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Xiang Guo and Anastasios Tsiatis

Abstract

In many clinical trials related to diseases such as cancers and HIV, patients are treated by different combinations of therapies. This leads to two-stage designs, where patients are initially randomized to a primary therapy and then depending on disease remission and patients' consent, a maintenance therapy will be randomly assigned. In such designs, the effects of different treatment policies, i.e., combinations of primary and maintenance therapy are of great interest. In this paper, we propose an estimator for the survival distribution for each treatment policy in such two-stage studies with right-censoring using the method of weighted estimation equations within risk sets. We also derive the large-sample properties. The method is demonstrated and compared with other estimators through simulations and applied to analyze a two-stage randomized study with leukemia patients.

KEYWORDS: Counting process; Induction therapy; Inverse Weighting; Maintenance therapy; Risk sets; Potential outcomes; Survival analysis

1 Introduction

Two-stage randomization designs are becoming more common in many clinical trials related to diseases such as cancer and HIV, where an induction therapy is given followed by a maintenance therapy depending on patients' response and consent. One such two-stage randomized clinical trial, Protocol 8923, was conducted by the Cancer and Leukemia Group (CALGB) and reported by Stone et al. (1995). It was a double-blind, placebo controlled two-stage trial examining the effects of infusions of granulocyte-macrophage colony-stimulating factor (GM-CSF) after initial chemotherapy in 388 elderly patients with acute myelogenous leukemia (AML). Patients were randomized initially to GM-CSF or placebo following standard chemotherapy. Later, patients who met the criteria for complete remission and consent were offered a second randomization to one of two intensification treatments.

A main interest is to compare combinations of induction and maintenance therapy and to find the combination leading to the longest average survival time. However, in practice, the data analysis is typically conducted separately in two stages: (i) estimating survival distributions under different induction therapies using all data while ignoring the maintenance therapies, (ii) estimating survival distributions using data for patients receiving maintenance therapies. These analysis do not directly address the question of finding the best combination of induction and maintenance therapies.

We believe that the appropriate statistical question should focus on inference for overall treatment policies, which, in such two-stage randomization designs, can be defined as "treat with a primary therapy followed by a maintenance therapy if and only if patients achieve remission and consent to second randomization". Estimation of the survival distributions under such treatment policies has an intent-to-treat interpretation.

Recently, estimation of the survival distributions of treatment policies in two-stage randomization designs has been studied by Lunceford et al. (2002) (subsequently referred to as LDT) and Wahed and Tsiatis (2004) (subsequently referred to as WT). The LDT estimators were defined on an ad hoc basis incorporating two forms of inverse weighting (Robins et al., 1994). These estimators are consistent but not necessarily efficient. Using the semiparametric theory of Robins et al. (1994), Wahed and Tsiatis characterized the most efficient estimator for the survival distributions in the case when there is no censoring. Both the LDT and the WT estimators are relatively complex and difficult to implement in practice. In this paper, we use the concepts of counting process and risk sets as described by Fleming and Harrington (1991) to find weighted estimating equations whose solution gives an estimate for the cumulative haz-

ard function which, in turn, is used to derive an estimator for the survival distributions with right- censored data. From now on, we call this estimator as the Weighted Risk Set Estimator (WRSE). Since the WRSE is a natural extension of the Aalen-Nelson estimator, it is more intuitive than the existing estimators. Other advantages of the WRSE include: it is easier to compute and, as we will demonstrate, is more efficient than previously proposed estimators.

We introduce the notation and the assumptions of the paper in section 2. Also, in this section, we give a brief review for the available methodologies. In section 3, we derive the WRSE for the survival functions in two-stage designs. We discuss the large sample properties in section 4 and obtain a consistent estimator for its asymptotic variance. We compare the WRSE with other available estimators through several simulations in section 5. In section 6, the method is illustrated on the CALGB dataset. Finally, some concluding remarks and extensions are given in section 7.

2 Model Framework and Notation

For concreteness, we will consider the two-stage clinical trial where patients are initially randomized to one of the induction therapies, say A_1 or A_2 . Then, if eligible and consent is given for maintenance therapies, patients are randomly assigned to one of the maintenance therapies B_1 or B_2 . Our objective is to compare the survival distributions under the treatment policies $A_j B_k (j, k = 1, 2)$, where $A_j B_k$ represents the policy "treat with A_j followed by B_k if patient is eligible and consents to maintenance therapy". As usual, survival time is defined as the time from initial randomization until death.

Since the data from patients who receive different induction treatments are independent, we will only focus on the data from the patients who receive induction treatment A_1 . The analysis of the data from patients who receive induction treatment A_2 is similar. Thus, from now on, we will index individuals in our study by $i = 1, 2, \dots, n$, and we will find the estimator for the survival distribution under the two treatment policies that are associated with the induction treatment A_1 , namely $A_1 B_1$ and $A_1 B_2$.

To define the survival distributions under policies $A_1 B_1$ and $A_1 B_2$, as in Lunceford et al. (2002), we conceptualize this problem through potential outcomes or counterfactuals (Holland, 1986). Assume that each subject i has an associated set of random variables $(R_i^*, (1 - R_i^*)T_{0i}, R_i^*T_i^R, R_i^*T_{1i}^*, R_i^*T_{2i}^*)$, where R_i^* is the remission/consent status if patient i were assigned to A_1 , i.e., $R_i^* = 1$ if patient i was eligible and would consent to subsequent maintenance treat-

ment; otherwise, $R_i^* = 0$. T_i^R is the time from the initial randomization to the time when the maintenance therapy is given to patient i . T_i^R is defined only when $R_i^* = 1$. T_{0i} is the survival time for patient i if $R_i^* = 0$, i.e., the patient is not eligible or refuses maintenance therapy. T_{1i}^* is the time from the randomization to the maintenance therapy until death if patient i is eligible, willing to receive maintenance therapy and is assigned treatment B_1 , and similarly for T_{2i}^* . In fact, we can never observe both T_{1i}^* and T_{2i}^* , which is why they are referred to as potential outcomes.

With these assumptions, the survival time for patient i , if assigned to treatment policy A_1B_k , would be $T_{ki} = (1 - R_i^*)T_{0i} + R_i^*(T_i^R + T_{ki}^*)$, $k = 1, 2$. T_{ki} , $k = 1, 2$, are also potential outcomes, as only one of them can be observed when patient i is assigned with a maintenance therapy. Notice that if $R_i^* = 0$, i.e., patient i is not eligible or refuses the maintenance therapy, then $T_{1i} = T_{2i} = T_{0i}$.

Let T_k represent the survival time for the population if all patients were assigned to the treatment policy A_1B_k . Hence inference on features of these distributions addresses directly the intent-to-treat question of interest. We will estimate the distribution for T_k using the observed data from a two-stage design.

Treatment policies A_1B_1 and A_1B_2 are examples of dynamic treatment regimes as defined by Murphy et al. (2001). In a dynamic treatment regime, rules for treatment assignment are based on time-varying measurements of the study subjects. So, for example, treatment policy A_1B_1 , dictates that patients receive treatment A_1 immediately and receive B_1 if and only if they respond and consent to further treatment. Here the time-varying measurement is the indicator of response and consent.

If there is no censoring, the observed data can be represented as a set of i.i.d random vectors $(R_i^*, R_i^*T_i^R, R_i^*Z_i, T_i)$, $i = 1, 2, \dots, n$, where R_i^*, T_i^R are defined as above. Z_i is an indicator for the B treatment assignment, defined only if $R_i^* = 1$, where $Z_i = 1$, if patient i is assigned to B_1 and 0 if assigned to B_2 . T_i is the observed survival time, which is related to the potential outcomes as following:

$$T_i = (1 - R_i^*)T_{0i} + R_i^*\{T_i^R + Z_iT_{1i}^* + (1 - Z_i)T_{2i}^*\}.$$

So patient i 's survival time would be T_{0i} if he/she doesn't receive maintenance therapy, $T_i^R + T_{1i}^*$ if he/she receives B_1 as maintenance therapy and $T_i^R + T_{2i}^*$ if he/she receives B_2 as maintenance therapy.

To account for right censoring, let C_i be the time to censoring for patient i . With censoring we will observe i.i.d. vectors $(R_i, R_iT_i^R, R_iZ_i, U_i, \Delta_i)$, where

$U_i = \min(T_i, C_i)$ is the observed death or censoring time and $\Delta_i = I(T_i \leq C_i)$ denotes the failure indicator. We take the observed response status $R_i = 0$ if patient i is censored without having had a remission prior to being censored; i.e. $C_i < \min\{R_i^* T_i^R, (1 - R_i^*) T_i\}$; otherwise, we let $R_i = R_i^*$. We also assume that C_i is independent of all other variables and

$$\pi = P(Z_i = 1 | R_i = 1, T_i^R, T_{1i}, T_{2i}, C_i) = P(Z_i = 1 | R_i = 1), \quad (1)$$

i.e., the second stage randomization is made independently of other potential outcomes. Here π is the probability of being randomized to B_1 , which is defined only when $R_i = 1$ and is known by design.

To estimate the survival function of one treatment policy, a naive method is to use the data from those patients who are consistent with that treatment policy. For treatment $A_1 B_1$, the NAIVE estimator is the Kaplan-Meier estimator for all the patients with $R_i = 0$ or $R_i = 1, Z_i = 1$, similarly for $A_1 B_2$. The survival distribution of treatment policy $A_1 B_1$ is determined both by the responders, to whom the maintenance therapy B_1 should be assigned, and the non-responders. But in a two-stage design, some of the responders are assigned to another maintenance therapy B_2 . Thus the NAIVE estimator overestimates the contribution of the non-responders to the survival distribution and is theoretically biased. Lunceford et al. (2002) proposed a class of estimators using the method of inverse-weighting,

$$\hat{S}_{1LDT}(t) = n^{-1} \sum_{i=1}^n \frac{\Delta_i(1 - R_i + R_i Z_i / \pi) I(U_i \leq t)}{\hat{K}(U_i)} - \alpha n^{-1} \sum_{i=1}^n \frac{\Delta_i(R_i Z_i / \pi - R_i)}{\hat{K}(U_i)},$$

where $\hat{K}(u)$ is the Kaplan-Meier estimator for the censoring distribution and α is a constant. Different α 's can lead to different estimators. Lunceford et al. (2002) derived the value of α which corresponds to the minimum variance estimator among all LDT estimators. (From now on, the LDT estimator will refer to the minimum variance estimator). With no censoring, Wahed and Tsiatis (2004) obtained the most efficient estimator using the semiparametric theory of Robins et al. (1994). However, since we are considering censored data in this paper, the results of Wahed and Tsiatis are not relevant.

3 Weighted Risk Set Estimator

In developing the estimator for the survival distribution of the treatment policy, we will rely heavily on the counting process notation as described by Fleming and Harrington (1991). For standard one-stage problem, which would be

relevant if we were estimating a treatment-specific survival distribution in a one-stage randomized study with censored survival data, the cumulative hazard rate can be estimated by the Aalen-Nelson estimator given by

$$\hat{\Lambda}(t) = \int_0^t \frac{dN(u)}{Y(u)} = \sum_{i \in D(t)} \left\{ \frac{1}{Y(U_i)} \right\},$$

where $D(t) = \{i : U_i \leq t, \Delta_i = 1\}$ denotes all the individuals who are observed to fail before or at time t , and $N(u)$ is the counting processe defined as

$$N(u) = \sum_{i=1}^n I(U_i \leq u, \Delta_i = 1),$$

and $Y(u)$ is the at risk process

$$Y(u) = \sum_{i=1}^n I(U_i \geq u).$$

$N(u)$ denotes the number of deaths up to and including time u and $Y(u)$ denotes the number at risk at the time u .

In our problem, the goal is to estimate the survival distributions of T_1 and T_2 . We will focus on the estimation of T_1 , since estimating T_2 follows similarly. To motivate the WRSE, consider the hypothetical experiment where all patients were assigned the treatment policy A_1B_1 , in which case, we could define the potential outcome T_1 for all patients and the observed death or censoring time $U_{1i} = \min(T_{1i}, C_i)$. Defining $N_{1i}(u) = I(U_{1i} \leq u, \Delta_i = 1)$ and $Y_{1i}(u) = I(U_{1i} \geq u)$, we could then get an estimator for the cumulative hazard function as

$$\hat{\Lambda}_{11}(t) = \int_0^t \frac{d \sum_{i=1}^n N_{1i}(u)}{\sum_{i=1}^n Y_{1i}(u)}.$$

However, in actuality, in a two-stage randomization design, some of the patients who could have received treatment B_1 are instead randomized to receive B_2 . Thus, from such observed data we cannot observe $N_{1i}(u)$ or $Y_{1i}(u)$ directly. Consequently, we propose an estimator for $\Lambda_{11}(u)$ incorporating the method of inverse weighting. We define a weight function depending on time u ,

$$W_i(u) = 1 - R_i(u) + R_i(u)Z_i/\pi,$$

where $R_i(u) = R_i I(T_i^R \leq u)$ and R_i, Z_i, π, T_i^R are defined as in section 2. Note that if at time u , for patient i , a response has not been observed, i.e., $R_i(u) = 0$. This patient is still consistent with treatment policy A_1B_1 at

time u , thus we assign him/her with weight 1, i.e., $W_i(u) = 1$; if patient i responds and is assigned with maintenance treatment B_2 , i.e., $R_i(u) = 1$ and $Z_i = 0$, this patient is no longer consistent with A_1B_1 and get a weight of 0, i.e., $W_i(u) = 0$; if patient i responds and receives treatment B_1 at time u , he/she represents $\frac{1}{\pi}$ remitting/consent subjects who could have potentially been assigned to B_1 , and thus, at time u , receives a weight of $W_i(u) = \frac{1}{\pi}$. With $W_i^*(u) = 1 - R_i(u) + R_i(u)(1 - Z_i)/(1 - \pi)$, an analogous argument may be made for policy A_1B_2 . In contrast, the LDT estimators do not assign weights that are time-dependent. Consequently, if a patient has a remission, consents to the second randomization, and is randomized to B_2 , then such a patient receives a weight of 0 at any time u , including time prior to the second randomization, leading to a loss of efficiency.

With this weight function, we propose an estimator for the cumulative hazard for T_1 under policy A_1B_1 as:

$$\hat{\Lambda}_{11}(t) = \int_0^t \frac{\sum_{i=1}^n W_i(u) dN_i(u)}{\sum_{i=1}^n W_i(u) Y_i(u)}, \quad (2)$$

where $N_i(u) = I(U_i \leq u, \Delta_i = 1)$ and $Y_i(u) = I(U_i \geq u)$. This leads to an estimator for the survival function of T_1 as:

$$\hat{S}_1(t) = \exp \left\{ - \int_0^t \frac{\sum_{i=1}^n W_i(u) dN_i(u)}{\sum_{i=1}^n W_i(u) Y_i(u)} \right\}. \quad (3)$$

4 Large-sample Properties

We give a heuristic sketch of steps involved in showing that the WRSE is consistent and asymptotically normal. First, we give two propositions:

Proposition 1 $E\{W_i(u)Y_i(u)\} = E\{Y_{1i}(u)\}$.

To prove this proposition, we first show that $W_i(u)Y_i(u) = W_i(u)Y_{1i}(u)$, i.e.

$$\begin{aligned} & \{1 - R_i(u) + R_i(u)Z_i(u)/\pi\}I(T_i \geq u)I(C_i \geq u) \\ &= \{1 - R_i(u) + R_i(u)Z_i(u)/\pi\}I(T_{1i} \geq u)I(C_i \geq u). \end{aligned} \quad (4)$$

If $R_i(u) = 1$ and $Z_i = 0$, i.e., patient i is assigned to B_2 , $W_i(u) = 0$. Thus equation (4) holds and is equal to zero. If $R_i(u) = 1$ and $Z_i = 1$, i.e., patient i is assigned to B_1 , then $T_i = T_{1i}$ and equation (4) holds again. When $R_i(u) = 0$ and $T_i < u$, which implies that patient i dies before time u without response, then patient i 's treatment policy is consistent with A_1B_1 , i.e.,

$T_i = T_{1i}$. Therefore equation (4) holds. When $R_i(u) = 0$ and $T_i \geq u$, we conclude that $I(T_i \geq u) = I(T_{1i} \geq u) = 1$.

We complete the proof of proposition 1 as follows:

$$\begin{aligned}
 E\{W_i(u)Y_i(u)\} &= E\{W_i(u)Y_{1i}(u)\} \\
 &= E\{W_i(u)I(U_{1i} \geq u)\} \\
 &= E[E\{W_i(u)I(U_{1i} \geq u)|R_i, R_iT_i^R, T_{1i}, T_{2i}, C_i\}] \\
 &= E[E\{W_i(u)I(T_{1i} \geq u)I(C_i \geq u)|R_i, R_iT_i^R, T_{1i}, T_{2i}, C_i\}] \\
 &= E(I(T_{1i} \geq u)I(C_i \geq u)[1 - R_i(u) \\
 &\quad + E\{R_i(u)Z_i/\pi|R_i, R_iT_i^R, T_{1i}, T_{2i}, C_i\}]) \\
 &= E\{I(U_{1i} \geq u)\} \\
 &= E\{Y_{1i}(u)\}.
 \end{aligned} \tag{5}$$

The key to the proof above is that in equation (5),

$$E\{R_i(u)Z_i/\pi|R_i, R_iT_i^R, T_{1i}, T_{2i}, C_i\} = R_i(u),$$

which follows from assumption (1).

Proposition 2 *For a deterministic function $K(u)$,*

$$E\left[\int_0^t K(u)W_i(u)\{dN_i(u) - Y_i(u)d\Lambda_{11}(u)\}\right] = 0.$$

Proof of proposition 2:

The left hand side of the last equation may be written as the difference of

$$\sum_{i=1}^n E\{\Delta_i I(U_i \leq t)K(U_i)W_i(U_i)\} \tag{6}$$

and

$$E\left\{\int_0^t K(u)W_i(u)Y_i(u)d\Lambda_{11}(u)\right\}. \tag{7}$$

For expression (7), from proposition 1 and under suitable regularity conditions that allow us to interchange integration and expectation,

$$\begin{aligned}
 E\left\{\int_0^t K(u)W_i(u)Y_i(u)d\Lambda_{11}(u)\right\} &= \int_0^t K(u)E\{W_i(u)Y_i(u)\}d\Lambda_{11}(u) \\
 &= \int_0^t K(u)E\{Y_{1i}(u)\}d\Lambda_{11}(u) \\
 &= E\left\{\int_0^t K(u)Y_{1i}(u)d\Lambda_{11}(u)\right\}.
 \end{aligned}$$

When $\Delta_i = 0$, the summand of expression (6) is equal to zero. When $\Delta_i = 1$, we have $U_i = T_i$ and $R_i(U_i) = R_i^*$. Therefore, the summand of (6) can be written as

$$E \{K(T_i)I(T_i \leq t)I(C_i \geq T_i)(1 - R_i^* + R_i^*Z_i/\pi)\},$$

or

$$E \{(1 - R_i^*)K(T_i)I(T_i \leq t)I(C_i \geq T_i)\} + E \{R_i^*(Z_i/\pi)K(T_i)I(T_i \leq t)I(C_i \geq T_i)\}.$$

When $R_i^* = 0$, $T_i = T_{1i}$, which reduces to

$$E \{(1 - R_i^*)K(T_{1i})I(T_{1i} \leq t)I(C_i \geq T_{1i})\}; \quad (8)$$

When $R_i^* = 1$ and $Z_i = 1$, $T_i = T_{1i}$, which reduces to

$$E \{R_i^*(Z_i/\pi)K(T_{1i})I(T_{1i} \leq t)I(C_i \geq T_{1i})\} = E \{R_i^*K(T_{1i})I(T_{1i} \leq t)I(C_i \geq T_{1i})\}. \quad (9)$$

Thus, (6) = $\sum_{i=1}^n \{(8) + (9)\}$, i.e.

$$\begin{aligned} \sum_{i=1}^n E \{\Delta_i I(U_i \leq t)K(U_i)W_i(U_i)\} &= \sum_{i=1}^n E \{K(T_{1i})I(T_{1i} \leq t)I(C_i \geq T_{1i})\} \\ &= E \left\{ \int_0^t K(u) dN_{1i}(u) \right\}. \end{aligned}$$

Define $M_{1i}(u) = N_{1i}(u) - \int_0^t Y_{1i}(u) d\Lambda_{11}(u)$, we know from counting process theory (Fleming and Harrington, 1991, chapter 2) that $M_{1i}(u)$ is a martingale process. Consequently,

$$E \left\{ \int_0^t K(u) dM_{1i}(u) \right\} = 0,$$

which completes the proof of proposition 2.

Define $S_1^{(c)}(u) = P(U_{1i} \geq u)$ and $\hat{S}_1^{(c)}(u) = n^{-1} \sum_{i=1}^n W_i(u)Y_i(u)$. From proposition 1 we know that $E\{W_i(u)Y_i(u)\} = S_1^{(c)}(u)$. Consequently, using the large sample theory, we deduce that $\{\hat{S}_1^{(c)}(u) - S_1^{(c)}(u)\}$ converges in probability to 0 uniformly in u . By adding and subtracting common terms, $\{\hat{\Lambda}_{11}(t) - \Lambda_{11}(t)\}$ can be expressed as:

$$\hat{\Lambda}_{11}(t) - \Lambda_{11}(t) = n^{-1} \sum_{i=1}^n \int_0^t \frac{W_i(u)\{dN_i(u) - Y_i(u)d\Lambda_{11}(u)\}}{S_1^{(c)}(u)} \quad (10)$$

$$+n^{-1} \sum_{i=1}^n \int_0^t \left\{ 1/\hat{S}_1^{(c)}(u) - 1/S_1^{(c)}(u) \right\} W_i(u) \{dN_i(u) - Y_i(u)d\Lambda_{11}(u)\}. \quad (11)$$

To show consistency, we first notice that

$$E \left[\int_0^t \frac{W_i(u) \{dN_i(u) - Y_i(u)d\Lambda_{11}(u)\}}{S_1^{(c)}(u)} \right] = 0.$$

This follows from proposition 2 by taking $K(u) = 1/S_1^{(c)}(u)$. Since expression (10) is the sample average of mean zero i.i.d random variables, it converges in probability to zero by the weak law of large numbers. Consequently, to show that $\hat{\Lambda}_{11}(t)$ is a consistent estimator of $\Lambda_{11}(t)$, it suffices to show that expression (11) converges in probability to zero. It follows from the inequality:

$$\begin{aligned} & \left| \int_0^t \left\{ 1/\hat{S}_1^{(c)}(u) - 1/S_1^{(c)}(u) \right\} n^{-1} \sum_{i=1}^n W_i(u) \{dN_i(u) - Y_i(u)d\Lambda_{11}(u)\} \right| \\ & \leq \sup_{u \leq t} \left| 1/\hat{S}_1^{(c)}(u) - 1/S_1^{(c)}(u) \right| \end{aligned} \quad (12)$$

$$\times \left\{ n^{-1} \sum_{i=1}^n \int_0^t W_i(u) dN_i(u) + n^{-1} \sum_{i=1}^n \int_0^t W_i(u) Y_i(u) d\Lambda_{11}(u) \right\}. \quad (13)$$

Expression (12) will converges to zero as long as $S_1^{(c)}(t) > 0$. The first term of expression (13) is bounded by $1/\pi$ and the second term converges in probability to $E[\int_0^t W_i(u) Y_i(u) d\Lambda_{11}(u)]$. Collecting these developments demonstrates that (11) converges in probability to zero.

Now we argue that $n^{1/2}\{\hat{\Lambda}_{11}(t) - \Lambda_{11}(t)\}$, which equals $n^{1/2}\{(10) + (11)\}$, converges in distribution to a normal with mean zero. Since (10) is made up of a sum of i.i.d mean zero random variables, a simple consequence of the central limit theorem leads to the asymptotic normality of $n^{1/2}\{(10)\}$. To complete the proof, we need to show that $n^{1/2}\{(11)\}$ converges in probability to zero. Expression (11) times $n^{1/2}$ can be written as:

$$\int_0^t n^{1/2} \left\{ 1/\hat{S}_1^{(c)}(u) - 1/S_1^{(c)}(u) \right\} n^{-1} \sum_{i=1}^n W_i(u) \{dN_i(u) - Y_i(u)d\Lambda_{11}(u)\}. \quad (14)$$

Define $\hat{H}_n(t) = n^{-1} \int_0^t \sum_{i=1}^n W_i(u) \{dN_i(u) - Y_i(u)d\Lambda_{11}(u)\}$, from proposition 2 and under suitable regularity conditions, $\hat{H}_n(t)$ converges in probability to zero uniformly in t. Expression (14) may be rewritten as:

$$\int_0^t n^{1/2} \left\{ 1/\hat{S}_1^{(c)}(u) - 1/S_1^{(c)}(u) \right\} d\hat{H}_n(t). \quad (15)$$

Under suitable regularity conditions, $n^{1/2} \left\{ 1/S_1^{(c)}(u) - 1/S_1^{(c)}(u) \right\}$ will converge to a Gaussian process with continuous paths and by using method similar to Breslow and Crowley (1974) or Tsiatis (1981), (15) will converge in probability to zero. Hence we have,

$$n^{1/2} \{ \hat{\Lambda}_{11}(t) - \Lambda_{11}(t) \} = n^{-1/2} \sum_{i=1}^n \int_0^t \frac{W_i(u) \{ dN_i(u) - Y_i(u) d\Lambda_{11}(u) \}}{S_1^{(c)}(u)} + o_p(1),$$

where $o_p(1)$ is a term that converges in probability to zero.

Thus, $\hat{\Lambda}_{11}(t)$ is a consistent estimator of $\Lambda_{11}(t)$ and $n^{1/2} \{ \hat{\Lambda}_{11}(t) - \Lambda_{11}(t) \} \sim N(0, \sigma^2)$, where $\sigma^2 = E \left(\left[\int_0^t \frac{W_i(u) \{ dN_i(u) - Y_i(u) d\Lambda_{11}(u) \}}{S_1^{(c)}(u)} \right]^2 \right)$. Replacing $d\Lambda_{11}(u)$ and $S_1^{(c)}(u)$ by consistent estimators $\widehat{d\Lambda_{11}}(u) = \frac{\sum_{i=1}^n W_i(u) dN_i(u)}{\sum_{i=1}^n W_i(u) Y_i(u)}$ and $\hat{S}_1^{(c)}(u) = n^{-1} \sum_{i=1}^n W_i(u) Y_i(u)$, we can get a consistent estimator for σ^2 as:

$$\hat{\sigma}^2 = n^{-1} \sum_{i=1}^n \left(\int_0^t \frac{W_i(u) \left[dN_i(u) - Y_i(u) \left\{ \frac{\sum_{i=1}^n W_i(u) dN_i(u)}{\sum_{i=1}^n W_i(u) Y_i(u)} \right\} \right]}{n^{-1} \sum_{i=1}^n W_i(u) Y_i(u)} \right)^2,$$

and a consistent estimator for $VAR(\hat{\Lambda}_{11}(y))$ as $n^{-1} \hat{\sigma}^2$. By the delta method, $\hat{S}_1(t)$ is also consistent and we obtain a consistent variance estimator for $\hat{S}_1(t)$ as :

$$\widehat{VAR}(\hat{S}_1(t)) = n^{-1} \{ \hat{S}_1(t) \}^2 \hat{\sigma}^2. \quad (16)$$

5 Simulation Study

In this section, we conduct several simulation studies to investigate the large sample properties of the WRSE and compare the WRSE with the existing NAIVE estimator and LDT estimator for right-censored data. For simplicity, we only simulate data for "A₁" patients.

We take R_i , the response and consent indicator, to be a Bernoulli with $P(R_i = 1) = \theta$. Two different values 0.5 and 0.8 for θ are used in the simulations. If R_i equals zero, we then generate a survival time T_{0i} , which follows an exponential distribution with mean 182.5 days. T_{0i} is the survival time of the patients who do not respond or do not consent for maintenance therapy, and it is generated only if $R_i = 0$. When $R_i = 1$, a time to response T_i^R is generated following a exponential distribution with mean 365 days. If $R_i = 1$, we also generate a treatment B assignment indicator Z_i

from Bernoulli(0.5) distribution. If $Z_i = 1$, a survival time T_{1i}^* will be generated from an exponential distribution with mean 365 days and if $Z_i = 0$, another survival time T_{2i}^* will be generated from an exponential distribution with mean 547.5 days. T_{1i}^* is the survival time from the response/consent to death time if B_1 is assigned as the maintenance treatment and T_{2i}^* is the survival time from the response/consent to death time when B_2 is assigned. The observed survival time for the i th individual thus can be defined as $T_i = (1 - R_i)T_{0i} + R_i\{T_i^R + Z_iT_{1i}^* + (1 - Z_i)T_{2i}^*\}$. We set the censoring time C_i to be uniformly distributed between zero and 3.5 years. And then define the observed death or censoring time to be $U_i = \min(T_i, C_i)$. For simplicity, we only calculate the estimate for $S_1(t) = P(T_1 > t)$, which is the survival distribution for the treatment policy A_1B_1 .

For each of 2000 Monte Carlo data sets, $S_1(t)$ is estimated using (3) at $t = 150, 500$ and 700 days. The variance of $\hat{S}_1(t)$ is also estimated using (16). For each estimand, the 95% Wald confidence interval is constructed as the estimator plus or minus the appropriate standard error from (16) times 1.96. Both NAIVE estimates and LDT estimates are also considered.

Table 1:

t	θ	$S_1(t)$	$\hat{S}_{WRSE}(t)$	$\hat{S}_{1LDT}(t)(R.E.)$	$\hat{S}_{1NAIVE}(t)$
$n = 300$					
150	0.5	0.6875	0.6880	0.6851 (0.98)	0.5966
	0.8	0.8363	0.8366	0.8334 (0.96)	0.7676
500	0.5	0.3334	0.3342	0.3308 (0.78)	0.2397
	0.8	0.4947	0.4974	0.4937 (0.79)	0.4218
700	0.5	0.2251	0.2285	0.2240 (0.69)	0.1549
	0.8	0.3473	0.3509	0.3458 (0.72)	0.2915
$n = 500$					
150	0.5	0.6875	0.6879	0.6860 (0.96)	0.6013
	0.8	0.8363	0.8369	0.8349 (0.95)	0.7640
500	0.5	0.3334	0.3348	0.3323 (0.82)	0.2424
	0.8	0.4947	0.4964	0.4937 (0.78)	0.4196
700	0.5	0.2251	0.2273	0.2239 (0.72)	0.1560
	0.8	0.3473	0.3504	0.3469 (0.73)	0.2910

Table 1. compares three estimators with respective to relative efficiency (R.E. = $\frac{\text{sample variance of our estimator}}{\text{sample variance of the LDT estimator}}$) for estimating the survival function. Since the NAIVE estimator is biased, we do not provide its relative efficiency. Table 2. presents some large sample properties of our estimator. We give

sample average of the estimated variance (SEV) and sample variance of the estimator (SVE) for the survival function. From Table 1., we find that the WRSE and the LDT estimator both are unbiased and there is significant bias for the NAIVE estimator. The WRSE is always more efficient than the LDT estimator, with the biggest gains in the right hand tail of the survival curve where censoring is more pronounced. Table 2. also shows our variance estimator behaves well. As for the Monte Carlo confidence interval coverage, when $n = 300$, the coverage is slightly lower than the nominal value of 0.95, but attains it when $n=500$.

Table 2:

t	θ	SEV	SVE	MC coverage
n=300				
150	0.5	0.8414E-03	0.9053E-03	93.55%
	0.8	0.6290E-03	0.6135E-03	94.85%
500	0.5	1.3172E-03	1.3710E-03	93.85%
	0.8	1.7516E-03	1.7853E-03	93.75%
700	0.5	1.3224E-03	1.3678E-03	93.80%
	0.8	1.9713E-03	2.0554E-03	94.20%
n=500				
150	0.5	0.5079E-03	0.5007E-03	94.95%
	0.8	0.3792E-03	0.3944E-03	94.90%
500	0.5	0.8013E-03	0.8037E-03	94.15%
	0.8	1.0599E-03	1.0040E-03	95.55%
700	0.5	0.8141E-03	0.8008E-03	95.40%
	0.8	1.1981E-03	1.2046E-03	94.50%

6 Application to CALGB Data

We demonstrate how to apply the proposed methodology to a two-stage randomization design using the data from CALGB 8923. Because of thorough follow-up after the initial findings were reported and short survival time ($> 75\%$ mortality within two years), the data did not contain appreciable censoring. In order to illustrate the performance of various estimators with censored survival data, we artificially censored the data by restricting the follow-up period to 2.5 years after the first enrollment. By doing so, the censoring rate is approximately 27%. Of this data set, 79 out of 193 patients in the GM-CSF

group and 90 out of 195 in the placebo group achieved remission and consented to further randomization to intensification therapies; and of these, 37 GM-CSF and 45 placebo patients were randomized to intensification therapy I and the rest to intensification therapy II.

Our method was used to estimate the survival distributions for all four combinations. The estimates for the four treatment policies do not show appreciable differences, consistent with the reported interpretation of CALGB 8923 in Stone et al. (1995).

Table 3:

	$\hat{S}_{WRSE}(t)$	Stand Error	$\hat{S}_{1LDT}(t)$	Stand Error	$\hat{S}_{1NAIVE}(t)$
$t = 250$					
GM-CSF/Int. I	0.507	0.042	0.515	0.040	0.399
GM-CSF/Int. II	0.509	0.042	0.497	0.041	0.407
Placebo/Int. I	0.566	0.041	0.560	0.041	0.464
Placebo/Int. II	0.520	0.043	0.523	0.043	0.435
$t = 365$					
GM-CSF/Int. I	0.399	0.046	0.407	0.045	0.308
GM-CSF/Int. II	0.410	0.045	0.396	0.046	0.322
Placebo/Int. I	0.456	0.046	0.444	0.045	0.360
Placebo/Int. II	0.420	0.046	0.426	0.047	0.338
$t = 730$					
GM-CSF/Int. I	0.194	0.046	0.198	0.046	0.129
GM-CSF/Int. II	0.206	0.045	0.193	0.048	0.140
Placebo/Int. I	0.282	0.048	0.266	0.048	0.213
Placebo/Int. II	0.248	0.046	0.250	0.051	0.193

In Table 3., we present the estimates of the survival probabilities for each of the four treatment policies using NAIVE estimator, LDT estimator and WRSE, respectively, at times 250, 365 and 730 days. The LDT and our estimator give similar estimates while the NAIVE estimator gives significantly smaller estimate. The NAIVE estimator is theoretically biased and the result is underestimated. From Table 3., we also notice that at 250 days and 365 days the variance estimates of the LDT and our method are very similar. At 730 days, when the estimation is at the end of the survival curve, the WRSE gives slightly smaller estimated standard errors consistent with the simulation results presented in section 5. Since, in this study, the response to the induction treatment, if it occurs, occurs early in the study as compared to the survival times, we would not expect appreciable gains using our risk-set

method as compared to those of LDT. Although not reported here, we also bootstrapped the data and found that the bootstrap sample standard errors are very similar to our estimated standard errors.

7 Discussion

We have presented an approach for improving the efficiency of estimators for the survival distributions of treatment policies for two-stage randomization designs with censored survival data. The approach we use is motivated by the concepts of risk set and counting process, which makes it possible to use information from non-remitting patients and patients assigned to other treatment policies. The Weighted Risk Set estimator is a natural extension of the Aalen-Nelson estimator for the survival curve, which makes it more intuitive. The improved estimator not only gains efficiency over other available estimators, such as the estimators proposed by Lunceford et al. (2002), but also is easier to implement.

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References

- [1] Breslow, N. E. and Crowley, J. J. (1974) A Large Sample Study of the life table and product limit estimates under random censorship. *Ann. Statist.*, **2**, 437-453.
- [2] Fleming, T. R., and Harrington, D. P. (1991) *Counting Process and Survival Analysis*, New York: Wiley.
- [3] Holland, P. W. (1986) Statistics and causal inference. *J. Am. Statist. Ass.*, **81**, 945-960.
- [4] Lunceford, J. K., Davidian, M., and Tsiatis, A. A. (2002) Estimation of Survival Distributions of Treatment Policies in Two-Stage Randomization Designs in Clinical Trials. *Biometrics*, **58**, 48-57.
- [5] Murphy S. A., van der Lan, M. J., and Robins, J. M. (2002) Marginal Mean MOdels for Dynamic Regimes. *J. Am. Statist. Ass.*, **96**, 1410-1423.

- [6] Robins, J. M., Rotnitzky, A., and Zhao, L. P. (1994) Estimation of regression coefficients when some regressors are not always observed. *J. Am. Statist. Ass.*, **89**, 846-866.
- [7] Stone, R. M., Berg, D. T., George, S. L., Dodge, R. K., Paciucci, P. A., Schulman, P., Lee, E. J., Moore, J. O., Powell, B. L., and Schiffer, C. A. (1995) Granulocyte-macrophage colony-stimulating factor after initial chemotherapy for elder patients with primary acute myelogenous leukemia. *The New England J. of Medicine*, **332**, 1671-1677.
- [8] Tsiatis, A. A. (1981) A Large Sample Study of Cox's regression model. *Ann. Statist.*, **9**, 93-108.
- [9] Wahed, A. S. and Tsiatis, A. A. (2004) Optimal Estimator for the Survival Distribution and Related Quantities for Treatment Policies in Two-Stage Randomization Designs in Clinical Trials. *Biometrics*, **60**, 124-133.