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Optimal Estimator for the Survival Distribution and Related Quantities for Treatment Policies in Two-Stage Randomization Designs in Clinical Trials

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Summary. Two-stage designs, where patients are initially randomized to an induction therapy and then depending upon their response and consent, are randomized to a maintenance therapy, are common in cancer and other clinical trials. The goal is to compare different combinations of primary and maintenance therapies to find the combination that is most beneficial. In practice, the analysis is usually conducted in two separate stages which does not directly address the major objective of finding the best combination. Recently Lunceford, Davidian, and Tsiatis (2002, *Biometrics* **58,** 48–57) introduced ad hoc estimators for the survival distribution and mean restricted survival time under different treatment policies. These estimators are consistent but not efficient, and do not include information from auxiliary covariates. In this article we derive estimators that are easy to compute and are more efficient than previous estimators. We also show how to improve efficiency further by taking into account additional information from auxiliary variables. Large sample properties of these estimators are derived and comparisons with other estimators are made using simulation. We apply our estimators to a leukemia clinical trial data set that motivated this study.

Key words: Induction therapy; Influence functions; Intent-to-treat; Inverse probability weighted estimator; Maintenance therapy; Missing data; Potential outcomes; Survival analysis.

1. Introduction

In many clinical trials, two-stage designs are common. In a two-stage design, patients are treated initially with an induction therapy followed by maintenance therapy at some later time. Depending on the clinical trial, the maintenance therapy may be offered to a subset of the patients, for example, those patients who showed some response to the induction treatment. To compare different combinations of induction and maintenance therapies, two-stage randomized studies may be considered where patients are initially randomized to one of several induction therapies and then patients who are eligible for maintenance therapy are randomized to one of several maintenance therapies. The primary goal of such randomized studies is to determine the combination of induction and maintenance therapies that will result in the best prognosis such as the longest average survival. However, like the randomization scheme used in these trials, data analysis typically is separated into two parts: (i) comparing induction therapies using all the data ignoring maintenance therapy and (ii) comparing only those individuals randomized to maintenance therapy. Neither of these two analyses directly addresses the question of finding the best combination of maintenance and induction treatments.

This research was motivated from such a two-stage randomized clinical trial conducted by the Cancer and Leukemia Group B (CALGB). Protocol 8923 was a double-blind, placebo-controlled two-stage trial reported by Stone et al. (1995) 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 meeting the criteria for complete remission were offered a second randomization to one of two intensification treatments.

For concreteness, we will consider the two-stage clinical trial where patients are initially randomized to one of the induction treatments, say A_1 or A_2, upon entry into the trial. Among those eligible for maintenance therapy, a second randomization is offered to one of the maintenance therapies B_1

or B_2. Our objective is to compare the survival probabilities and related quantities associated with the treatment policies A_jB_k, j, $k = 1, 2$, where A_jB_k represents the policy "treat with A_j followed by B_k if the patient is eligible and consents to subsequent maintenance therapy." As usual, survival time is defined as the time from initial randomization until death. Lunceford, Davidian, and Tsiatis (2002; subsequently referred to as LDT) derived estimators for the mean restricted survival time and the survival distribution for treatment policies in a two-stage clinical trial. The LDT estimators were defined in ad hoc basis and did not include the most efficient estimator. In this article we use the theory of Robins, Rotnitzky, and Zhao (1994) to characterize the most efficient estimator for this problem and show how to derive estimators which are easily computable and are more efficient than the LDT estimator.

The article is organized as follows. In Section 2, using potential outcomes, we make explicit the model framework necessary to define the survival distribution for treatment policy A_jB_k. Also, in this section we elucidate all the assumptions made and give a brief review of available methodologies. In Section 3, we derive the class of all regular asymptotically linear estimators and find the most efficient estimator within this class. Section 4 describes the construction of feasible locally efficient estimators. Another strategy, where we derive efficient estimators within a restricted class of regular asymptotically linear estimators that are easy to compute, is described in Section 5. Section 6 gives a brief description of how to modify the estimators for complete data in the presence of right censoring. In Section 7, we apply the different estimators to estimate and test for differences in the mean survival time for the different combinations of induction/maintenance treatment regimes in the CALGB data set. In Section 8, we report on results from several simulation studies comparing our estimators with the available estimators. Finally, in Section 9, we give a brief discussion.

2. Model Framework and Notation

Since the data from the patients who receive induction treatment A_1 are independent of the data that are collected from patients with induction treatment A_2, we will restrict attention to the two treatment policies that are associated with the induction treatment A_1; namely A_1B_1 and A_1B_2. (The methods follow analogously for policies A_2B_1 and A_2B_2.) We will index individuals in our study by i, $i = 1, 2, \ldots, n$.

As in Lunceford et al. (2002), we conceptualize this problem through the use of a set of random variables some of which may not be observed for all individuals. Assume that each patient i has an associated set of random variables $\{R_i,\ (1 - R_i)T_{0i},\ R_iT_i^{\mathrm{R}},\ R_iT_{1i}^*,\ R_iT_{2i}^*,\ R_iV_i\}$, where R_i is the eligible/consent status if patient i were assigned to A_1; that is, $R_i = 1$ 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 $R_i = 0$; that is, the survival time for a patient who was not eligible or refused subsequent maintenance treatment; T_i^{R} is the time from initial randomization to the time he/she receives maintenance therapy and is defined only if $R_i = 1$; T_{1i}^* is the survival time of patient i if the patient was eligible, willing to receive maintenance treatment and received treatment B_1, and similarly for T_{2i}^*; and V_i is a vector of auxiliary covariates collected on individual i prior to their second randomization and is defined only if $R_i = 1$. The auxiliary covariates V_i may include baseline covariates, as well. In the CALGB data, some examples of auxiliary covariates include elapsed time between response to the induction therapy and second randomization, age, and white blood cell count. In actuality, if patient i were eligible and consented to the maintenance randomization ($R_i = 1$), we could not observe both T_{1i}^* and T_{2i}^* which is why these are referred to as potential outcomes.

Continuing with this conceptualization, the survival time for patient i, if assigned to treatment policy A_1B_k, would be $T_{1ki} = (1 - R_i)T_{0i} + R_iT_{ki}^*$, $k = 1, 2$. The variables (T_{11i}, T_{12i}) are also potential outcomes since they are not necessarily both observed for each individual, rather, they represent what might occur under policies, contrary to that which the individual might actually be exposed.

Under this setup, the distribution of T_{1k}, $k = 1, 2$ represents the distribution of the potential survival time for the population, were all patients to be assigned to A_1B_k, realizing that some patients eligible for maintenance therapy B_k may refuse additional treatment, so that inference on features of these distributions addresses directly the "intent-to-treat" question of interest. Our goal is to draw inference on the distribution of variables of interest T_{1k} from the observed data from a two-stage design described in Section 1.

In contrast to the potential outcomes defined above, the observed data can be characterized as the set of i.i.d. random vectors $(R_i,\ R_iT_i^{\mathrm{R}},\ R_iV_i,\ R_iZ_i,\ T_i)$, $i = 1, 2, \ldots, n$, where R_i, T_i^{R}, V_i are defined exactly as above, but now Z_i denotes the B treatment assignment indicator, defined only if $R_i = 1$, where $Z_i = 1$, if assigned to treatment B_1, 0, if assigned to B_2 and T_i is the observed survival time. We make the reasonable assumption that the observed survival time for patient i is related to the potential outcomes by

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

to reflect the belief that patient's i survival time would be T_{0i} if he/she did not receive maintenance therapy, T_{1i}^* if he/she received B_1 as maintenance therapy, and T_{2i}^* if he/she received B_2 as maintenance therapy.

In addition, we assume that

$$P\left(Z_i = 1 \,|\, R_i = 1, T_i^{\mathrm{R}}, V_i, T_{1i}^*, T_{2i}^*\right) = P(Z_i = 1 \,|\, R_i = 1), \tag{2}$$

to reflect the fact that, by design, the second-stage randomization is made independently of prognosis $(T_{1i}^*,\ T_{2i}^*)$ or any pre-second-stage randomization characteristics $(T_i^{\mathrm{R}},\ V_i)$ of the patient. We define $\pi_1 = P(Z_i = 1 \,|\, R_i = 1)$ and $\pi_2 = 1 - \pi_1 = P(Z_i = 0 \,|\, R_i = 1)$ to denote the probability of being randomized to treatments B_1 or B_2, respectively.

Our primary goal is to estimate parameters involving the distribution of the treatment policy survival times T_{1k} for $k = 1, 2$. For example, we may want to estimate $\mu_{1k} = \mathrm{E}\{h(T_{1k})\}$ for some function $h(\cdot)$ of T_{1k}. This allows us to consider the estimation of parameters such as the mean survival time or the survival distribution for treatment policy A_1B_k by taking $h(T_{1k}) = T_{1k}$, or $h(T_{1k}) = I(T_{1k} \geq t)$, respectively. One naive approach in estimating such quantities is to average the function $h(T_i)$ over those patients whose data are consistent with

the treatment policies they are randomized to. Explicitly, one might use the estimator

$$\hat{\mu}_{1k}^{\mathrm{NAIVE}} = \left\{ \sum_{i=1}^{n} (1 - R_i + R_i X_{ki}) \right\}^{-1} \times \sum_{i=1}^{n} (1 - R_i + R_i X_{ki})\, h(T_i), \tag{3}$$

where X_k is the assignment indicator for treatment B_k, $X_1 = Z$, and $X_2 = (1 - Z)$. This estimator, as we will demonstrate, is biased.

In order to find unbiased and consistent estimators, we first need to show that the distribution of the potential outcome T_{1k} can be identified from the distribution of the observed random variables. It was shown in LDT that under assumptions (1) and (2) that

$$\mu_{1k} = \mathrm{E}\{h(T_{1k})\} = \mathrm{E}\left\{ \left(1 - R + \frac{RX_k}{\pi_k} \right) h(T) \right\}. \tag{4}$$

Relationship (4) leads to one of the estimators for μ_{1k} given by LDT, namely,

$$\hat{\mu}_{1k} = \frac{1}{n} \sum_{i=1}^{n} \left(1 - R_i + \frac{R_i X_{ki}}{\pi_k} \right) h(T_i). \tag{5}$$

A useful way to think about this problem is as follows: If everyone in our sample were given treatment according to policy A_1B_k, then we would have complete data that could be used to estimate μ_{1k} in a straightforward fashion. Some individuals, however, were assigned treatment inconsistent with treatment policy A_1B_k, namely, those individuals randomized to receive the other maintenance therapy B_{3-k}, $k = 1, 2$. The data from such individuals can be viewed as missing data for the purpose of estimating μ_{1k}. However, because of randomization, such individuals are similar prognostically to those randomized to treatment B_k. Consequently, by weighting the individuals randomized to treatment B_k by $1/\pi_k$, then, roughly speaking, the response of an individual randomized to treatment B_k counts for him/herself as well as the response of $(1/\pi_k - 1)$ similar individuals who have "missing data" with respect to treatment policy A_1B_k; i.e., those individuals randomized to the other treatment B_{3-k}. This also makes clear why the naive estimator given by (3), which does not weight, results in a biased estimator.

Other ad hoc estimators were also given by LDT. The problem we address in this article is how to efficiently estimate parameters involving the distribution of the treatment policy survival times T_{1k} for $k = 1, 2$ using the observed data including the auxiliary covariates. Because this problem can be cast as a missing data problem, we can use the theory developed by Robins et al. (1994) to characterize the class of all estimators and find the most efficient estimator.

3. Efficient Estimator

Most estimators used in practice are regular asymptotically linear estimators (RAL) precisely defined by Newey (1990). Specifically, an estimator $\hat{\eta}$ of the parameter η is asymptotically linear if $n^{1/2}(\hat{\eta} - \eta) = n^{-1/2} \sum_{i=1}^{n} \psi_i + o_p(1)$, where ψ_i, $i = 1, \ldots, n$ are i.i.d. mean zero random variables and $o_p(1)$ denotes a term that converges in probability to zero. The random variable ψ_i is referred to as the ith influence function of the estimator $\hat{\eta}$.

The estimator given by (5) is an example of an inverse-probability-of-missing-weighted (IPMW) estimator for μ_{1k}. The influence function for this estimator can be shown to be equal to

$$\left\{ (1 - R_i) + \frac{R_i X_{ki}}{\pi_k} \right\} h(T_i) - \mu_{1k}. \tag{6}$$

Using the semiparametric theory of Robins et al. (1994), all RAL estimators for μ_{1k} have an influence function belonging to the class

$$\left\{ (1 - R_i) + \frac{R_i X_{ki}}{\pi_k} \right\} \{h(T_i) - \mu_{1k}\} + R_i \left(\frac{X_{ki} - \pi_k}{\pi_k} \right) f\big(T_i^{\mathrm{R}}, V_i\big), \tag{7}$$

where $f(T_i^{\mathrm{R}}, V_i)$ is an arbitrary function of T_i^{R} and V_i. Note that both T_i^{R} and V_i are defined only for patients i such that $R_i = 1$. The choice of the function $f(\cdot,\cdot)$ will determine how efficient the corresponding estimator for μ_{1k} will be. The goal would be to appropriately define the function $f(\cdot,\cdot)$ so that we can improve the efficiency of our estimators. The use of auxiliary information in gaining efficiency has previously been considered by several authors such as Robins and Rotnitzky (1992), Laan and Hubbard (1998, 1999), Xu and Zeger (2001), and Faucett, Schenker, and Taylor (2002). The following proposition characterizes the most efficient influence function in the class of influence functions (7).

PROPOSITION 1: *Among all influence functions in* (7), *the most efficient one is given by*

$$\left\{ (1 - R_i) + \frac{R_i X_{ki}}{\pi_k} \right\} h(T_i) - R_i \left(\frac{X_{ki} - \pi_k}{\pi_k} \right) \theta_h\big(T_i^{\mathrm{R}}, V_i\big) - \mu_{1k}, \tag{8}$$

where $\theta_h(T_i^{\mathrm{R}}, V_i) = \mathrm{E}\{h(T_i) \,|\, T_i^{\mathrm{R}}, V_i, R_i = 1, X_{ki} = 1\}$.

The proof of Proposition 1 is given in Appendix A. If $\theta_h(T_i^{\mathrm{R}}, V_i)$ were known (which is not the case in practice), then the estimating equation

$$\sum_{i=1}^{n} \left[\left\{ (1 - R_i) + \frac{R_i X_{ki}}{\pi_k} \right\} h(T_i) - R_i \left(\frac{X_{ki} - \pi_k}{\pi_k} \right) \theta_h\big(T_i^{\mathrm{R}}, V_i\big) - \mu_{1k} \right] = 0. \tag{9}$$

could be used to find the efficient estimator

$$\hat{\mu}_{1k}^{\mathrm{ME}} = \frac{1}{n} \sum_{i=1}^{n} \left[\left\{ (1 - R_i) + \frac{R_i X_{ki}}{\pi_k} \right\} h(T_i) - R_i \left(\frac{X_{ki} - \pi_k}{\pi_k} \right) \theta_h\big(T_i^{\mathrm{R}}, V_i\big) \right]. \tag{10}$$

Theoretically, $\hat{\mu}_{1k}^{\mathrm{ME}}$ is referred to as optimal in the sense that it has the smallest variance among the class of all RAL estimators and its variance is said to achieve the semiparametric efficiency bound (Newey, 1990). Since the conditional expectation $\theta_h(T_i^{\mathrm{R}}, V_i)$ is not known, it must be estimated from the data leading to locally efficient estimators.

4. Locally Efficient Estimators

If we want to use the estimator defined in (10), we need to estimate the conditional expectation $\theta_h(T_i^{\mathrm{R}}, V_i)$ from the data. To do so, one can posit a regression model, linear or nonlinear, of the form $\mathrm{E}\{h(T_i) \mid T_i^{\mathrm{R}}, V_i, R_i = 1, X_{ki} = 1\} = g(T_i^{\mathrm{R}},\ V_i,\ \boldsymbol{\gamma})$, in terms of a finite number of parameters $\boldsymbol{\gamma}$ which can be estimated using standard techniques such as least squares using the subset of the data for individuals $\{i : R_i = 1,\ X_{ki} = 1\}$. Then $\hat{\theta}_h(T_i^{\mathrm{R}}, V_i) = g(T_i^{\mathrm{R}}, V_i, \hat{\boldsymbol{\gamma}})$ can be substituted in (10) to give the locally efficient estimator of μ_{1k}

$$\hat{\mu}_{1k}^{\mathrm{LE}} = \frac{1}{n}\sum_{i=1}^{n}\left[\left\{(1-R_i) + \frac{R_i X_{ki}}{\pi_k}\right\}h(T_i) - R_i\left(\frac{X_{ki}-\pi_k}{\pi_k}\right)g\big(T_i^{\mathrm{R}}, V_i, \hat{\boldsymbol{\gamma}}\big)\right]. \quad (11)$$

We give a brief argument in Appendix B to show that this estimator is consistent and asymptotically normal even if the posited regression relationship is incorrectly specified. In addition, if the posited regression model is correctly specified, then it will be the most efficient estimator for μ_{1k}. The way this estimator is constructed suggests that the efficiency gain for this estimator over IPMW or LDT estimators depends on how correlated the response time and the auxiliary variables are to the survival time among responders. As will be seen in simulation studies, the higher the correlation, the larger the gain. The variance of this estimator can be estimated by the sandwich variance given by

$$\hat{\sigma}_{\mathrm{LE}}^2 = \frac{1}{n^2}\sum_{i=1}^{n}\left[\left\{(1-R_i) + \frac{R_i X_{ki}}{\pi_k}\right\}h(T_i) - R_i\left(\frac{X_{ki}-\pi_k}{\pi_k}\right)g\big(T_i^{\mathrm{R}}, V_i, \hat{\boldsymbol{\gamma}}\big) - \hat{\mu}_{1k}^{\mathrm{LE}}\right]^2. \quad (12)$$

For instance, if we assume that $g(T_i^{\mathrm{R}},\ V_i,\ \boldsymbol{\gamma}) = \gamma_0 + \gamma_1 T_i^{\mathrm{R}} + \boldsymbol{\gamma}_2^{\mathrm{T}} V_i$ and estimate $\boldsymbol{\gamma} = (\gamma_0\ ,\ \gamma_1,\ \boldsymbol{\gamma}_2^{\mathrm{T}})^{\mathrm{T}}$ by the least squares estimates $\hat{\boldsymbol{\gamma}}$ from the subset of data corresponding to the individuals $\{i : R_i = 1,\ X_{ki} = 1\}$, then we obtain the locally efficient estimator

$$\hat{\mu}_{1k}^{\mathrm{LS}} = \frac{1}{n}\sum_{i=1}^{n}\left[\left\{(1-R_i) + \frac{R_i X_{ki}}{\pi_k}\right\}h(T_i) - R_i\left(\frac{X_{ki}-\pi_k}{\pi_k}\right)\big(\hat{\gamma}_0 + \hat{\gamma}_1 T_i^{\mathrm{R}} + \hat{\boldsymbol{\gamma}}_2^{\mathrm{T}} V_i\big)\right]. \quad (13)$$

Alternatively, the conditional expectation $\theta_h(T_i^{\mathrm{R}},\ V_i)$ can be estimated by local non(semi)parametric regression methods such as LOESS (Cleveland and Devlin, 1988) for cases with few independent variables or generalized additive models (GAM; Hastie and Tibshirani, 1990) when considering many independent variables. Let us denote this estimator by $\tilde{\theta}_h(T_i^{\mathrm{R}}, V_i)$. Substituting this estimated conditional expectation in (10) we obtain another estimator for μ_{1k}. Estimators that use local regression methods do not depend on the choice of a particular model but the slow convergence rates may have an effect on overall consistency and asymptotic normality. This will be investigated numerically in our simulation study. The variance of these estimators can be easily estimated by (12) by replacing $g(T_i^{\mathrm{R}}, V_i, \hat{\boldsymbol{\gamma}})$ with $\tilde{\theta}_h(T_i^{\mathrm{R}}, V_i)$ and $\hat{\mu}_{1k}^{\mathrm{LE}}$ by the corresponding estimator.

5. Improved Estimator

The construction of the first set of locally efficient estimators that were derived in Section 4 involves the selection of an appropriate model for the conditional expectation, which may or may not be correct. If the regression relationship is incorrectly specified, then there is no guarantee that the estimator will gain efficiency over the IPMW estimator. Another approach that guarantees improved efficiency is to restrict the class of estimators to those whose influence functions are of the form

$$\left\{(1-R_i) + \frac{R_i X_{ki}}{\pi_k}\right\}\{h(T_i) - \mu_{1k}\} + R_i\left(\frac{X_{ki}-\pi_k}{\pi_k}\right)\boldsymbol{\gamma}^{\mathrm{T}}\boldsymbol{W}_i, \quad (14)$$

where $\boldsymbol{W}_i$ is a fixed q-dimensional vector of prespecified functions of T_i^{R} and V_i, and $\boldsymbol{\gamma}$ is an arbitrary q-dimensional constant vector. The influence functions (14), for $\boldsymbol{\gamma} \in \mathcal{R}^q$, define a linear subspace of the space of influence functions (7) and the goal is to find the optimal restricted estimator whose influence function is the one within the class (14) with smallest variance. This entails finding the q-dimensional vector $\boldsymbol{\gamma}^{\mathrm{opt}}$ which gives the smallest variance. Formalizing this as a multiple regression problem, $\boldsymbol{\gamma}^{\mathrm{opt}}$ is given by $\boldsymbol{\gamma}^{\mathrm{opt}} - \boldsymbol{\gamma}^{*} + \boldsymbol{\gamma}^{**}\mu_{1k}$, where $\boldsymbol{\gamma}^{*}$ and $\boldsymbol{\gamma}^{**}$ are respectively given by

$$\boldsymbol{\gamma}^{*} = \big[\mathrm{E}\big\{R_i(X_{ki}-\pi_k)^2\boldsymbol{W}_i\boldsymbol{W}_i^{\mathrm{T}}\big\}\big]^{-1} \times \mathrm{E}\left\{R_i X_{ki}(X_{ki}-\pi_k)h(T_i)\boldsymbol{W}_i\right\} \quad (15)$$

and

$$\boldsymbol{\gamma}^{**} = \big[\mathrm{E}\big\{R_i(X_{ki}-\pi_k)^2\boldsymbol{W}_i\boldsymbol{W}_i^{\mathrm{T}}\big\}\big]^{-1} \times \mathrm{E}\big\{R_i X_{ki}(X_{ki}-\pi_k)\boldsymbol{W}_i\big\}. \quad (16)$$

If the coefficient vectors $\boldsymbol{\gamma}^{*}$ and $\boldsymbol{\gamma}^{**}$ were known, one could solve the estimating equation

$$\sum_{i=1}^{n}\left[\left\{(1-R_i) + \frac{R_i X_{ki}}{\pi_k}\right\}\big\{h(T_i) - \mu_{1k}\big\} - R_i\left(\frac{X_{ki}-\pi_k}{\pi_k}\right)\big(\boldsymbol{\gamma}^{*} - \mu_{1k}\boldsymbol{\gamma}^{**}\big)^{\mathrm{T}}\boldsymbol{W}_i\right] = 0 \quad (17)$$

to obtain the optimal restricted estimator

$$\hat{\mu}_{1k}^{\mathrm{MEL}} = \frac{\displaystyle\sum_{i=1}^{n}\left[\left\{(1-R_i) + \frac{R_i X_{ki}}{\pi_k}\right\}h(T_i) - R_i\left(\frac{X_{ki}-\pi_k}{\pi_k}\right)\boldsymbol{\gamma}^{*\mathrm{T}}\boldsymbol{W}_i\right]}{\displaystyle\sum_{i=1}^{n}\left[\left\{(1-R_i) + \frac{R_i X_{ki}}{\pi_k}\right\} - R_i\left(\frac{X_{ki}-\pi_k}{\pi_k}\right)\boldsymbol{\gamma}^{**\mathrm{T}}\boldsymbol{W}_i\right]}. \quad (18)$$

It can be shown that substituting root-n consistent estimators for $\boldsymbol{\gamma}^*$ and $\boldsymbol{\gamma}^{**}$ in (17) and (18) will yield estimators that are asymptotically equivalent to those where $\boldsymbol{\gamma}^*$ and $\boldsymbol{\gamma}^{**}$ are known. Thus, replacing the expectations in (15) and (16) by their corresponding empirical averages we obtain estimates $\hat{\boldsymbol{\gamma}}^*$ and $\hat{\boldsymbol{\gamma}}^{**}$ which can then be substituted in (18) to obtain an improved estimator which we will denote by $\hat{\mu}_{1k}^{\mathrm{IMP}}$. The variance of this estimator can be estimated by the sandwich variance given by

$$\hat{\sigma}^2_{\mathrm{IMP}} = \frac{1}{n^2}\sum_{i=1}^{n}\left[\left\{(1-R_i)+\frac{R_iX_{ki}}{\pi_k}\right\}\left\{h(T_i)-\hat{\mu_{1k}}^{\mathrm{IMP}}\right\} - R_i\left(\frac{X_{ki}-\pi_k}{\pi_k}\right)\left(\hat{\boldsymbol{\gamma}}^* - \hat{\mu}_{1k}^{\mathrm{IMP}}\hat{\boldsymbol{\gamma}}^{**}\right)^{\mathrm{T}}\boldsymbol{W}_i\right]^2. \quad (19)$$

If we take $\boldsymbol{W}_i$ to be a scalar constant, then this reduces to the estimator $\hat{\mu}''_{1k}$, one of the LDT estimators. From here on we will refer to the estimator $\hat{\mu}''_{1k}$ as the LDT estimator.

It is also argued in Appendix B that the estimator $\hat{\mu}_{1k}^{\mathrm{IMP}}$ is consistent and asymptotically normal. It is easy to compute and because it is the most efficient estimator among a class of estimators that include the IPMW estimator and the LDT estimator, it is guaranteed to be at least as efficient as the best of these. Moreover, if the conditional expectation $\theta_h(T_i^{\mathrm{R}}, V_i)$ given by (8) is equal to $\boldsymbol{\gamma}^{\mathrm{T}}\boldsymbol{W}_i$ for some $\boldsymbol{\gamma}$, then $\hat{\mu}_{1k}^{\mathrm{IMP}}$ is the most efficient among all RAL estimators.

6. Censoring

The methods described in previous sections apply only to the case where we observe complete data. However, in many time-to-event studies, censoring is a major factor. For situations where data are subject to right censoring, inverse-probability-weighted versions of our proposed estimators can be used. To see how the estimators can be modified for right-censored data, let C_i denote the censoring time for the *ith* individual. Assume that C_i is independent of any other variables that are being observed. The proposed estimators with censored data use the observed data $(U_i, \Delta_i, \Delta_iR_i, \Delta_iR_iT_i^{\mathrm{R}}, \Delta_iR_iZ_i, \Delta_iR_iV_i)$, $i = 1, 2, \ldots, n$, where $\Delta_i = I(C_i \geq T_i)$, $U_i = \min(T_i, C_i)$. An inverse probability weighted version (in the presence of right censoring) of the estimator (11), defined in Section 4, is given by

$$\hat{\mu}_{1k}^{\mathrm{LEcens}} = \frac{1}{n}\sum_{i=1}^{n}\frac{\Delta_i}{\hat{K}(U_i)}\left[\left\{(1-R_i)+\frac{R_iX_{ki}}{\pi_k}\right\}h(U_i) - R_i\left(\frac{X_{ki}-\pi_k}{\pi_k}\right)g\left(T_i^{\mathrm{R}}, V_i, \hat{\boldsymbol{\gamma}}\right)\right], \quad (20)$$

where $\hat{K}(u)$ is the Kaplan–Meier estimator of the censoring survival distribution $K(u) = P(C_i \geq u)$ at time u. For estimating the parameters $\boldsymbol{\gamma}$ for the regression, one may solve the inverse-probability-weighted estimating equation

$$\sum_{i=1}^{n}\frac{\Delta_i}{\hat{K}(U_i)}\left[R_iX_{ki}\frac{\partial g\left(T_i^{\mathrm{R}}, V_i, \hat{\boldsymbol{\gamma}}\right)}{\partial \gamma}\left\{h(U_i) - g\left(T_i^{\mathrm{R}}, V_i, \hat{\boldsymbol{\gamma}}\right)\right\}\right] = 0, \quad (21)$$

where $\partial g(\cdot)/\partial\gamma$ denotes the vector of partial derivatives with respect to the components of the vector γ.

To get the standard errors we use the formula from Zhao and Tsiatis (2000). Letting $\phi_i = \{(1-R_i)+(R_iX_{ki})/\pi_k\} \times h(U_i) - R_i\{(X_{ki}-\pi_k)/\pi_k\}g(T_i^{\mathrm{R}}, V_i, \hat{\boldsymbol{\gamma}})$, the estimated variance for $\hat{\mu}_{1k}^{\mathrm{LEcens}}$ is given by

$$n^{-1}\left[n^{-1}\sum_{i=1}^{n}\frac{\Delta_i}{\hat{K}(U_i)}\left(\phi_i - \hat{\mu}_{1k}^{\mathrm{LEcens}}\right)^2 + \sum_{i=1}^{n}(1-\Delta_i)\left\{\frac{\hat{G}(\phi^2, U_i)}{\hat{K}(U_i)} - \hat{G}^2(\phi, U_i)\right\}\right],$$

where $\hat{G}(\phi^\ell, u) = Y^{-1}(u)\sum_{j=1}^{n}\Delta_j/\hat{K}^{-1}(U_j)\phi_j^\ell I(U_j \geq u)$, $\ell = 1, 2$, and $Y(u) = \sum_{j=1}^{n} I(U_j \geq u)$. We acknowledge that (20) is not optimal among the competing estimators with censored data, but this estimator is easy to implement and in the case where censoring is light, the modified estimator should behave well.

7. Analysis of CALGB 8923 Data

We apply the methods developed for improving efficiency described in the previous sections to estimate the survival distribution and mean lifetime for the different combinations of induction/maintenance treatment policies using the data from CALGB 8923 described earlier in Section 1. We also use Wald tests, constructed using these estimators, to test various treatment policy contrasts. There were 388 patients who participated in CALGB 8923. Of these, 79 out of 193 patients in the GM-CSF group and 90 out of 195 in the placebo group achieved remission (responded) and consented to further randomization to the intensification therapy; and, of these, 37 GM-CSF and 45 placebo patients were randomized to intensification therapy I and the rest to intensification therapy II. This study has matured and all 388 patients have been followed for at least 2521 days of whom 356 have died. Since we have complete data for 2521 days, we consider restricted survival time truncated at 2521 days for all 388 patients. Thus, in the analysis, we will estimate and test the mean restricted survival time for the different treatment policies.

In our analysis, there were three variables that we considered as auxiliary variables V_i; namely, time between the response and the second randomization, age, and white blood cell count. For modeling the conditional expectation $\theta_h(T_i^{\mathrm{R}}, V_i)$, first we used a least squares linear regression on these auxiliary variables plus the time of response T_i^{R}. Then we used proc GAM with default options in SAS to fit the generalized additive model in these four variables to estimate the conditional expectation $\theta_h(T_i^{\mathrm{R}}, V_i)$. For details of how this is implemented, the reader is refered to SAS Institute Inc. (2001, Chapter 5). For modeling the conditional survival probability, logistic distribution was used in the generalized additive model. Similarly, for the improved estimator, we defined the prespecified vector function $\boldsymbol{W}_i$ as the column vector whose elements are the random variables T_i^{R}, time between the response and the second randomization, age, white blood cell count, and a constant function identically equal to 1.

Table 1 shows the estimates of mean restricted survival time for each of the four treatment policies using the estimators NAIVE, IPMW, LDT, LS, IMP, and GAM. Most estimators gave similar estimates except for the NAIVE estimator

Table 1
Results from the analysis of CALGB 8923 data

Policy	LS	IMP	NAIVE	IPMW	LDT	GAM
Estimates of restricted mean and their standard errors						
GM-CSF/Int. I	471.9 (49.4)	468.7 (49.3)	360.3 (—)	441.1 (62.2)	461.2 (49.9)	422.8 (45.5)
GM-CSF/Int. II	487.0 (60.9)	484.1 (60.9)	396.0 (—)	517.4 (75.0)	492.4 (61.5)	481.9 (58.8)
placebo/Int. I	561.7 (60.1)	566.0 (59.8)	485.6 (—)	579.4 (74.8)	579.4 (60.9)	553.0 (58.3)
placebo/Int. II	586.7 (64.4)	580.5 (64.3)	481.1 (—)	572.4 (77.7)	572.4 (65.0)	552.9 (62.6)
Survival probability estimates at 183 days and their standard errors						
GM-CSF/Int. I	0.60 (0.036)	0.60 (0.036)	0.49 (—)	0.57 (0.057)	0.59 (0.036)	0.55 (0.035)
GM-CSF/Int. II	0.58 (0.038)	0.57 (0.038)	0.49 (—)	0.60 (0.059)	0.58 (0.038)	0.55 (0.035)
placebo/Int. I	0.64 (0.035)	0.63 (0.035)	0.53 (—)	0.64 (0.059)	0.64 (0.035)	0.59 (0.035)
placebo/Int. II	0.58 (0.040)	0.57 (0.039)	0.49 (—)	0.57 (0.057)	0.57 (0.040)	0.55 (0.036)
Survival probability estimates at 548 days and their standard errors						
GM-CSF/Int. I	0.26 (0.038)	0.26 (0.038)	0.18 (—)	0.25 (0.046)	0.26 (0.038)	0.24 (0.034)
GM-CSF/Int. II	0.23 (0.039)	0.22 (0.039)	0.17 (—)	0.24 (0.045)	0.23 (0.039)	0.22 (0.036)
Placebo/Int. I	0.31 (0.041)	0.32 (0.041)	0.27 (—)	0.33 (0.050)	0.33 (0.042)	0.32 (0.038)
Placebo/Int. II	0.32 (0.041)	0.32 (0.041)	0.25 (—)	0.31 (0.048)	0.31 (0.041)	0.31 (0.038)

***P*-values for different tests**

	Testing mean restricted surv. times						Testing survival prob. at $t = 548$ days					
Hyp.	LS	IMP	NAIVE	IPMW	LDT	GAM	LS	IMP	NAIVE	IPMW	LDT	GAM
H_0	0.70	0.69	0.19	0.51	0.63	0.40	0.52	0.44	0.22	0.53	0.43	0.33
H_1	0.17	0.16	0.03	0.12	0.15	0.13	0.11	0.08	0.02	0.08	0.08	0.04
H_2	0.68	0.75	0.59	0.67	0.81	0.51	0.70	0.57	0.66	0.75	0.39	0.62

which underestimates the mean restricted lifetime reflecting the bias of this method. The IPMW estimator gave the largest estimated standard error as would be expected by the theory. In most cases the GAM estimator has the smallest estimated standard error, but, as noted earlier, we cannot be confident of the small sample accuracy of this estimated standard error because of the slow convergence rate of such smoothing methods. However, in such cases bootstrapping may provide better small sample results. The other three estimators LDT, LS, and IMP gave very similar results both in terms of the estimates as well as the standard errors. Among responders, the time-to-response and the auxiliary covariates were weakly related to survival time (as seen in Figure 1) which explains why there was not any appreciable gain in efficiency of the LS and IMP estimators as compared to the LDT estimator. Similar conclusions follow the survival probability estimates as is evident from the results in Table 1.

Estimated survival curves were computed using these different estimation techniques for the four treatment policies. The treatment policy–specific curves using the IMP method are depicted in Figure 2. We looked at estimated survival curves using the different estimators for all the policies and as expected by the theory, except for the NAIVE estimator, all other survival curves were similar.

A Wald chi-square test of equality of treatment means ($\mathrm{H}_0 : \mu_{11} = \mu_{21} = \mu_{12} = \mu_{22}$) did not show any significant differences. Similar conclusions, showing no significant difference in mean survival times, follow for comparing main effects of GM-CSF which is tested by the null hypothesis $\mathrm{H}_1 : (\mu_{11} + \mu_{12})/2 = (\mu_{21} + \mu_{22})/2$ and a comparison of the two intensification therapies which is tested by the null hypothesis $\mathrm{H}_2 : (\mu_{11} + \mu_{21})/2 = (\mu_{12} + \mu_{22})/2$. The conclusion is the same no matter which estimator we use except for the NAIVE estimators. Equivalent hypotheses were tested for survival probabilities and resulted in similar conclusions for survival probability at 548 days except that the test using the GAM estimator for the main effects of induction therapies turned out to be statistically significant. The results of all these tests are summarized in Table 1.

Test results for hypotheses related to the survival probability at other time points also showed no significant differences among the four policies.

8. Simulation Study

To assess the accuracy of the large sample properties of our estimators with moderate sample sizes and to compare the relative performance of the different estimators, we conducted several simulation experiments. For simplicity, in our simulation studies, we only allowed the survival time to depend on the response time T_i^{R} and did not consider any additional auxiliary variables. We only simulate data for "A_1-patients."

We took R_i, the eligible/consent indicator, to be Bernoulli with $P(R_i = 1) = \pi_R$ and considered two different values of π_R, 0.5 and 0.7. When $R_i = 0$, a survival time T_{0i} is generated from an exponential distribution with mean λ truncated at b_2. When $R_i = 1$, treatment B assignment indicator Z_i is generated from Bernoulli(.5) distribution. Also when $R_i = 1$, a response time T_i^{R} is generated from an exponential distribution with mean α truncated at b_1. To examine the effect that correlation among responders, between the survival time and the auxiliary variables has on the relative efficiency of the various estimators, we considered a linear relationship between the survival time of responders and the auxiliary variable (response time in this case) generated by

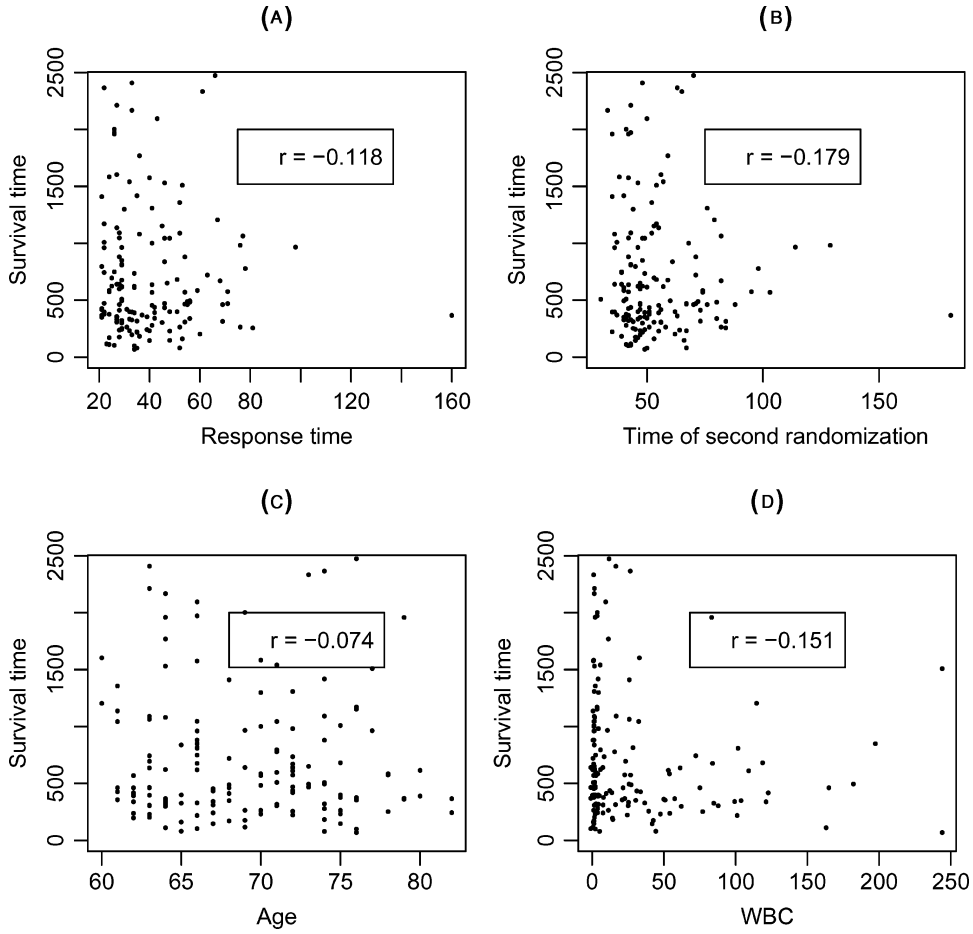

Figure 1. Scatter plot of survival time and auxiliary variables from CALGB 8923 data: (**A**) versus response time, (**B**) versus time of second randomization, (**C**) versus age, and (**D**) versus white blood cell count.

$$T^*_{ki} = T^{\mathrm{R}}_i + \left(\beta_1 + \beta_2 T^{\mathrm{R}}_i\right) U_{ki}, \quad k = 1, 2, \tag{22}$$

where U_{ki}, $k = 1$, 2 is generated from a uniform(0, θ_k) distribution. The strength of the correlation is determined by the choice of β_2. Finally we defined $T_i = (1 - R_i)T_{0i} + R_i\{Z_i T^*_{1i} + (1 - Z_i)T^*_{2i}\}$ to generate the observed survival time for the ith individual.

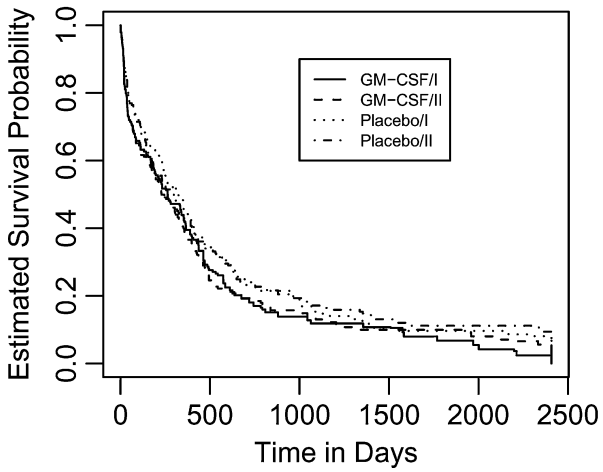

Figure 2. Estimated survival curves under IMP method.

In the first simulation scenario, we considered $\lambda = 365$, $b_2 = 1095$, $\alpha = 365$, $b_1 = 730$, $\beta_1 = 1.0$, $\beta_2 = 1.0$, $\theta_1 = 1.5$, $\theta_2 = 1$ so that when $\pi_R = 0.5$, $\mu_{11} = 510.4$ days, $\mu_{12} = 433.4$ days, and $\mu_{11} = 591.5$ days, $\mu_{12} = 483.6$ days when $\pi_R = 0.7$. We considered 5000 Monte-Carlo samples of sizes 200 and 500. Under this scenario, the correlation among responders between T^{R}_i and T^*_{1i} is 0.53, and 0.70 between T^{R}_i and T^*_{2i} representing moderate to high correlations.

For each of the 5000 simulated data sets, $\mu_{1k} = E(T_{1k})$ and $S_{1k}(t) = P(T_{1k} > t)$ were estimated for $k = 1$, 2 and for $t = 183$ and 548 days representing an earlier and later time point of the study. All estimators discussed in earlier sections were considered. For improved and locally efficient estimators, linear regression of survival time on the response time was used. For the LOESS regression, the smoothing parameter was set to 0.4. Other values of the smoothing parameters such as 0.2, 0.3, 0.5, 0.6 were also considered. These gave similar results and are not presented here.

Table 2 presents the coverage probabilities for 95% Wald intervals and relative efficiencies for all the estimators under consideration with respect to the LDT estimator. The relative

Table 2

Monte-Carlo coverage probability and relative efficiency for estimators based on 5000 *data sets: Entries in parentheses are relative efficiencies (e.g., for the LS row,* $\mathrm{MSE}(\hat{\mu}_{1k}^{\mathrm{LDT}})/\mathrm{MSE}(\hat{\mu}_{1k}^{\mathrm{LS}})$)

	$\hat{\mu}_{11}$				$\hat{\mu}_{12}$			
	$n = 200$		$n = 500$		$n = 200$		$n = 500$	
Estimator	$\pi_R = 0.5$	$\pi_R = 0.7$	$\pi_R = 0.5$	$\pi_R = 0.7$	$\pi_R = 0.5$	$\pi_R = 0.7$	$\pi_R = 0.5$	$\pi_R = 0.7$
Results for estimating mean survival: moderate to strong correlation								
NAIVE	40.5 (0.25)	54.3 (0.29)	08.2 (0.11)	20.4 (0.13)	60.9 (0.35)	69.5 (0.40)	27.1 (0.16)	40.2 (0.19)
IPMW	93.8 (0.51)	93.8 (0.48)	93.9 (0.51)	94.4 (0.48)	94.5 (0.53)	94.7 (0.48)	95.1 (0.52)	95.1 (0.47)
LDT	92.6 (1.00)	93.6 (1.00)	94.1 (1.00)	94.4 (1.00)	94.3 (1.00)	94.3 (1.00)	94.7 (1.00)	95.1 (1.00)
LOESS	89.4 (1.09)	91.1 (1.17)	92.4 (1.18)	93.2 (1.26)	90.7 (1.15)	92.0 (1.23)	93.1 (1.22)	93.8 (1.30)
IMP	91.5 (1.15)	92.7 (1.22)	93.4 (1.22)	93.6 (1.29)	92.2 (1.18)	93.0 (1.25)	94.1 (1.24)	94.2 (1.33)
LS	93.7 (1.29)	94.4 (1.36)	94.0 (1.28)	94.4 (1.34)	95.9 (1.35)	96.1 (1.42)	96.2 (1.32)	96.5 (1.40)
Results for estimating mean survival: low correlation								
NAIVE	28.7 (0.15)	38.5 (0.16)	02.5 (0.06)	05.8 (0.07)	49.8 (0.19)	69.5 (0.19)	13.3 (0.09)	16.6 (0.09)
IPMW	94.5 (0.37)	94.1 (0.31)	94.1 (0.37)	94.5 (0.31)	94.9 (0.36)	94.7 (0.28)	94.8 (0.36)	94.7 (0.27)
LDT	94.1 (1.00)	94.2 (1.00)	94.5 (1.00)	94.5 (1.00)	94.3 (1.00)	94.3 (1.00)	94.7 (1.00)	95.1 (1.00)
LOESS	91.9 (0.91)	92.1 (0.91)	93.1 (0.96)	93.8 (0.97)	92.1 (0.90)	92.0 (0.91)	94.0 (0.96)	94.2 (0.96)
IMP	93.0 (0.92)	93.2 (0.93)	94.0 (0.97)	94.2 (0.98)	92.9 (0.91)	93.0 (0.91)	94.2 (0.95)	94.5 (0.96)
LS	94.4 (1.05)	94.6 (1.06)	94.5 (1.03)	94.8 (1.03)	96.4 (1.06)	96.1 (1.06)	96.8 (1.02)	96.9 (1.02)
Results for estimating survival prob. at 548 days: moderate to strong correlation								
NAIVE	53.8 (0.29)	65.4 (0.34)	18.6 (0.14)	12.6 (0.17)	74.8 (0.53)	80.9 (0.61)	50.7 (0.27)	37.9 (0.34)
IPMW	94.4 (0.68)	94.5 (0.64)	93.9 (0.70)	94.7 (0.66)	94.8 (0.79)	94.3 (0.75)	94.9 (0.79)	95.1 (0.76)
LDT	94.3 (1.00)	94.4 (1.00)	94.1 (1.00)	94.9 (1.00)	94.6 (1.00)	94.3 (1.00)	94.6 (1.00)	95.0 (1.00)
LOESS	92.7 (1.06)	93.3 (1.11)	93.0 (1.12)	94.9 (1.17)	92.9 (1.17)	93.2 (1.25)	93.9 (1.19)	95.0 (1.27)
IMP	93.6 (1.07)	93.9 (1.12)	93.4 (1.10)	94.5 (1.16)	93.6 (1.17)	93.8 (1.24)	94.2 (1.18)	94.9 (1.25)
LS	94.2 (1.15)	94.5 (1.17)	94.1 (1.15)	94.6 (1.18)	94.8 (1.23)	94.9 (1.28)	94.9 (1.22)	95.6 (1.26)

efficiencies are defined in terms of the ratio of the Monte-Carlo mean squared errors compared to the LDT estimator. The LS, IMP, and LOESS estimators were always more efficient than the LDT estimator. The IPMW estimator was by far the least efficient of these five estimators and the LS estimator was the most efficient. This is not surprising since the model for conditional expectation is correct. If the conditional expectation had been nonlinear in T_i^{R}, then the LS estimator might not be as efficient. The NAIVE estimator, as expected, performs very poorly with coverage probability always below 60% (80%, for the survival probability estimates) and sometimes as low as 8% (13%). The LOESS estimator tended to have some bias with smaller sample sizes as evidenced by the poor coverage probabilities. The coverage probabilities for the LOESS estimator improved with increasing sample sizes. We believe this is due to the slow convergence rate for such local regression methods. We expect this difficulty would be exacerbated if one considered many auxiliary variables where we would run into the curse of dimensionality. In such cases, the use of generalized additive or spline models may be a useful alternative for estimating high dimensional conditional expectations with sufficient data.

From the above analysis it is clear that when the auxiliary variables are at least moderately correlated to the survival times among the responders, the locally efficient estimators gain sufficiently over the LDT or IPMW estimators. A second simulation scenario was also considered where the correlation between the time-to-response and time-to-death among the responders were weakly correlated (similar to those observed in the CALGB study). The setup for this simulation is the same as the first one except that the RHS of equation (22) is replaced by $\mathrm{E}(T_i^{\mathrm{R}}) + \{\beta_1 + (2/3)\ \mathrm{E}(T_i^{\mathrm{R}}) + (\beta_2/3)T_i^{\mathrm{R}}\}U_{ki}$, $k = 1, 2$. This allowed us to preserve the values for μ_{11} and μ_{12} from the first scenario, but with a low correlation among responders (0.17 and 0.18, respectively) between T_i^{R} and T_{1i}^*, and T_i^{R} and T_{2i}^*. The results for estimating the mean survival time for this scenario are given in Table 2. In this case, there is virtually no gain in using the locally efficient or the improved estimators. In terms of relative mean squared errors, the LS estimators always performed well while the LOESS and IMP estimators showed some loss of efficiency with smaller sample sizes. Also for small samples, the LOESS estimator had the worst coverage. For larger sample sizes, all the four estimators LDT, LS, IMP, and LOESS gave similar results.

9. Discussion

We have presented several approaches for improving the efficiency of estimators for the quantities related to the survival distribution of treatment policies for two-stage randomization designs. The improved estimators are guaranteed to gain efficiency over other available estimators such as the inverse-probability-of-missing-weighted estimator or the estimators proposed by Lunceford et al. (2002). Therefore, for inferential procedures using the data from a two-stage design, our estimators will give more accurate results than the existing ones. These methods allow us to consider auxiliary covariates, either baseline covariates or other variables that are collected prior to the second randomization, which, if correlated

with the survival time among responders, will allow for additional gain in efficiency. For this problem, we also derived the semiparametric efficient estimator and the corresponding semiparametric bound. This result guarantees that no other RAL estimator can have smaller variance.

In some cases, it might be of interest to estimate the median or other quantiles rather than the mean survival time or survival probability at a certain time point. In such cases, for instance, for estimating the median survival time, an entirely similar strategy can be followed by replacing $h(T_i) - \mu_{1k}$ in (7) by $I(T_i > \mu_{1k}) - 0.5$. Although we have used survival time as the response variable in this article, the methods could be applied to estimating the mean response for a treatment policy for any response variable, discrete or continuous. We focused here on situations where we have complete restricted survival times on all the patients in the study. This was the case for the CALGB 8923 data that was used to motivate this problem. However, in many two-stage clinical trials the survival data may be right-censored. We have shown a simple ad hoc modification of our estimators for the cases where data are noninformatively right-censored. Methods for improving efficiency with censored data is a subject of future research.

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Résumé

Les essais avec une randomisation en deux étapes, où les patients sont d'abord randomisés pour le traitement d'induction, puis, en fonction de leur réponse au traitement et de leur consentement, randomisés pour le traitement d'entretien sont fréquents en cancérologie et dans d'autres domaines. L'objectif est de comparer différentes combinaisons de traitement d'induction et de traitement d'entretien afin de déterminer laquelle est la plus efficace. Habituellement, l'analyse est réalisée en deux temps séparés qui ne répondent pas directement à cet objectif de recherche de la meilleure combinaison possible. Récemment, Lunceford et al. (2002, *Biometrics* **58,** 48–57) ont proposé des estimateurs adaptés aux distributions de survie et au temps moyen de survie en fonction de différentes stratégies thérapeutiques. Ces estimateurs sont consistants mais pas efficients, et ne permettent pas d'inclure l'information fournie par des covariables. Dans ce papier, nous proposons des estimateurs simples à calculer et plus efficients que les estimateurs précédents. Nous montrons également comment améliorer encore cette efficience en tenant compte de l'information fournie par des covariables. Les propriétés de ces estimateurs et leur comparaison aux autres estimateurs sont calculées à partir de données simulées sur de grands échantillons. Nous avons appliqué ces estimateurs aux données d'un essai clinique dans les leucémies, essai qui avait motivé ce travail.

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Appendix A

Proof of Proposition 1

As in Robins et al. (1994), we consider the Hilbert space $\mathcal{H}$ consisting of all mean zero random functions of the observed data with finite variance equipped with the covariance inner product. Within this space we define the closed linear subspace $\mathcal{U}$ consisting of random functions

$R_i((X_{ki}-\pi_k)/\pi_k)f(T_i^{\mathrm{R}}, V_i)$, where $f(T_i^{\mathrm{R}}, V_i)$ is an arbitrary function with finite variance. Our aim is to find the function $f(\cdot\,,\cdot)$ which minimizes the variance in (7), or equivalently, to find the element in $\mathcal{U}$ which minimizes the distance (square root of variance) from $\{(1-R_i)+(R_iX_{ki})/\,\pi_k\}\{h(T_i)-\mu_{1k}\}$ to some element in $\mathcal{U}$. By the projection theorem for Hilbert spaces (Luenberger, 1969), the optimal $f(\cdot\,,\cdot)$ is given by the unique $f^*(\cdot\,,\cdot)$, where f^* satisfies

$$\begin{aligned}\mathrm{E}\Bigg[&\left\{(1-R_i)+\frac{R_iX_{ki}}{\pi_k}\right\}\{h(T_i)-\mu_{1k}\}\\&+R_i\left(\frac{X_{ki}-\pi_k}{\pi_k}\right)f^*\big(T_i^{\mathrm{R}},V_i\big)\Bigg]\\&\times\left\{R_i\left(\frac{X_{ki}-\pi_k}{\pi_k}\right)f\big(T_i^{\mathrm{R}},V_i\big)\right\}=0\end{aligned}\tag{A.1}$$

for all $f(\cdot\,,\cdot)$. Since $(1-R_i)R_i=0$, equation (A.1) can be simplified to

$$\begin{aligned}\mathrm{E}\Bigg(\Bigg[&\frac{R_iX_{ki}(X_{ki}-\pi_k)}{\pi_k^2}\{h(T_i)-\mu_{1k}\}\\&+R_i\left(\frac{X_{ki}-\pi_k}{\pi_k}\right)^2f^*\big(T_i^{\mathrm{R}},V_i\big)\Bigg]f\big(T_i^{\mathrm{R}},V_i\big)\Bigg)=0.\end{aligned}\tag{A.2}$$

Using iterated conditional expectations one can write (A.2) as

$$\begin{aligned}\mathrm{E}\big(R_i\big[&\mathrm{E}\big\{h(T_i)-\mu_{1k}\,\big|\,R_i=1,X_{ki}=1,T_i^{\mathrm{R}},V_i\big\}\\&+f^*\big(T_i^{\mathrm{R}},V_i\big)\big]f\big(T_i^{\mathrm{R}},V_i\big)\big)=0\end{aligned}\tag{A.3}$$

for all $f(T_i^{\mathrm{R}}, V_i)$. In order for (A.3) to hold for all $f(T_i^{\mathrm{R}}, V_i)$, we must have

$$\begin{aligned}f^*\big(T_i^{\mathrm{R}},V_i\big)&=-\mathrm{E}\big\{h(T_i)-\mu_{1k}\,\big|\,R_i=1,X_{ki}=1,T_i^{\mathrm{R}},V_i\big\}\\&=\theta_h\big(T_i^{\mathrm{R}},V_i\big)+\mu_{1k}.\end{aligned}\tag{A.4}$$

Substituting $f^*(\cdot\,,\cdot)$ into (7) and simplifying further we get the most efficient influence function (8). This completes the proof.

Appendix B

Consistency and Asymptotic Normality

Under mild regularity conditions, all the estimators $\hat\mu_{1k}^{\mathrm{LE}}, \hat\mu_{1k}^{\mathrm{LS}}$, and $\hat\mu_{1k}^{\mathrm{IMP}}$ are consistent. Consider $\hat\mu_{1k}^{\mathrm{LE}}$. We will assume that $\hat{\boldsymbol\gamma}$ converges in probability to $\boldsymbol\gamma_0$. We write

$$\begin{aligned}\hat\mu_{1k}^{\mathrm{LE}}=\frac{1}{n}\sum_{i=1}^{n}\Bigg[&\left\{(1-R_i)+\frac{R_iX_{ki}}{\pi_k}\right\}h(T_i)\\&-R_i\left(\frac{X_{ki}-\pi_k}{\pi_k}\right)g\big(T_i^{\mathrm{R}},V_i,\boldsymbol\gamma_0\big)\Bigg]\end{aligned}\tag{B.1}$$

$$-\frac{1}{n}\sum_{i=1}^{n}R_i\left(\frac{X_{ki}-\pi_k}{\pi_k}\right)\big\{g\big(T_i^{\mathrm{R}},V_i,\hat{\boldsymbol\gamma}\big)-g\big(T_i^{\mathrm{R}},V_i,\boldsymbol\gamma_0\big)\big\}.\tag{B.2}$$

Now the term (B.1) is the sample average of i.i.d. quantities having mean μ_{1k} and constant variance, and hence converges to its mean μ_{1k} in probability. A Taylor's series expansion of $g(T_i^{\mathrm{R}},V_i,\hat{\boldsymbol\gamma})$ in (B.2) shows that we can write the second term as

$$(\hat{\boldsymbol\gamma}-\boldsymbol\gamma_0)^{\mathrm{T}}n^{-1}\sum_{i=1}^{n}R_i\left(\frac{X_{ki}-\pi_k}{\pi_k}\right)\left\{\frac{\delta}{\delta\boldsymbol\gamma}g\big(T_i^{\mathrm{R}},V_i,\boldsymbol\gamma\big)\Big|_{\boldsymbol\gamma=\tilde{\boldsymbol\gamma}}\right\},\tag{B.3}$$

where $\tilde{\boldsymbol\gamma}$ lies between $\hat{\boldsymbol\gamma}$ and $\boldsymbol\gamma_0$. Now in addition if we assume that

$$\operatorname*{Sup}_{\boldsymbol\gamma\in\Gamma(\hat{\boldsymbol\gamma},\tilde{\boldsymbol\gamma})}\frac{\delta}{\delta\boldsymbol\gamma}g\big(T_i^{\mathrm{R}},V_i,\boldsymbol\gamma\big)\le H\big(T_i^{\mathrm{R}},V_i;\boldsymbol\gamma_0\big)$$

with $\mathrm{E}\{H(T_i^{\mathrm{R}}, V_i;\boldsymbol\gamma_0)\}<\infty$, where $\Gamma(\hat{\boldsymbol\gamma},\tilde{\boldsymbol\gamma})$ is the set of all $\boldsymbol\gamma$ that lies between $\hat{\boldsymbol\gamma}$ and $\tilde{\boldsymbol\gamma}$, then it follows that (B.3), hence (B.2) is $o_p(1)$. Combining these results, we see that $\hat\mu_{1k}^{\mathrm{LE}}\xrightarrow{p}\mu_{1k}$. Since least squares estimators are consistent, $\hat\mu_{1k}^{\mathrm{LS}}$ being a special case of $\hat\mu_{1k}^{\mathrm{LE}}$ is also consistent. Similar arguments can be applied to show the consistency of $\hat\mu_{1k}^{\mathrm{IMP}}$.

Under mild regularity conditions, all the estimators $\hat\mu_{1k}^{\mathrm{LE}}$, $\hat\mu_{1k}^{\mathrm{LS}}$, and $\hat\mu_{1k}^{\mathrm{IMP}}$ are asymptotically normal. We sketch the proof for $\hat\mu_{1k}^{\mathrm{LE}}$. The rest follows immediately.

If $\hat{\boldsymbol\gamma}$ is $n^{1/2}$-consistent, then

$$n^{\frac{1}{2}}\big(\hat\mu_{1k}^{\mathrm{LE}}-\mu_{1k}\big)=n^{-\frac{1}{2}}\sum_{i=1}^{n}(Y_{1ki}-\mu_{1k})+o_p(1),\tag{B.4}$$

where $Y_{1ki}=\{(1-R_i)+(R_iX_{ki})/\pi_k\}h(T_i)-R_i\{(X_{ki}-\pi_k)/\pi_k\}g(T_i^{\mathrm{R}},V_i,\boldsymbol\gamma_0)$, $i=1,2,\ldots,n$ are i.i.d. with mean zero and variance $\sigma^2=\mathrm{E}(Y_{1ki}^2)$. Therefore, by Slutsky's theorem, $n^{1/2}(\hat\mu_{1k}^{\mathrm{LE}}-\mu_{1k})\xrightarrow{d}(0,\sigma^2)$. The asymptotic variance of $\hat\mu_{1k}^{\mathrm{LE}}$ can be estimated by (12).