_k^{IPMW}(t)$ in equation (2) is an example of an inverse-probability-of-missing-weighted (IPMW) estimator (Horvitz-Thompson estimator, Horvitz and Thompson [5]). The second estimator was obtained by averaging using a probabilistically adjusted sample size, i.e.,

$$\hat{S}_k^{PA}(t) = 1 - \left\{\sum_{i=1}^{n} \frac{\Delta_i Q_{ki}}{\hat{K}(U_i)}\right\}^{-1} \sum_{i=1}^{n} \frac{\Delta_i Q_{ki}}{\hat{K}(U_i)} I(U_i \leq t), \quad k = 1, 2 \tag{4}$$

Lunceford et al. observed that both $\hat{S}_k^{IPMW}(t)$ and $\hat{S}_k^{PA}(t)$ are solutions of the equations of the form $\sum_{i=1}^{n} \frac{\Delta_i}{\hat{K}(U_i)}\{Q_{ki} I(U_i \leq t) + S_k(t) - 1 - \alpha_k(Q_{ki} - 1)\}$ $= 0$ with $\alpha_k$ set to 0 and $1 - S_k(t)$, respectively. Thus the third estimator was constructed by choosing the $\alpha_k$ that minimizes the variance among all solutions. To be specific, the third estimator has the form

$$\hat{S}_k^{LDT}(t) = 1 - n^{-1}\sum_{i=1}^{n} \frac{\Delta_i Q_{ki}}{\hat{K}(U_i)} I(U_i \leq t) + \hat{\alpha}_k n^{-1} \sum_{i=1}^{n} \frac{\Delta_i}{\hat{K}(U_i)}(Q_{ki} - 1), k = 1, 2, \tag{5}$$

where

$$\hat{\alpha}_k = \left[ n^{-1}\sum_{i=1}^{n} \Delta_i Q_{ki}(Q_{ki} - 1)\frac{I(U_i \geq u)}{\hat{K}(V_i)} + \int_0^L \mathrm{d}N^c(u)\{\hat{K}(u)Y(u)\}^{-1}\hat{E}\{L_{1k}^{\alpha}(t, u)\} \right]$$

$$\div \left[ n^{-1}\sum_{i=1}^{n} (Q_{ki} - 1)^2 + \int_0^L \mathrm{d}N^c(u)\{\hat{K}(u)Y(u)\}^{-1}\hat{E}\{G_k^{\alpha}(u)\} \right],$$

with

$$\hat{E}\{L_k^{\alpha}(t,\, u)\} = n^{-1}\sum_{i=1}^{n}\Delta_i\{Q_{ki}I(U_i \le t) - \hat{G}_{1k}(t,\, u)\}$$

$$\times\{Q_{ki} - 1 - \hat{G}_{Q_k}(u)\}\frac{I(U_i \ge u)}{\hat{K}(U_i)},$$

$$\hat{E}\{G_k^{\alpha}(u)\} = n^{-1}\sum_{i=1}^{n}\Delta_i\{Q_{ki} - 1 - \hat{G}_{Q_k}(u)\}^2\frac{I(U_i \ge u)}{\hat{K}(U_i)},$$

$$\hat{G}_{Q_k}(u) = \{n\hat{S}_k(u)\}^{-1}\sum_{i=1}^{n}\Delta_i(Q_{ki} - 1)\frac{I(U_i \ge u)}{\hat{K}(U_i)},$$

$$\hat{G}_{1k}(u) = \{n\hat{S}_k(u)\}^{-1}\sum_{i=1}^{n}\Delta_i Q_{ki}I(U_i \le t)\frac{I(U_i \ge u)}{\hat{K}(U_i)}.$$

The three estimators $\hat{S}_k^{IPMW}(t)$, $\hat{S}_k^{PA}(t)$ and $\hat{S}_k^{LDT}(t)$ are consistent and asymptotically normal. For details on the asymptotic property of these estimators we refer our readers to Lunceford et al. [7]. These estimators were defined on an ad hoc basis and the formal efficiency issue was not discussed.

### 4.3. Semi-parametric efficient estimator

Under the same framework, assumptions and objective of study, for data without censoring, Wahed and Tsiatis [15] used the semi-parametric theory of missing data described in Robins et al. [9] to characterize the most efficient regular asymptotically linear (RAL; Newey [8]) estimator. They observed that any RAL estimator can be characterized by its influence function and their approach was to find the most efficient influence function for all RAL estimators of $S_k(t)$. However, the most efficient influence function for this problem contains a nuisance parameter in the form of the conditional expectation $\Pr(T_{ki} > t \mid T_i^R, V_i, R_i = 1, X_{ki} = 1)$. One way to construct useful estimators from the most

efficient influence function is to approximate these conditional probability based on patient data history leading to locally efficient estimators. A natural way of estimating $\Pr(T_{ki} > t \mid T_i^R, V_i, R_i = 1, X_{ki} = 1)$ is to use a logistic regression of the binary outcome $I(T_i > t)$ on the covariates $V_i$ and $T_i^R$ within the subgroup of patients with $R = 1$ and $x_k = 1$. For instance, a logistic regression model

$$\Pr(T_{ki} > t \mid T_i^R, V_i, R_i = 1, X_{ki} = 1) = \frac{1}{1 + e^{-(\gamma_0 + \gamma_1 T_i^R + \gamma_2^T V_i)}} = g(T_i^R, V_i; \gamma)$$

will give rise to the locally efficient estimator

$$\hat{S}_k^{LE} = \frac{1}{n}\sum_{i=1}^{n}\left[\left\{(1 - R_i) + \frac{R_i X_{ki}}{\pi_k}\right\} I(U_i > t) - R_i\left(\frac{X_{ki} - \pi_k}{\pi_k}\right) g(T_i^R, V_i; \hat{\gamma})\right] \quad (6)$$

for $k = 1, 2$. This estimator remains consistent even if the function form $g(\cdot)$ is not correctly specified, but if the regression relationship was incorrectly specified, then the gain of efficiency over the IPMW or LDT estimator could not be guaranteed. In the presence of right censoring, an inverse probability weighted version of the locally efficient estimator (6) is given by

$$\hat{S}_k^{IPCWLE}$$

$$= \frac{1}{n}\sum_{i=1}^{n}\frac{\Delta_i}{\hat{K}(U_i)}\left[\left\{(1 - R_i) + \frac{R_i X_{ki}}{\pi_k}\right\} I(U_i > t) - R_i\left(\frac{X_{ki} - \pi_k}{\pi_k}\right) g(T_i^R, V_i; \hat{\gamma})\right] \quad (7)$$

for $k = 1, 2$. We will refer to it as the Inverse Probability of Censoring Weighted Local Efficient (IPCWLE) estimator. The properties of this estimator have not been investigated in previous studies. This estimator is asymptotically unbiased. In addition, in our simulation studies presented later, we find that the relative efficiency of this estimator over IPMW, PA or LDT estimator is close to unity. But this estimator also depends on the specification of the model $g$ and therefore, is subjected to model misspecification.

Wahed and Tsiatis [16] then extended the semi-parametric method to obtain the most efficient estimator in the presence of right censoring. In order to avoid cumbersome calculation in the construction of most efficient estimator, they restricted the search for the optimal estimator to a subclass of the RAL estimators that contains the existing estimators. Letting

$$U_i^* = \min(C_i, T_i^R),\ \Delta_i^* = I(C_i < T_i^R),\ Y_i(u) = I(U_i \geq u),$$

$$\hat{E}_1(u) = \sum_{i=1}^n R_i I(U_i^* < u) X_{ki} Y_i(u) / Y(u),$$

$$\hat{E}_2(u) = Y^{-1}(u) \sum_{i=1}^n \{1 - R_i I(U_i^* < u)\} Y_i(u)$$

and $L_{1i} = \{R_i I(U_i^* < u) X_{ki} - \hat{E}_1(u)\}/\pi_k$, $L_{2i} = 1 - R_i I(U_i^* < u) - \hat{E}_2(u)$, a simplified version of the regular asymptotic linear efficient (RALE) estimator is given by

$$\hat{S}_k^{RALE}(t) = A_n / B_n, \tag{8}$$

where

$$A_n = \frac{1}{n} \sum_{i=1}^n \frac{\Delta_i Q_{ki}}{\hat{K}(U_i)} I(U_i > t) - \frac{1}{n} \sum_{i=1}^n \frac{\Delta_i^* (Q_{ki} - 1)}{\hat{K}(U_i^*)} \hat{\gamma}^T W_i$$

$$+ \sum_{j=1}^2 \frac{1}{n} \sum_{i=1}^n \int \frac{dN_i^c(u)}{\hat{K}(u)} \hat{\varphi}_j(u) L_{ji}(u),$$

and

$$B_n = \frac{1}{n} \sum_{i=1}^n \frac{\Delta_i Q_{ki}}{\hat{K}(U_i)} - \frac{1}{n} \sum_{i=1}^n \frac{\Delta_i^* (Q_{ki} - 1)}{\hat{K}(U_i^*)} \hat{\gamma}_\mu^T W_i$$

$$+ \sum_{j=1}^2 \frac{1}{n} \sum_{i=1}^n \int \frac{dN_i^c(u)}{\hat{K}(u)} \hat{\varphi}_{j\mu}(u) L_{ji}(u),$$

where $\hat{\gamma} = \alpha^{-1}\beta$, $\hat{\gamma}_\mu = -\alpha^{-1}\beta_\mu$, $\hat{\varphi}_1(u) = \zeta^{-1}(u)\eta(u)$, $\hat{\varphi}_{1\mu}(u) = 1$, $\hat{\varphi}_2(u) = \kappa^{-1}(u)\tau(u)$, $\hat{\varphi}_{2\mu}(u) = \kappa^{-1}(u) - \tau_\mu(u)$, where

$$\alpha = n^{-1}\sum_{n}^{i=1}\frac{\Delta_i}{\hat{K}(U_i)}\{K^{-1}(U_i^*)(Q_{ki}-1)^2 W_i W_i^T\},$$

$$\beta = n^{-1}\sum_{n}^{i=1}\frac{\Delta_i}{\hat{K}(U_i)}\{K^{-1}(U_i^*)Q_{ki}(Q_{ki}-1)I(U_i > t)\, W_i\},$$

$$\beta_\mu = n^{-1}\sum_{n}^{i=1}\frac{\Delta_i}{\hat{K}(U_i)}\{K^{-1}(U_i^*)Q_{ki}(Q_{ki}-1)W_i\},$$

$$\tau(u) = n^{-1}\sum_{n}^{i=1}\frac{\Delta_i}{\hat{K}(U_i)}\left[\left\{(1-R_i)I(U_i^* \geq u) + \frac{R_i X_{ki}}{\pi}\right\}I(U_i > t)\right],$$

$$\tau_\mu(u) = n^{-1}\sum_{n}^{i=1}\frac{\Delta_i}{\hat{K}(U_i)}\left\{(1-R_i)I(U_i^* \geq u) + \frac{R_i X_{ki}}{\pi}\right\},$$

$$\kappa(u) = n^{-1}\sum_{n}^{i=1}\frac{\Delta_i}{\hat{K}(U_i)}[I(U_i \geq u)\{1 - R_i I(T_i^R < u)\}],$$

$$\eta(u) = n^{-1}\sum_{n}^{i=1}\frac{\Delta_i}{\hat{K}(U_i)}\{I(U_i^* < u \leq U_i)R_i X_{ki} I(U_i > t)\},$$

$$\zeta(u) = n^{-1}\sum_{n}^{i=1}\frac{\Delta_i}{\hat{K}(U_i)}\{I(U_i^* < u \leq U_i)R_i X_{ki}\}.$$

The estimator $\hat{S}_k^{RALE}$ is consistent and asymptotically normal and is guaranteed to be asymptotically more efficient than the IPMW and LDT estimators since it is the most efficient estimator among a class of estimators including the IPMW and LDT estimators. For details on the proof of asymptotic properties, variance estimates, and the estimates of covariance between $\hat{S}_1^{RALE}(t)$ and $\hat{S}_2^{RALE}(t)$, we refer the readers to Wahed and Tsiatis [16].

### 4.4. Weighted risk set estimator

Guo and Tsiatis [2] derived the Weighted Risk Set Estimator (WRSE) using the concepts of counting process and risk sets, which is an extension of the Aalen-Nelson estimator. This estimator is more intuitive and easier to compute than the above ones. The intention was to use Aalen-Nelson estimator to estimate the cumulative hazard function, however, due to the property of two-stage design, not all counting processes $N_i(u) = I(U_i \le u, \Delta_i = 1)$ and at risk process $Y_i(u) = I(U_i \ge u)$ could be observed, so a time-varying weight function was defined: $W_i(u) = 1 - R_i(u) + R_i(u)Z_i/\pi_z$, where $R_i(u) = R_i I(T_i^R \le u)$ is the indicator of response at time $u$ for patient $i$. With this weight function, the extended Aalen-Nelson estimator for the cumulative hazard under policy $A_1B_1$ is defined as

$$\hat{\Delta}_1(t) = \int_0^t \frac{\sum_{i=1}^n W_i(u)\mathrm{d}N_i(u)}{\sum_{i=1}^n W_i(u)Y_i(u)} \tag{9}$$

and the corresponding estimator for the survival function follows as

$$\hat{S}_1^{WRSE}(t) = \exp\left\{-\int_0^t \frac{\sum_{i=1}^n W_i(u)\mathrm{d}N_i(u)}{\sum_{i=1}^n W_i(u)Y_i(u)}\right\}. \tag{10}$$

It has been shown that WRSE is consistent and asymptotically normal. Detailed proof of the consistency and asymptotically normality of the WRSE is given in Guo and Tsiatis [2].

### 4.5. Cox proportional hazard model

Because of the wide use of Cox regression model in the analysis of survival data, Lokhnygina and Helterbrand [6] derived a consistent estimator for the log hazard in the Cox model. Here we use $X_i = 0(1)$ to denote the randomization for patient $i$ to $B_1(B_2)$. In addition to the sequential randomization assumption and the assumption of independent censoring, this construction like other applications using Cox model,

requires the proportional hazard assumption between two treatment policies. As in a usual Cox proportional hazard model, consider the hazard corresponding to policy $A_1B_{j+1}$ be $\lambda(t \mid X = j)$, $j = 0, 1$, where $\lambda(t \mid X) = \lambda_0(t)\exp(X\beta)$. The estimate of β can be obtained by solving the pseudo-score equation

$$U_{wn}(\beta) = \sum_{i=1}^{n} \int_0^{\infty} w_i \{X_i - \overline{X}_w(u, \beta)\} dN_i(u) = 0, \tag{11}$$

where $w_i = 1 - R_i + R_i(u)(1 - Z_i)/(1 - \pi_z)$ acts as an inverse probability weight, and

$$\overline{X}_w(u, \beta) = \frac{\sum_{j=1}^{n} w_j X_j Y_j(u) \exp(X_j\beta)}{\sum_{j=1}^{n} w_j Y_j(u) \exp(X_j\beta)}.$$

Lokhnygina and Helterbrand [6] showed that the estimator of β is consistent and asymptotically normal. This estimator is easier to implement with available software and intuitively appealing.

## 5. Simulation Study

To evaluate the performance of the methods reviewed in the previous section, several simulations were carried out following Lunceford et al. [7] strategy. We only simulated data for policy $AB_1$ and $AB_2$ since the data from $A_1$ and $A_2$ are independent. All simulations were based on a 2.5-year study for $n = 200$ and 500 subjects. For each individual, censoring time $C$ was generated as uniform (0, 2.5) independent of all other variables. Remission/consent status $R$ were sampled from Bernoulli $(\pi_R)$. Two values of the response rate $\pi_R = 0.4$ and $\pi_R = 0.6$ were used in this simulation. The $B$ treatment indicators were generated from Bernoulli (0.5) distribution. For non-responders $(R = 0)$, a survival time $T_\lambda^*$ was generated from exponential $(\lambda)$, where λ was taken to be 2.22 so that $E(T_\lambda^*)/L = 0.3$, where $L = 1.5$ was the upper limit of the restricted observed lifetime. For responders, a remission/consent time

$T^R$ was drawn from exponential (α). We take $T_1^{**} \sim EXP(e^{\beta_1})$, $T_2^{**} \sim EXP(e^{\beta_1+\beta_2 T_1^{**}})$, where $T_1^{**}$ and $T_2^{**}$ are post-remission survival time under $B_1$ and $B_2$, respectively. The parameters α, $\beta_1$ and $\beta_2$ were chosen to be 6.67, 0.29 and –0.67, respectively, so that $E(T^R)/L = 0.1$, $E(T_1^{**})/L = 0.5$, and $E(T_2^{**})/L = 1.0$. The potential restricted survival times were calculated as $T_1 = \min\{(1 - R)T_\lambda^* + R(T^R + T_1^{**}), L\}$ and $T_2 = \min\{(1 - R)T_\lambda^* + R(T^R + T_2^{**}), L\}$.

**Table 1.** Monte Carlo means, relative biases (bias as a percentage of the true value) and mean squared errors (MSE, expressed as multiples of $10^3$) for estimation of survival probabilities based on 1000 data sets of sizes 200 each. The true values were $S_1(0.5) = 0.450$, $S_2(0.5) = 0.492$, $S_1(1.0) = 0.196$, $S_2(1.0) = 0.261$ for 40% response and $S_1(0.5) = 0.511$, $S_2(0.5) = 0.575$, $S_1(1.0) = 0.240$, $S_2(1.0) = 0.339$ for 60% response

| | | $\pi_R = 0.4$ | | | | | | $\pi_R = 0.6$ | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Policy $AB_1$ | | | Policy $AB_2$ | | | Policy $AB_1$ | | | Policy $AB_2$ | | |
| t(years) | Estimator | $\hat{S}(t)$ | Bias(%) | MSE | $\hat{S}(t)$ | Bias(%) | MSE | $\hat{S}(t)$ | Bias(%) | MSE | $\hat{S}(t)$ | Bias(%) | MSE |
| 0.5 | IPMW | 0.452 | 0.4 | 4.28 | 0.493 | 0.2 | 4.42 | 0.511 | 0.0 | 5.48 | 0.578 | 0.5 | 5.93 |
| | PA | 0.450 | 0.0 | 2.44 | 0.492 | 0.0 | 2.38 | 0.511 | 0.0 | 2.73 | 0.575 | 0.0 | 2.56 |
| | LDT | 0.447 | 0.7(–) | 2.11 | 0.489 | 0.6(–) | 2.00 | 0.508 | 0.6(–) | 2.41 | 0.571 | 0.7(–) | 2.23 |
| | IPCWLE | 0.450 | 0.0 | 2.18 | 0.492 | 0.0 | 2.03 | 0.510 | 0.2(–) | 2.51 | 0.574 | 0.2(–) | 2.27 |
| | WRSE | 0.453 | 0.7 | 1.91 | 0.495 | 0.6 | 1.93 | 0.514 | 0.6 | 2.20 | 0.578 | 0.5 | 2.15 |
| | RALE | 0.446 | 0.9(–) | 2.07 | 0.489 | 0.6(–) | 1.98 | 0.508 | 0.6(–) | 2.35 | 0.572 | 0.5(–) | 2.18 |
| 1.0 | IPMW | 0.197 | 0.5 | 2.84 | 0.263 | 0.8 | 3.58 | 0.239 | 0.4 | 3.84 | 0.341 | 0.6 | 4.81 |
| | PA | 0.196 | 0.0 | 2.29 | 0.262 | 0.4 | 2.65 | 0.238 | 0.8(–) | 2.93 | 0.338 | 0.2(–) | 3.17 |
| | LDT | 0.193 | 1.5 | 2.03 | 0.259 | 0.8(–) | 2.20 | 0.237 | 1.3(–) | 2.62 | 0.335 | 1.2(–) | 2.75 |
| | IPCWLE | 0.194 | 1.0(–) | 2.13 | 0.261 | 0.0 | 2.36 | 0.238 | 0.8(–) | 2.72 | 0.337 | 0.6(–) | 2.92 |
| | WRSE | 0.200 | 2.0 | 1.71 | 0.267 | 1.5 | 2.00 | 0.243 | 1.3 | 2.25 | 0.343 | 1.2 | 2.53 |
| | RALE | 0.192 | 2.0(–) | 1.87 | 0.259 | 0.8(–) | 2.09 | 0.236 | 1.7(–) | 2.41 | 0.336 | 0.9(–) | 2.60 |

**Table 2.** Monte Carlo means, relative biases (bias as a percentage of the true value) and mean squared errors (MSE, expressed as multiples of $10^3$) for estimation of survival probabilities based on 1000 data sets of sizes 500 each. The true values were $S_1(0.5) = 0.450$, $S_2(0.5) = 0.492$, $S_1(1.0) = 0.196$, $S_2(1.0) = 0.261$ for 40% response and $S_1(0.5) = 0.511$, $S_2(0.5) = 0.575$, $S_1(1.0) = 0.240$, $S_2(1.0) = 0.339$ for 60% response

| | | $\pi_R = 0.4$ | | | | | | $\pi_R = 0.6$ | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Policy $AB_1$ | | | Policy $AB_2$ | | | Policy $AB_1$ | | | Policy $AB_2$ | | |
| t(years) | Estimator | $\hat{S}(t)$ | Bias(%) | MSE | $\hat{S}(t)$ | Bias(%) | MSE | $\hat{S}(t)$ | Bias(%) | MSE | $\hat{S}(t)$ | Bias(%) | MSE |
| 0.5 | IPMW | 0.451 | 0.2 | 1.54 | 0.494 | 0.4 | 1.71 | 0.512 | 0.2 | 2.10 | 0.576 | 0.2 | 2.23 |
| | PA | 0.451 | 0.2 | 0.95 | 0.493 | 0.2 | 0.94 | 0.512 | 0.2 | 1.05 | 0.575 | 0.0 | 0.97 |
| | LDT | 0.450 | 0.0 | 0.85 | 0.492 | 0.0 | 0.79 | 0.511 | 0.0 | 0.92 | 0.574 | 0.2 (–) | 0.85 |
| | IPCWLE | 0.450 | 0.0 | 0.85 | 0.493 | 0.2 | 0.80 | 0.511 | 0.0 | 0.97 | 0.576 | 0.2 | 0.85 |
| | WRSE | 0.452 | 0.4 | 0.77 | 0.494 | 0.4 | 0.79 | 0.513 | 0.4 | 0.85 | 0.576 | 0.2 | 0.81 |
| | RALE | 0.450 | 0.0 | 0.78 | 0.492 | 0.0 | 0.78 | 0.511 | 0.0 | 0.87 | 0.574 | 0.2 (–) | 0.82 |
| 1.0 | IPMW | 0.197 | 0.0 | 1.07 | 0.263 | 0.8 | 1.36 | 0.241 | 0.4 | 1.50 | 0.341 | 0.6 | 1.89 |
| | PA | 0.197 | 0.0 | 0.88 | 0.263 | 0.8 | 1.03 | 0.241 | 0.4 | 1.14 | 0.340 | 0.3 | 1.27 |
| | LDT | 0.196 | 0.0 | 0.80 | 0.262 | 0.4 | 0.87 | 0.240 | 0.0 | 1.02 | 0.339 | 0.0 | 1.11 |
| | IPCWLE | 0.197 | 0.5 | 0.87 | 0.263 | 0.8 | 0.89 | 0.241 | 0.4 | 1.09 | 0.340 | 0.3 | 1.14 |
| | WRSE | 0.199 | 1.5 | 0.68 | 0.264 | 1.2 | 0.82 | 0.243 | 1.3 | 0.88 | 0.342 | 0.9 | 1.01 |
| | RALE | 0.197 | 0.5 | 0.69 | 0.262 | 0.8 | 0.81 | 0.241 | 0.4 | 0.89 | 0.339 | 0.0 | 1.01 |



For each of 1000 Monte Carlo data sets, $P(T_k) > t$, $k = 1, 2$ were estimated at time point 0.5 year and 1.0 year, reflecting early and late period of study. The mean squared errors were calculated from the bias of the estimated mean probability and the variance of the 1000 estimates. In calculating the IPCWLE and RALE estimators, the response time $T_i^R$ was considered as the only auxiliary variable which the survival time could depend upon. For IPCWLE, to model the conditional expectation of survival probability among the responders who are consistent with the policy, logistic regression of survival probability on the response time was

fitted. We did not include the Lokhnygina and Helterbrand [6]'s Cox regression method in our simulation because its distinct property makes comparison less feasible.

Table 1 presents the mean, relative bias and mean squared errors for survival probability estimates based on 1000 samples of size 200 each. As shown in Table 1, almost all the relative biases, calculated as (bias/true value) $\times 100$, were less than 2%. By closely examining the table we notice that the relative biases were larger for $t = 1.0$ than $t = 0.5$, that is, the estimators were more biased for survival estimates at times towards the end of the study when there were more censoring present. In comparing the biases of different estimators in small samples, the PA estimator was generally the least biased, followed by the IPCWLE and IPMW estimators. LDT and RALE estimators always underestimated the true values whereas WRSE estimator overestimated them.

Comparing the MSE's, IPMW estimates were the least efficient as one would expect since no information from the censored patients or any auxiliary information is used in construction of such estimator. Among the IPMW, PA, LDT and RALE estimates whose influence functions belong to the same class, LDT estimates showed substantial gains in efficiency relative to both the first two, and RALE estimates are more efficient than LDT estimates in all scenarios, with the relative efficiency ranging from 1.01 to 1.18. The MSE of IPCWLE estimates were slightly larger than that of LDT estimates but substantially smaller than that of IPMW or PA estimates. In most instances WRSE estimator appeared to be the most efficient among all the estimates. The relative efficiencies of WRSE estimates with respect to LDT estimates ranged from 1.00 to 1.19 and the gain is bigger when more censoring is present. In general, the MSEs followed the pattern: IPMW ≥ PA ≥ IPCWLE ≥ LDT ≥ RALE ≥ WRSE.



Table 2 presents the mean, relative bias and mean squared errors for survival probability estimates based on 1000 samples of size 500 each. When the sample size was increased to 500, all the biases dropped to less than 1% except for the WRSE estimator. It was not surprising since the asymptotic unbiasness of WRSE estimator is achieved via the exponential functional of the cumulative hazard function. When the sample size was

increased from 200 to 500, the efficiency of all the estimators improved, but the trend of relative efficiencies remained mostly unaffected.

## 6. Discussion

We have reviewed the theory and methods for the inferential approaches in estimating the survival distribution of treatment strategies in two-stage randomization designs. These designs can be viewed as special cases of dynamic treatment regimes with two stages of randomization. These designs are preferable to upfront randomization designs when the number of patients available for randomization is small and the assignment of the second treatment depends on the intermediate outcome observed prior to the randomization. For more details on the comparison between two-stage designs and upfront randomization designs, see Wahed and Tsiatis [16].

Two-stage randomization designs are being broadly accepted in clinical trials. While traditional methods of data analysis cannot make efficient use of all the information obtained from such trials, recent methodologies have shown considerable advancement in this area. Lunceford et al. [7] first proposed methods for estimating survival distribution and mean restricted survival time for two-stage randomization designs. The inverse-probability-weighted estimators proposed by them are consistent and asymptotically normal. However, these estimators are not asymptotically efficient, mainly because they fails to take into account the information from censored observations. Nevertheless, their method was the first valid approach towards statistical inference from two-stage designs. The estimators developed by Wahed and Tsiatis [15, 16] improves efficiency over Lunceford et al. estimators by taking into account auxiliary covariates, which provides additional gain in efficiency when the covariates are prognostic of the survival time among responders. These estimators are not as simple or intuitive as the inverse-probability-weighted estimator or the weighted risk set estimator defined by Guo and Tsiatis [2]. The weighted risk set estimator defined as a natural extension of the Aalen-Nelson estimator is more intuitive and easier to implement than other estimators such as inverse-probability-weighted estimator or the regular asymptotically linear efficient estimator. Our simulation study shows that weighted risk

set estimator is the most efficient among the ones discussed in this paper, however, the estimate of survival probability shows some bias in small samples mainly because of its non-linear functional dependence on the cumulative hazard function. The small-sample bias of this estimator is larger than other estimates in most cases. The regular asymptotically linear estimator is the most efficient in its class, as discussed in Wahed and Tsiatis [16] although the idea is not as intuitive and computationally involved.

Readers familiar with Cox proportional hazard model can apply the methodologies described in Lokhnygina and Helterbrand [6] to analyze survival data from two-stage randomization designs. It is easy to implement using common statistical software packages such as SAS and *S*-Plus.

Overall, all of the recently developed estimators introduced in this article have an intention-to-treat interpretation. Accordingly, all the studies discussed treated the non-responders and non-consenters in a similar fashion. One question remain unanswered is: "How to estimate the causal effect of a treatment policy?" How could one estimate the survival distribution of a population where every member of the population is treated with say, $A_1$ and then if responded treated with say, $B_1$ ? Future work in this area also includes the development of log-rank-type test procedures to test hypotheses regarding policy means. There is also an opportunity to investigate this study from a likelihood and Bayesian point of view.



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