Published in final edited form as:

Stat Probab Lett. 2016 February 1; 109: 152–158. doi:10.1016/j.spl.2015.11.014.

Nonparametric restricted mean analysis across multiple follow-up intervals

Nabihah Tayob^{a,*} and Susan Murray^b

^aThe University of Texas MD Anderson Cancer Center, Department of Biostatistics, 1400 Pressler St, Houston, TX 77030, U.S.A.

^bUniversity of Michigan, Department of Biostatistics, Ann Arbor, Michigan 48109, U.S.A.

Abstract

We provide a nonparametric estimate of τ -restricted mean survival using follow-up information beyond τ when appropriate to improve precision. The variance accounts for correlation between follow-up windows. Both asymptotic calculations and simulation studies recommend follow-up intervals spaced approximately $\tau/2$ apart.

Keywords

Correlated times-to-events; Follow-up intervals; Residual life; Restricted mean survival

1 Introduction

Yearly progression predictions are commonly reported for clinical longitudinal data. For example, Raghu et al. (2011) report that mild to moderate idiopathic pulmonary fibrosis (IPF) patients tend to lose 0.2 liters in forced vital capacity lung function per year. This is a valuable summary statistic that has not been sufficiently explored for censored time to event data. It would be clinically useful to be able to report that IPF patients followed for 10 years were observed to live 91% of each year, on average, given they were alive at the start of the year. This concise estimate describes how the disease will affect patients in the short term and indicates stability of the disease where appropriate. Health economists have noted that patient's value life-years closer to the present more than those in the future, Gyrd-Hansen and Sogaard (1998).

*Corresponding author: ntayob@mdanderson.org, Phone: +1-734-239-4235.

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Software

Software in the form of R code, together with a sample input data set and complete documentation is available on request from the corresponding author (skmurray@umich.edu).

Conflict of Interest: The authors have declared no conflict of interest.

The restricted mean residual life function (RMRL) is the expected days of life per year for those surviving at the beginning of the year and may be used to view trends in these summary statistics over time. Ghorai et al. (1982) proposed an estimator based on integrated conditional Kaplan-Meier estimates (Ghorai and Rejto, 1987) and Na and Kim (1999) proposed a smooth-spline estimator for this quantity, among others. Yu (2003) developed confidence bands for restricted mean residual life functions estimated via Nelson-Aalen estimates, Cox model hazard estimates and inverse weighted hazard estimates, calling them expected life prosper functions (ELPF). Stability of these functions suggests an opportunity for producing an overall summary statistic that is more precise.

In Section 2 we review RMRL estimation and confidence band construction. Section 3 describes the nonparametric τ -restricted mean survival estimator that combines information across different τ -length intervals of follow-up. The proposed variance described in Section 3 is based on a linearization of random components of the estimator, similar to the approach recommended by Woodruff (1971) and more recently Williams (1995). In Section 4 we consider how to choose the number of follow-up intervals useful for obtaining efficiency gains. A simulation study that assesses the performance of the proposed estimate and its variance against currently available competitors is presented in Section 5. Examples of the proposed analysis approach pertaining to IPF patients and diabetic retinopathy patients are given in Section 6. A discussion follows in Section 7.

2 τ -restricted mean residual life

2.1 Notation

For each of n patients we define observed event time, $X_i = \min(T_i, C_i)$, with failure indicator $\delta_i = I(T_i \leq C_i)$, based on true failure time, T_i , and censoring time, C_i , $i = 1, \dots, n$. Calendar time, t , is measured from the start of the study. We define the residual life observed at t as $X_i(t) = (X_i - t)I(X_i \geq t)$ with failure indicator variable $\delta_i(t) = \delta_i I(X_i \geq t)$.

For a τ -length interval starting at calendar time, t , the τ -restricted mean residual lifetime is $\mu(t, \tau) = E\{\min(T - t, \tau) | T > t\} = \int_0^\tau Pr(T > t + u | T > t) du$. Here, u denotes an internal time scale measured from calendar time t . We examine values of $\mu(t, \tau)$ measured at different calendar times $t \in \{t_1, \dots, t_b\}$, with $t_1 = 0$ in all that follows.

Counting process notation includes the two timescales described, t and u . For individual i , the event counting process is $N_i(t, u) = I\{X_i(t) \leq u, \delta_i(t) = 1\}$ with at-risk process $Y_i(t, u) = I\{X_i(t) \geq u\}$. At t , the total number of events occurring no later than u is

$N(t, u) = \sum_{i=1}^n N_i(t, u)$ and the number at risk at u is $Y(t, u) = \sum_{i=1}^n Y_i(t, u)$. We require notation combining counting process quantities across calendar times, $\{t_1, \dots, t_b\}$. For

individual i and internal time u , $N_i(u) = \sum_{k=1}^b N_i(t_k, u)$. Combining information across follow-up intervals and patients gives us $Y_i(u) = \sum_{k=1}^b Y_i(t_k, u)$, total number of events occurring no later than u , and $N_i(u) = \sum_{k=1}^b N_i(t_k, u)$, total number at risk at u .

2.2 Estimation of τ -restricted mean residual life

The τ -restricted mean residual lifetime function, $\mu(t, \tau)$, tracks subsequent expected lifetime during an interval of length τ given the patient has survived up to time t . Henceforth we call $\mu(t, \tau)$ the RMRL function. Using notation from the previous section, a consistent nonparametric estimator of the RMRL function is

$$\hat{\mu}(t, \tau) = \int_0^\tau \hat{P}(t, s) ds \quad \text{where} \quad \hat{P}(t, s) = \exp \left\{ - \int_0^s dN(t, u) / Y(t, u) \right\}$$

2.3 Confidence Bands

We slightly modify work from Yu (2003) for RMRL confidence band calculations applied to times $\{t_1, \dots, t_b\}$. Plotting the RMRL function with its corresponding bands is useful in suggesting whether follow-up windows may be combined for estimation or not.

Technical development of confidence bands for $\{\mu(t_1, \tau), \dots, \mu(t_b, \tau)\}$ is based on the Gaussian process $B(t, \tau) = n^{1/2} \{\hat{\mu}(t, \tau) - \mu(t, \tau)\}$ and the covariance of this process at times t_{j_1} and t_{j_2} , $j_1 = 1, \dots, b$, $j_2 = 1, \dots, b$. The estimated covariance matrix $\sum_{b \times b}$, with estimates of $\text{cov}\{B(t_{j_1}, \tau), B(t_{j_2}, \tau)\}$ as the (j_1, j_2) elements, is

$$n \int_0^\tau \int_0^\tau \hat{P}(t_{j_1}, s) \hat{P}(t_{j_2}, s') \sum_{i=1}^n \int_0^s \int_0^{s'} \frac{dN_i(t_{j_1}, u) dN_i(t_{j_2}, v)}{Y(t_{j_1}, u) Y(t_{j_2}, v)} ds ds'$$

Following Lin et al. (1994), the asymptotic distribution of $\{B(t_1, \tau), \dots, B(t_b, \tau)\}$ is approximated by generating a large number of mean zero multivariate Normal samples using the observed covariance structure, $\sum_{b \times b}$. Using these samples, we calculate q_α satisfying $Pr \left\{ \max_{t \in \{t_1, \dots, t_b\}} |\hat{B}(t, \tau)| > q_\alpha \right\} = \alpha$. Level $100(1 - \alpha)\%$ confidence band values surrounding $\mu(t, \tau)$ become $\left[\hat{\mu}(t, \tau) - n^{-1/2} \times q_\alpha, \hat{\mu}(t, \tau) + n^{-1/2} \times q_\alpha \right]$, calculated at times $t = \{t_1, \dots, t_b\}$. In practice, these confidence bands perform well provided that there are at least 25 event times following t_b (Yu, 2003).

3 Overall τ -restricted mean survival

The RMRL plots and associated confidence bands are a useful diagnostic tool to assist in deciding whether disease progression is stable, i.e. the RMRL is the same at each $t_1, \dots, t_b$, or not. When the RMRL and its corresponding confidence bands do not indicate a strong trend, we develop a more efficient estimate of the expected number of days lived in the next τ years by pooling appropriate follow-up periods beginning at times $t \in \{t_1, \dots, t_b\}$.

3.1 Estimation

The proposed estimate of the overall τ -restricted mean survival is

$$\hat{\mu}^*(\tau) \int_0^\tau \exp \left\{ - \int_0^s \frac{dN(u)}{Y(u)} \right\} ds. \quad (1)$$

Let

$$\begin{aligned} \lambda(t_k, u) &= \lim_{\Delta u \rightarrow 0} [Pr \{u \leq X_i(t_k) < u + \Delta u, \delta_i(t_k) = 1 | X_i(t_k) \geq u\} / \Delta u] \quad \text{and} \quad \lambda^W(u) \\ &= \sum_{k=1}^b [\lambda(t_k, u) Pr \{X_i(t_k) \geq u\}] \\ &\quad / \sum_{l=1}^b Pr \{X_i(t_l) \geq u\} \end{aligned}$$

. In Appendix A of Supplementary Materials, we show that (1) converges in probability to

$\mu^*(\tau) = \int_0^\tau \exp \left[- \int_0^s \lambda^W(u) du \right] ds$, which is the mean of the mixture distribution created from combining follow-up times across the different intervals. If the overall dataset reflects a single distribution, that is, $\lambda(t_{k1}, u) = \lambda(t_{k2}, u)$ for $0 \leq u \leq \tau$ and $k_1, k_2 \in \{1, \dots, b\}$, then $\mu^*(\tau)$ reduces to $\mu(t_1, \tau)$, the usual restricted mean that is typically estimated using a single follow-up period. We also suspect that in cases where the integrated survival curves within the follow-up windows are equivalent, our estimate is consistent estimator of $\mu(t_1, \tau)$. A rigorous proof backing up this intuition has eluded us, although special cases of distributions with this property have given $\mu^*(\tau) = \mu(t_1, \tau)$.

Variance calculations in the following section acknowledge the potential mixture of hazards that might occur when combining follow-up times across intervals.

3.2 Variance of proposed estimate

The proposed variance estimate is calculated via linearizing components of $\sqrt{n}\hat{\mu}^*(\tau)$ via Taylor series approximations. Suppose that in the dataset of combined follow-up times we observe M events at internal times $\{0 < J_1 < \dots < J_M < \tau\}$ where events from the same individual during different follow-up windows are correlated; for convenience, we define $J_0 = 0$ and $J_{M+1} = \tau$. Let $F_j \{dN(J_j), Y(J_j)\} = dN(J_j) / Y(J_j)$. In the following we temporarily submerge arguments of F_j . We define $G_m(F_0, F_1, \dots, F_m) = \exp \left(- \sum_{j=0}^m F_j \right)$. After rewriting $\sqrt{n}\hat{\mu}^*(\tau)$ in term of $G_m(F_0, F_1, \dots, F_m)$, the variance of $\sqrt{n}\hat{\mu}^*(\tau)$ becomes

$$Var \left\{ \sqrt{n} \sum_{m=0}^M (J_{m+1} - J_m) G_m(F_0, F_1, \dots, F_m) \right\}$$

The non-linear terms $G_0, G_1, \dots, G_M$ may be made more tractable for variance calculations via linearization based on a Taylor series expansion of $G_m(F_0, F_1, \dots, F_m)$ about

$\lambda^W(J_j) dJ_j, j=0, \dots, m$. The variance of $\sqrt{n}\hat{\mu}^*(\tau)$ is then

$$Var \left(\sqrt{n} \sum_{m=0}^M (J_{m+1} - J_m) \exp \left\{ - \sum_{j'}^m \right\} \lambda^W(J_{j'}) dJ_{j'} \right) \quad (2a)$$

$$+ \sqrt{n} \sum_{m=0}^M (J_{m+1} - J_m) \left[\sum_{j=0}^m - \exp \left\{ - \sum_{j'}^m \lambda^W (J_{j'}) dJ_{j'} \right\} F_j \right] \quad (2b)$$

$$- \sqrt{n} \sum_{m=0}^M (J_{m+1} - J_m) \left[\sum_{j=0}^m - \exp \left\{ - \sum_{j'}^m \lambda^W (J_{j'}) dJ_{j'} \right\} \lambda^W (J_{j'}) dJ_{j'} \right] \quad (2c)$$

$$+ \sqrt{n} \sum_{m=0}^M (J_{m+1} - J_m) \frac{1}{2!} \exp \left\{ - \sum_{j'}^m \lambda^W (J_{j'}) dJ_{j'} \right\} \left[\sum_{j=0}^m \left\{ F_j - \lambda^W (J_j) dJ_j \right\} \right]^2 \quad (2d)$$

$$+ \sqrt{n} \sum_{m=0}^M (J_{m+1} - J_m) [\text{higher order terms}] \quad (2e)$$

Terms (2a) and (2c) are nonrandom and therefore do not contribute to the variance. The fourth term (2d) converges to zero in probability, details given in Appendix B of Supplementary Materials. Similarly all higher order terms of the Taylor series linearization (2e) converge to zero in probability and the variance reduces to

$Var \left[\sqrt{n} \sum_{m=0}^M (J_{m+1} - J_m) \exp \left\{ - \sum_{j'=0}^m \lambda^W (J_{j'}) dJ_{j'} \right\} \sum_{j=0}^m F_j \right]$, the variance of a linear sum of non-linear components $F_0, F_1, \dots, F_M$.

Each of the non-linear F_j terms may be made more tractable for variance calculations via further linearization based on a Taylor series expansion of $F_j \{dN(J_j), Y(J_j)\}$ about the expected values of $dN(J_j)$ and $Y(J_j)$. The variance of $\sqrt{n}\hat{\mu}^*(\tau)$ is then

$$Var \left[\sqrt{n} \sum_{m=0}^M (J_{m+1} - J_m) \exp \left\{ - \sum_{j'=0}^m \lambda^W (J_{j'}) dJ_{j'} \right\} \times \right.$$

$$\left. \sum_{j=0}^m F_j [E \{dN(J_j)\}, E \{Y(J_j)\}] \right] \quad (3a)$$

$$+ \sum_{j=0}^m \left\{ \frac{dN(J_j) - E \{dN(J_j)\}}{E \{Y(J_j)\}} \right\} \quad (3b)$$

$$- \sum_{j=0}^m \left\{ \frac{E \{dN(J_j)\} [Y(J_j) - E \{Y(J_j)\}]}{E \{Y(J_j)\}^2} \right\} \quad (3c)$$

$$+ \sum_{j=0}^m \frac{1}{2!} \left\{ 0 - 2 \frac{[Y(J_j) - E\{Y(J_j)\}][dN(J_j) - E\{dN(J_j)\}]}{E\{Y(J_j)\}^2} + \frac{2E\{dN(J_j)\}}{E\{Y(J_j)\}^3} [Y(J_j) - E\{Y(J_j)\}]^2 \right\} \quad (3d)$$

$$+ \sum_{j=0}^m \{\text{higher order terms}\}. \quad (3e)$$

Term (3a) is a constant and therefore does not contribute to the variance. Terms (3b) and (3c) simplify to $\sum_{j=0}^m [dN(J_j) - Y(J_j) E\{dN(J_j)\} / E\{Y(J_j)\}] / E\{Y(J_j)\}$. The fourth term (3d) converges in probability to zero, details given in Appendix B of Supplementary Materials. Similarly, all higher order terms of the Taylor series linearization (3e) converge to zero in probability. Recall that

$dN(J_j) \sum_{i=1}^n \sum_{k=1}^b dN_i(t_k, J_j)$ and $Y(J_j) \sum_{i=1}^n \sum_{k=1}^b Y_i(t_k, J_j)$. The expected value of $dN(J_j)$ is $n \sum_{k=1}^b \lambda(t_k, J_j) Pr\{X_i(t_k) \geq J_j\} dJ_j$ and the expected value of $Y(J_j)$ is $n \sum_{k=1}^b Pr\{X_i(t_k) \geq J_j\}$. The variance then reduces to $Var\left[\sqrt{n} \sum_{i=1}^n Z_i\{\hat{\mu}^*(\tau)\} / n\right]$ where $Z_i\{\hat{\mu}^*(\tau)\} = \sum_{k=1}^b Z_{ik}\{\hat{\mu}^*(\tau)\}$ and

$$Z_{ik}\{\hat{\mu}^*(\tau)\} = \sum_{m=0}^M (J_{m+1} - J_m) \exp\left\{-\sum_{j'=0}^m \lambda^{W_j}(J_{j'}) dJ_{j'}\right\} \sum_{j=0}^m \frac{dN_i(t_k, J_j) - \lambda^{W_j}(J_j) Y_i(t_k, J_j) dJ_j}{\sum_{l=1}^b Pr\{X_i(t_l) \geq J_j\}}$$

Whereas event times across overlapping follow-up periods are generally not i.i.d., the $Z_i\{\hat{\mu}^*(\tau)\}$ making empirical variance estimates based on $Z_i\{\hat{\mu}^*(\tau)\}$ appropriate for this setting. In practice, the empirical variance estimator of $Z_i\{\hat{\mu}^*(\tau)\}$ is

$$\sum_{i=1}^n \left[Z_i\{\hat{\mu}^*(\tau)\} - \bar{Z}\{\hat{\mu}^*(\tau)\} \right]^2 / n(n-1) \text{ where } \bar{Z}\{\hat{\mu}^*(\tau)\} = \sum_{i=1}^n Z_i\{\hat{\mu}^*(\tau)\} / n.$$

The sample estimates of $Z_{ik}\{\hat{\mu}^*(\tau)\}$ are given by

$$z_{ik}\{\hat{\mu}^*(\tau)\} = \sum_{m=0}^M (J_{m+1} - J_m) \exp\left\{-\sum_{j=0}^m \frac{dN(J_j)}{Y(J_j)}\right\} \sum_{j=0}^m \frac{dN_i(t_k, J_j) - \frac{dN(J_j)}{Y(J_j)} Y_i(t_k, J_j)}{Y(J_j) / n}$$

In understanding design issues discussed in Section 4, it is convenient to have the

asymptotic closed form variance, $\sigma^2 = Var\left[\sqrt{n} \sum_{i=1}^n Z_{ik}\{\hat{\mu}^*(\tau)\} / n\right]$, where

$$Z_{ik} \{ \hat{\mu}^* (\tau) \} = \int_0^T \exp \left\{ - \int_0^s \lambda^W (u) du \right\} \left[\frac{\int_0^s \frac{dN_i (t_k, u) - \lambda^W (u) Y_i (t_k, u) du}{\sum_{l=1}^b \Pr \{ X_i (t_l) \geq u \}} ds \right]$$

in asymptotically equivalent stochastic integral notation. In Appendix C of Supplementary Materials we show that

$$\begin{aligned} \sigma^2 &= \sum_{k=1}^b \sum_{l=1}^b \int_0^\tau \int_0^\tau \left\{ - \int_0^s \lambda^W (u) du \right\} \exp \left\{ - \int_0^{s'} \lambda^W (v) dv \right\} \\ &\quad \int_0^s \int_0^{s'} \frac{1}{\left[\sum_{l'}^b \Pr \{ X_i (t_{l'}) \geq u \} \right] \left[\sum_{l'}^b \Pr \{ X_i (t_{l'}) \geq v \} \right]} \\ &\quad \left[\lambda (t_k, u) \Pr \{ X_i (t_{l'}) \geq u \} I (v = u + t_k - t_l) du \right. \\ &\quad - \lambda^W (u) \lambda (t_l, v) \Pr \{ X_i (t_l) \geq v \} \{ I (u \leq v + t_l - t_k) + I (u = 0) I (v < t_k - t_l) \} dudv \\ &\quad - \lambda^W (v) \lambda (t_k, u) \Pr \{ X_i (t_k) \geq u \} \{ I (v \leq u + t_k - t_l) + I (v = 0) I (u < t_l - t_k) \} dudv \\ &\quad - \lambda^W (u) \lambda^W (v) \Pr \{ X_i (t_k) \geq u, X_i (t_l) \geq v \} dudv \\ &\quad \left. - \left\{ \lambda (t_k, u) - \lambda^W (u) \right\} \left\{ \lambda (t_l, v) - \lambda^W (v) \right\} \Pr \{ X_i (t_l) \geq v \} dudv \right] ds ds' \end{aligned}$$

4 Practical Issues

Number and spacing of follow-up windows should be chosen to increase precision of $\hat{\mu}^* (\tau)$. We examine the estimator's closed form variance σ^2 in the special case where $T_i \sim \text{Exp}(\lambda)$. This implies that for all k , $\lambda(t_k, u) = \lambda^W(u) = \lambda$. The censoring distribution is $C_i \sim \text{Uniform}[A - A^*, A]$, where A is the length of the study and A^* is the accrual time. A patient recruited at the start of the study would be followed until time A and a patient recruited at the end of the accrual period would be followed until time $A - A^*$. Standard probability calculations for $u, v \in (0, \tau]$ give

We consider $\tau = 1$ year. The parameter λ was chosen to give a constant 1-year RMRL of 11 months, $A^* = 1$ year, $A = 3$ years and $n = 100$. Figure 1 shows the behavior of σ^2/n , the finite sample size variance, for three one-year follow-up windows with $t_1 = 0$, $t_3 = 12$ months and t_2 varying between these values. The one-year windows starting at t_1 and t_3 do not overlap, so the choice of t_2 examines if there is an advantage to adding a 3rd follow-up window that overlaps the other two. The plot suggests that an additional 1-year window starting in the middle of $t_1 = 0$ and $t_3 = 12$ months, i.e. at $t_2 = 6$ months, reduces the variance the most.

Next consider (1) whether additional equally spaced follow-up windows further reduce σ^2/n and (2) the extent to which incorporating an additional year's worth of follow-up information, and corresponding 1-year windows, into construction of $\hat{\mu}^* (\tau)$ reduces its variability. The first entry of Table 1 corresponds to the variance obtained if estimating the standard 1-year restricted mean that doesn't use information from additional follow-up intervals. For a given t_b of 12 or 24 months, increasing the number of follow-up windows

improves the precision of the estimator. However, there are diminishing returns from introducing starting times more frequently than at 6-month intervals.

It seems clear from exploration of this special case that spacing of $t_1, \dots, t_b$ should be at 6month intervals when estimating an overall 1 year restricted mean, with $t_b = 24$. In general, the recommended number of intervals is based on available follow-up time and we propose

using intervals starting from $t_k = (k - 1) \frac{\tau}{2}$ for $k=1, \dots, b$, with t_b less than $A - \tau$.

5 Simulation Study

Simulation experiments were conducted to assess finite sample size performance of $\hat{\mu}^*(\tau)$. We consider whether augmenting the first observation window improved the estimator and the effect of the number of intervals on the performance of the estimator. The performance of our proposed variance estimate is compared to a variance estimate that assumes independence and the sandwich variance (formulae to calculate these are given in Appendix D of Supplementary Materials).

The simulation experiment design assumes we wish to estimate 12-month restricted mean survival in a 36-month study. We assume that 30% of the sample ($n = 100$) were recruited at the start of the study and were observed for the full 36 months. The remaining 70% were uniformly accrued over the first 12 months. T_i was simulated from a piecewise Weibull distribution with parameters chosen so that the 12-month restricted mean survival was 11 months at the recommended follow-up times $t_k \in \{0, 6, 12, 18, 24\}$, $k = 1, \dots, 5$. The hazard function of the piecewise Weibull distribution is given by $\lambda(x) = \alpha_i \lambda_i x^{\alpha_i - 1}$, where the parameters are constant within a 6 month interval. The parameters are defined as $\alpha = (1.1, 0.9, 1.1, 0.9, 1.1, 0.9)$ and $\lambda = (1.25, 2.01, 1.05, 2.00, 1.26, 0.10) \times 10^{-2}$.

Simulation results in Table 2 show that augmenting the data with additional follow-up time improves the precision of the estimator, with ARE ranging from 1.87 to 2.70. The bias is minimal in all cases. As expected, the case with $\{t_1, \dots, t_5\} = \{0, 6, 12, 18, 24\}$ outperforms other scenarios for, $b = 1, 2, 3$. All three variance methods perform well when $\{t_1, \dots, t_b\}$ produced disjoint intervals (rows 1 – 3 of Table 2). With overlapping intervals, the proposed variance gives the best coverage; independent and sandwich variances both underestimate the simulation empirical variance.

6 Examples

In a study by Schmidt et al. (2014), which aimed to provide better prognostic information to idiopathic pulmonary fibrosis (IPF) patients, 734 patients were identified through interstitial lung disease databases from three referral centers, the Royal Brompton and Harefield National Health Service Foundation Trust, National Jewish Health and the University of Michigan Health System, from 1981 through 2008. There is currently no effective treatment for IPF, with patients experiencing a steady average decline in lung function per year. A natural question is whether the expected number of days of life in the next year is also stable.

For each patient, calendar time begins at first pulmonary function test at their referral center within the study period. As recommended, one-year intervals with start times every six months are used. The final interval at 9.5 years, chosen to ensure at least 25 risk set deaths remaining, used follow-up through year 10.5. The RMRL in Figure 2(a) fluctuates between 321 and 350 days with more stability in the first 6 years, where there is more available data. The confidence bands suggest that it is still reasonable to report an overall point estimate that the average number of days of life lived in the next year is 333.6 (95% CI: 330.7-336.4). During the first decade of their disease, IPF patients are expected to live 91% of each year given they were alive at the start of the year.

The Early Treatment Diabetic Retinopathy Study (ETDRS) (ETDRS Research Group (1991a,b)) enrolled patients with severe diabetic retinopathy in both eyes who were taking Aspirin daily. In addition one eye of each patient was randomly assigned to early photocoagulation and the other to deferral of photocoagulation until a later time when high-risk proliferative retinopathy was detected. We focus on the 583 patients who were randomized to the deferred photocoagulation treatment group. The major endpoint of interest was time to severe vision loss, defined as visual acuity less than 5/200 at two consecutive visits.

One-year intervals with start times every six months are used. The final interval at 3.5 years, chosen to ensure at least 25 risk set deaths remaining, used follow-up through year 4.5. The RMRL in Figure 2(b) suggests a slightly declining trend, reflecting somewhat quicker eyesight deterioration over time despite initiation of therapy once patients became especially high risk. Given the narrow width of the confidence bands (< 10 days), one may argue that it is reasonable to report an overall point estimate of average days of sight per year, 362.2 days (95% CI: 361.3-363.1), which falls within the reported confidence bands through the 3.5 year period considered. In this case, it may also be instructive to include the graphic so that future potential trend may be monitored.

7 Discussion

Health economist literature emphasizes the value patients place on short-term versus long-term outcomes. This gives strong motivation for developing better estimates of short-term survival from the patient's point of view. In longitudinal settings, measures taken over time are easy to come by and software estimating average trends over time is widely available. In cases where measures are stable over time, it is common to estimate the average outcome across time as a summary measure. Our method of defining times-to-first event in different follow-up windows over time has a lot in common with these more standard longitudinal data structures, except that (1) our outcomes are subject to censoring and (2) the correlation structure due to potentially overlapping follow-up windows is estimable using counting process notation, without a need for parametric assumptions.

As in longitudinal data analysis, the user has the choice of describing the trend over time (RMRL function, see Section 2.2) or, for stable disease progression with no otherwise discernible time (follow-up window) effect, an overall mean can be given (overall τ -restricted mean survival, see Section 3.1). Our approach changes the way censored survival

data are traditionally organized for analysis, better reflecting short-term experiences of patients throughout follow-up that health economists find more attractive. Currently, if one wants to estimate a short-term τ -restricted mean survival, one traditionally uses only the first τ years of follow-up in estimation, ignoring all subsequent follow-up information. From the longitudinal data structure perspective, this wastes available statistical information that could be put to better use.

The methodology in this manuscript is completely nonparametric and is a reasonable starting point for understanding the newly introduced data structure, practical aspects of follow-up window choice, and efficiency gains when describing overall restricted means for outcomes with stable disease progression. It is our belief that this work can form the basis for developing further methodological tools for hypothesis testing and multivariable models of short-term times-to-event.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors would like to thank our University of Michigan collaborators: Kevin Flaherty, Shelley Schmidt, Meilan Han, Gaelen Toews and Fernando Martinez, for the use of their data. This work was supported in part by National Institute of Health grants NIH/NHLBI RC2 HL101740 and NIH/NHLBI K24 HL111316.

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Figure 1.

Closed form asymptotic variance of $\hat{\mu}^*(\tau)$ for 3 year study with $\tau=1$ year, $t_1 = 0$, $t_3 = 12$ months and varying t_2 . Dashed line corresponds to variance of estimator constructed using two follow-up windows $t_1 = 0$ and $t_3 = 12$.

Figure 2.
One-year restricted mean residual life function (solid) evaluated every six months.
Associated CB are given (dashed).

Table 1

Study of follow-up window choices based on calculated variance and Asymptotic Relative Efficiency (ARE) for the special case discussed in Section 4.

	Number of Windows	$\{t_1, \dots, t_b\}$	σ^2/n	ARE
$t_b = 0$	1	0	0.071	1.00
	2	0, 12	0.039	1.82
$t_b = 12$	3	0, 6, 12	0.035	2.03
	5	0, 3, 6, 9, 12	0.035	2.03
$t_b = 24$	3	0, 12, 24	0.030	2.37
	5	0, 6, 12, 18, 24	0.026	2.73
	9	0, 3, 6, 9, 12, 15, 18, 21, 24	0.025	2.84

Table 2

Study of follow-up windows and performance of variance estimators in 500 Monte Carlo simulations ($n = 100$) from a Piecewise Weibull Distribution

$\{t_1, \dots, t_b\}$	Est	Emp Var	Independent Variance		Sandwich Variance		Proposed Variance	
			Est	Coverage 95% CI	Est	Coverage 95% CI	Est	Coverage 95% CI
0	10.986	0.073	0.070	0.938	0.069	0.938	0.070	0.938
0, 12	10.993	0.039	0.039	0.938	0.039	0.934	0.039	0.940
0, 12, 24	10.975	0.030	0.031	0.954	0.031	0.952	0.031	0.952
0, 6, 12, 18, 24	10.980	0.027	0.018	0.878	0.021	0.902	0.028	0.948