Utility of Restricted Mean Survival Time in Oncology Clinical Trials

An Incomplete, Gentle Review of Current Developments and Methods

Chen Hu

Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins
Baltimore, MD, USA
NRG Oncology Statistics & Data Management Center
Philadelphia, PA, USA

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Treatment Effect on Survival

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EDITOR'S CHOICE

Understanding and Communicating Measures of Treatment Effect on Survival: Can We Do Better?

FREE

Everardo D Saad ✉, John R Zalcberg, Julien Péron, Elisabeth Coart, Tomasz Burzykowski, Marc Buyse

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Original Investigation

The Net Chance of a Longer Survival as a Patient-Oriented Measure of Treatment Benefit in Randomized Clinical Trials

Julien Péron, MD, PhD; Pascal Roy, MD, PhD; Brice Ozenne, PhD; Laurent Roche, PhD; Marc Buyse, ScD

Invited Commentary

Describing Differences in Survival Curves

Rick Chappell, PhD; Xiaotian Zhu, PhD

JAMA Oncology July 2016 Volume 2, Number 7

Acknowledgment

- Lee-Jen Wei
  - Hajime Uno
  - Lu Tian
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  - Lihui Zhao
- Rick Chappell
- Jim Dignam
- Ted Karrison
- Chiung-Yu Huang
- Yifei Sun
- Ravi Varadhan

Why is the Cox model so popular

- Traditionally, we use hazard ratio as a measurement of between treatment difference for event driven studies
  - and logrank test for hypothesis testing
- It is semi-parametric
- Allow time-dependent covariate (internal and external)
- Justification for the large sample theory
- Efficiency of the hazard ratio estimate
- Commercial software available
- No other alternatives to catch the profile of the difference between two groups over time

Cox model for association

- Define hazard (risk) level as a dependent variable which is being explained by the time-related component (so called baseline hazard) and covariates-related component
- Exploring the association between a covariate (independent variable) and survival time
- Like other regression models, it is an approximation to the true model
- It is difficult to validate an association?
- Model is based on several restrictive assumptions which need to be carefully verified before interpretation of parameters estimates
    - One assumption of proportional hazard which results directly from the model formula and means that hazard ratio needs to be constant over time

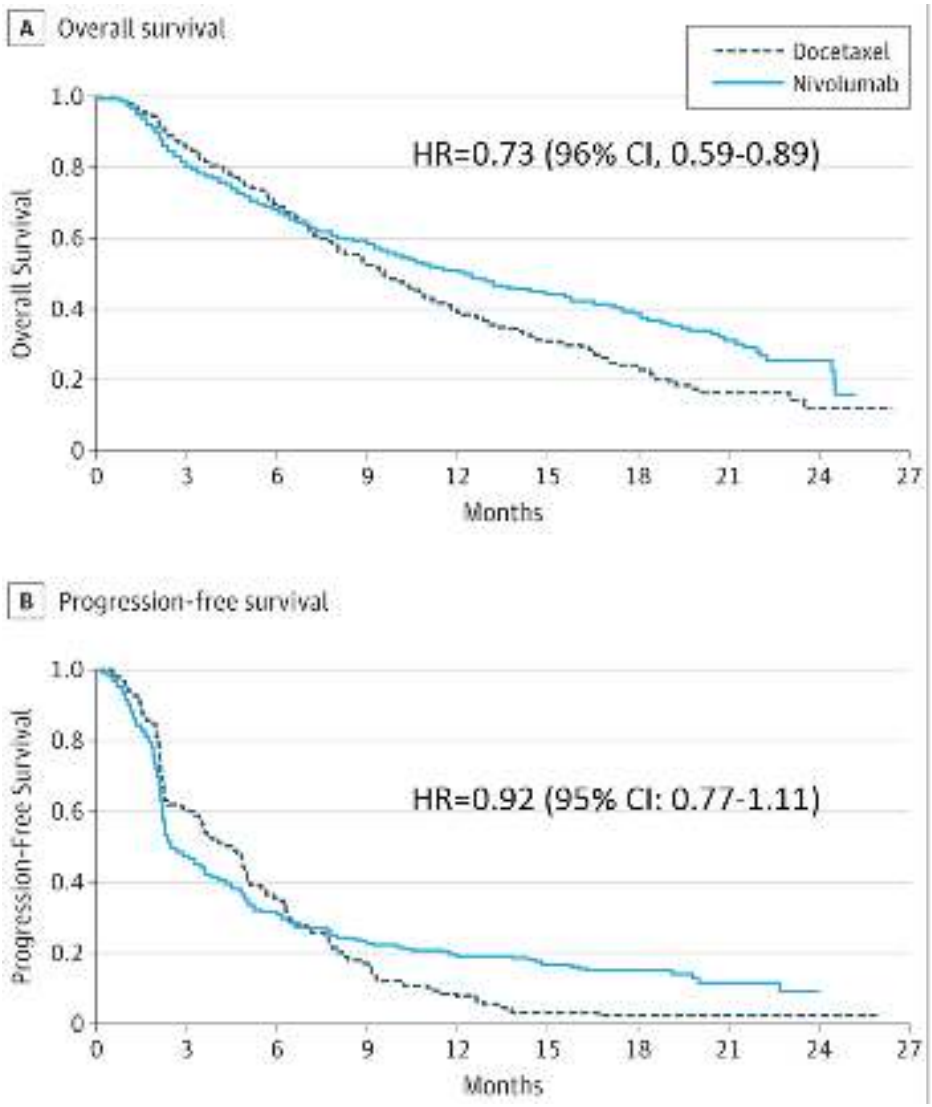
Different Measures of Treatment Effect

Table 1. Advantages and disadvantages of different measures of treatment effect

Measure	Advantages	Disadvantages
Hazard ratio	Almost always reported Clear interpretation Takes entire survival curve into account	Not practical for patient communication Difficult to interpret for nonproportional hazards
Difference between survival probabilities at different time points (t)	Easy to read off survival curves	Depends on choice(s) of t Loses information
Difference between medians	Easy to read off survival curves Easy to remember	Not directly patient-relevant Not always reached Affected by schedule of assessment for end points other than overall survival Loses information Statistically unstable
Difference between restricted means	Takes entire survival curve (until chosen time t) into account Does not depend on proportional hazards assumption Intuitive interpretation as difference between areas under the survival curves	Almost never reported Difficult interpretation if survival curves are far from 0 at the largest follow-up time t Potential for misunderstanding the key role of truncation time in its computation
Difference between unrestricted means	Easy to remember Takes entire survival curve into account Does not depend on proportional hazards assumption Intuitive interpretation	Almost never reported Estimation requires a parametric distribution assumption if survival curves do not reach 0 Imprecise estimation if data are not mature (survival curves far from 0 at the largest follow-up time t)
Net benefit	Can be readily interpreted as a net probability of benefit Can express benefit in terms of absolute gains in survival time Takes entire survival curve into account Does not depend on proportional hazards assumption Prioritizes the more relevant component of a composite end point	Recently proposed, hence little experience
Ratio of restricted means	Takes entire survival curve (until chosen t) into account Valid even when hazards are nonproportional	Almost never reported Doubtful interpretation if survival curves are far from 0 at time t
Win ratio	Takes entire curve into account Does not depend on proportional hazards assumption Prioritizes the more relevant component of a composite end point	Interpretation not straightforward Recently proposed, hence little experience

Understanding and Communicating Measures of Treatment Effect on Survival: Can We Do Better? (Saad et al. (2018))

Examples when PH fails: CheckMate 057



Nivolumab versus Docetaxel in Advanced Nonsquamous NonSmall-Cell Lung Cancer (Borghaei et al. (2015))

Challenges (and Issues) of Cox Model

- Interpretation
  - Critique: why methodological convenience should dictate the nature of scientific question
  - HR is NOT a simple average of the hazard ratio over time
  - HR depends on underlying study-specific censoring distributions (or follow-up time)
- Model Inconsistency
  - When the PH is correct in each subgroup, the PH does NOT hold in the pooled sample except some special cases
  - When the PH is correct the pooled sample, the PH does not hold in all subgroups except some special cases
  - Adjusted and unadjusted analyses are estimating different quantities each other

Challenges (and Issues) of Cox Model, cont.

- Challenges in non-inferiority trials
  - The scale of null hypothesis is especially important
    - for example, consider HR=1.3 as a "tolerable" margin?
    - If the event rates are low $\rightarrow$ HR=1.3 may be clinically meaningless from the absolute risk interpretation
    - If the event rates are high $\rightarrow$ we may need a NI margin of 1.1?
  - The usual null of "no effect" for superiority trials is invariant to scale
- Causality
  - While log-rank test is asymptotically consistent, the corresponding estimated HR cannot be considered as a casual estimate
  - Likelihood contributions beyond the first are conditioned on survival past larger and larger times (Aalen et al. (2015))

Restricted Mean Survival Time

- Area under the survival curve before (restricted to) a landmark time τ.
- Originally proposed by Irwin in 1948 but recently publicized by Uno et al. (2014).
- Interpreted as the mean of the minimum of the event and landmark times, or the mean life before the landmark.
  - Let $S(t)$ be the survival function for a random variable $T > 0$

$$\mu_\tau = \int_0^\tau S(t)dt = E[\min(T, \tau)]$$

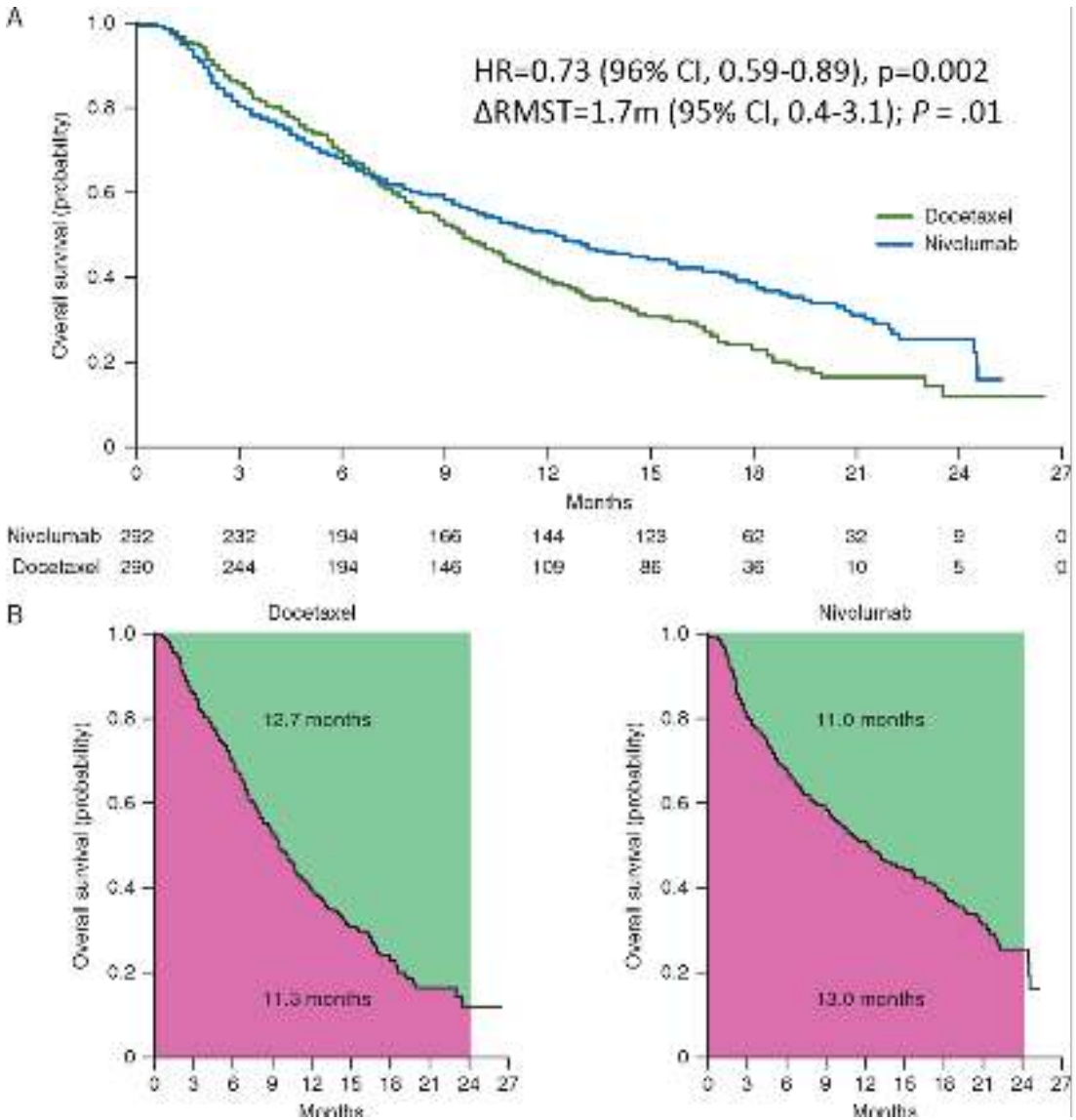
- Not the mean conditional on event occurring before that time.
  - E.g., the mean life of children in developed countries restricted to 5 years is nearly 5.
  - Life expectancy conditional on death before 5 is close to 0.

Treatment Effect based on RMST

- Difference: $\mu_{\tau,1} - \mu_{\tau,2}$
- Ratio: $\mu_{\tau,1}/\mu_{\tau,2}$
- Proportion of potential life years achieved: $\mu_{\tau,1}/\tau$
- Restricted mean time lost (RMTL),i.e.,RMTL $= \tau -$ RMST
  - Difference of RMTL
  - Ratio of RMTL
    - When the event rate is low and the event time distribution is exponential, the ratio of RMTL will be close to the HR

$$\frac{\int_0^\tau 1 - \exp^{-\lambda_1 t}\, dt}{\int_0^\tau 1 - \exp^{-\lambda_2 t}\, dt} \approx \frac{\int_0^\tau \lambda_1 t dt}{\int_0^\tau \lambda_2 t dt} = \frac{\lambda_1}{\lambda_2}$$

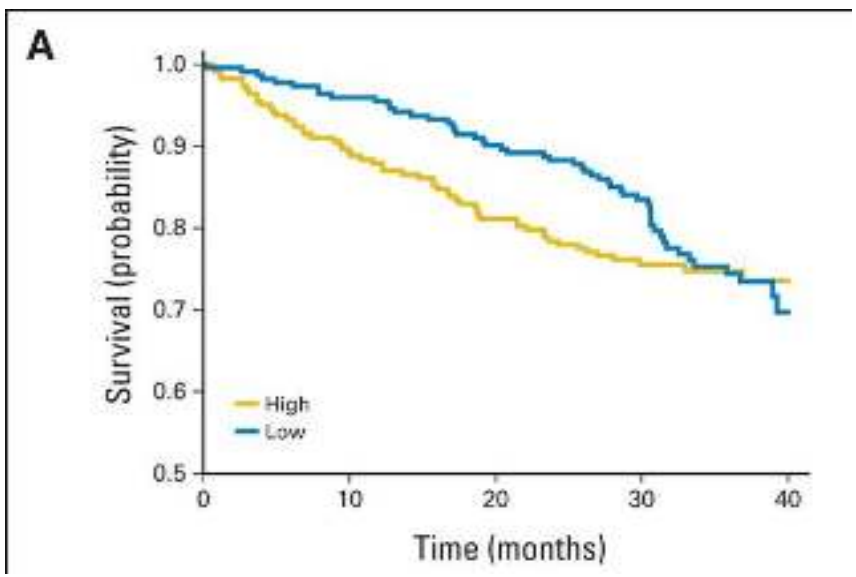
CheckMate 057 Revisit

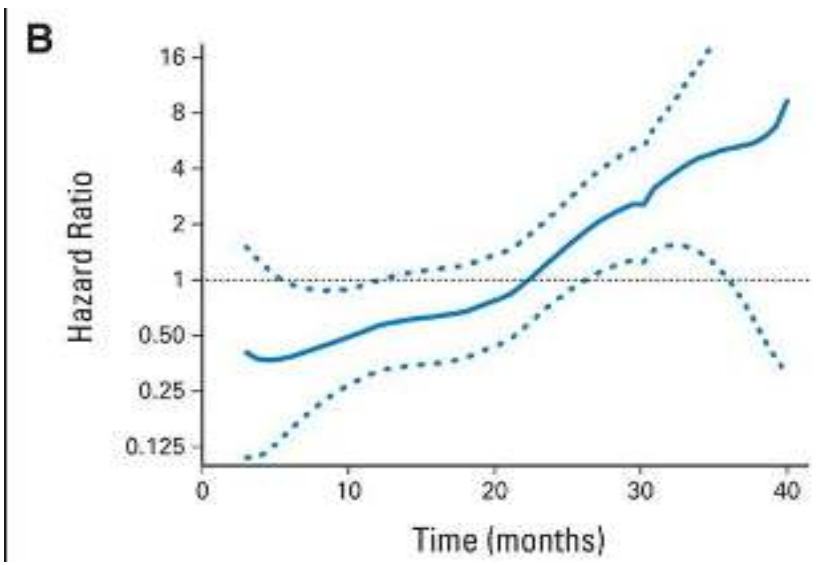


Pak et al. (2017)

Example 2: ECOG E4A03 Trial

- E4A03 trial to compare low- and high-dose dexamethasone for patients with newly diagnosed multiple myeloma
- One of the endpoints is overall survival, n = 445.
- The trial stopped early at the second interim analysis; the low dose was superior.





Uno et al. (2014)

ECOG E4A03 Trial: Result Summary

- Cox PH analysis
  - The proportional hazards assumption is not valid.
  - The PH estimator is estimating a quantity which cannot be interpreted and, worse, depends on the study-specific censoring distributions.
  - The logrank test is not powerful.
  - In conventional analysis, we have log-rank test: p = 0.47 and hazard ratio: HR=0.87 (0.60, 1.27).
- RMST analysis
  - Restricted mean (up to 40 months).
  - 35.4 months vs. 33.3 months.
  - Difference = 2.1 (0.1, 4.2) months; p = 0.04.
  - Ratio of RMST = 35.4/33.3 = 1.06 (1.00, 1.13).
  - Ratio of RMTL = 6.7/4.6 = 1.46 (1.02, 2.13).

Nonparametric Estimation and Inference of RMST

- Notations
  - T_i: failure time; C_i: (independent) censoring time
  - $Y_i = T_i \wedge C_i, \Delta_i = I(T_i \leq C_i)$
  - (Y_i, Δ_i, X_i): observed data
  - $Y_i^\tau = Y_i \wedge \tau$, $\Delta_i^\tau = I(T_i \wedge \tau \leq C_i)$
  - $(Y_i^\tau, \Delta_i^\tau, X_i)$: derived data based on τ
- KM-based estimator, where $\hat{S}$ is a KM estimator of T

$$\tilde{\mu}_\tau = \int_0^\tau \hat{S}(t)dt$$

- Inference: Based on the martingale approach (Andersen et al. (2012)), we have a variance estimator of $\tilde{\mu}_\tau$

$$\hat{V}(\tilde{\mu}_\tau) = \sum_{i=1}^{D} \left\{ \int_{t_i}^\tau \hat{S}(t)dt \right\} \frac{d_i}{R(t_i)[R(t_i) - d_i]}$$

where d_i and $R(t_i)$ is the number of events and risk set at t_i, for $t_1 < t_2 < \cdots < t_D$

Nonparametric Estimation and Inference of RMST,cont.

- Inverse probability censoring weighting (IPCW) approach

$$\hat{\mu}_\tau = n^{-1} \sum_{i=1}^{n} \frac{\Delta_i^\tau}{\hat{G}(Y_i^\tau)} Y_i^\tau$$

  where $\hat{G}(\cdot)$ is the KM estimator of censoring time C
- Based on results from Satten and Datta (2001), we also have

$$\hat{S}(t) = n^{-1} \sum_{i=1}^{n} \frac{I(Y_i > t)\Delta_i^\tau}{\hat{G}(Y_i^\tau)} + O_p(n^{-1/2})$$

  with some algebra, we can show $\hat{\mu_\tau} - \tilde{\mu}_\tau = O_p(n^{-1/2})$, e.g., $\hat{\mu_\tau}$ and $\tilde{\mu}_\tau$ are asymptotically equivalent at $n^{-1/2}$ rate.
- Provide a natural connection for building an ANCOVA-type regression model (Tian et al. (2014))

Two-sample Testing

- Logrank test
  - Robust
  - The most powerful under PH alternatives
  - Various weighted versions exist
- RMST-based testing
  - Convert the estimated treatment effect into a coherent test, e.g.,Uno et al. (2015),Tian et al. (2018)
  - Power *depends* on the pattern of difference, τ, etc.,
  - For a fixed τ, should *NOT* assume it will be better than log-rank test even under non-PH
    - if KM curves separate early $\rightarrow$ likely more powerful
    - if KM curves separate late $\rightarrow$ possibly less powerful

Non-Inferiority Design Example: SAVOR-TIMI 53 trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus

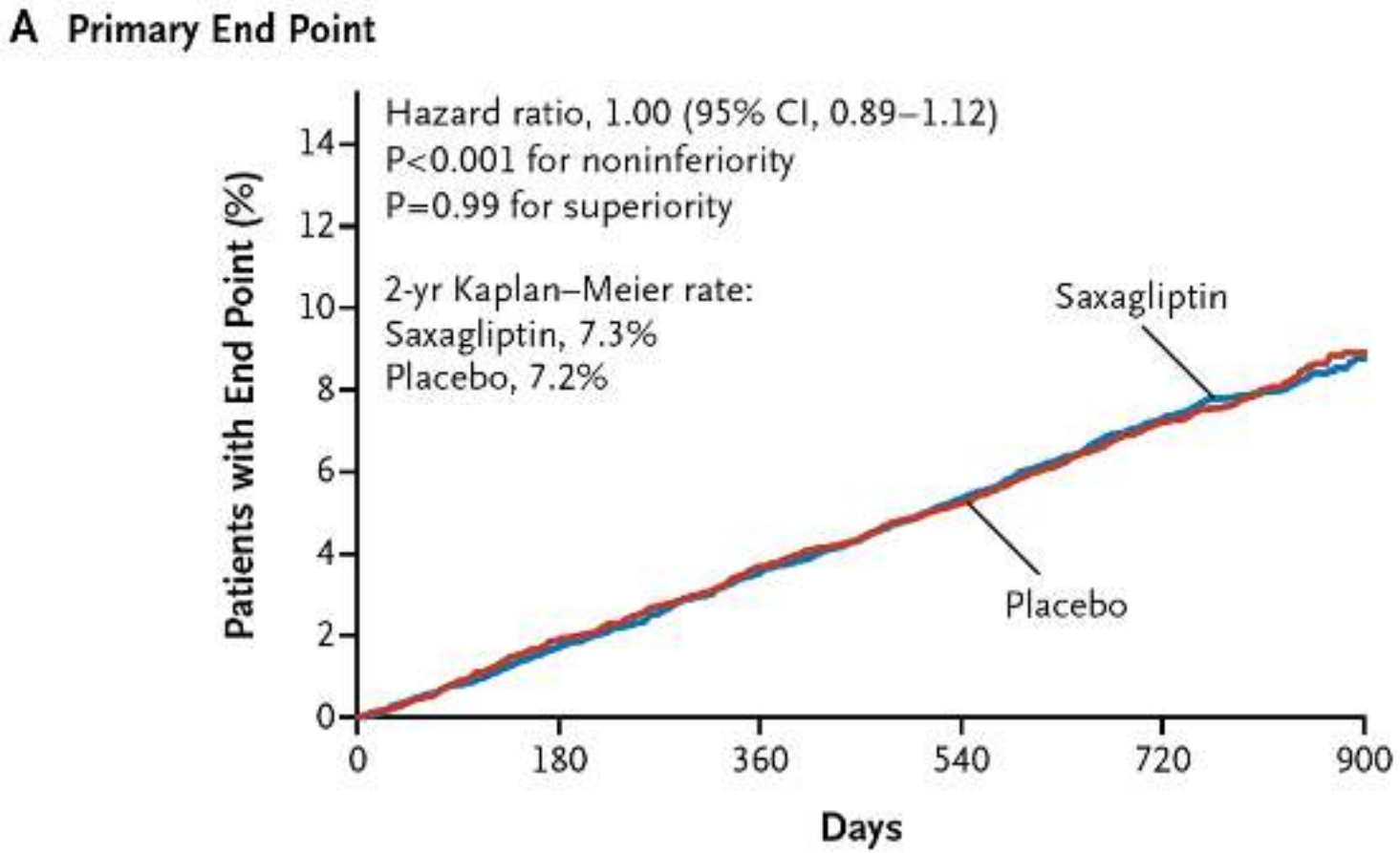
Benjamin M. Scirica, M.D., M.P.H., Deepak L. Bhatt, M.D., M.P.H., Eugene Braunwald, M.D., P. Gabriel Steg, M.D., Jaime Davidson, M.D., Boaz Hirshberg, M.D., Peter Ohman, M.D., Robert Frederich, M.D., Ph.D., Stephen D. Wiviott, M.D., Elaine B. Hoffman, Ph.D., Matthew A. Cavender, M.D., M.P.H., Jacob A. Udell, M.D., M.P.H., Nihar R. Desai, M.D., M.P.H., Ofri Mosenzon, M.D., Darren K. McGuire, M.D., Kausik K. Ray, M.D., Lawrence A. Leiter, M.D., and Itamar Raz, M.D., for the SAVOR-TIMI 53 Steering Committee and Investigators*

Scirica et al. (2013)

SAVOR-TIMI 53 (saxagliptin vs. placebo)

- Primary endpoint: time to CV death, nonfatal MI, or nonfatal ischemic stroke
- 1040 primary events needed to show superiority (efficacy)
- 457 primary events needed to show non-inferiority
  - upper bound of HR$<$1.3, for safety
  - no matter what the underlying event rates are
- A total of 16,492 patients were enrolled
- Median follow-up time: 2.1 years
- Observed events: 613 (Saxagliptin) vs. 609 (Placebo)

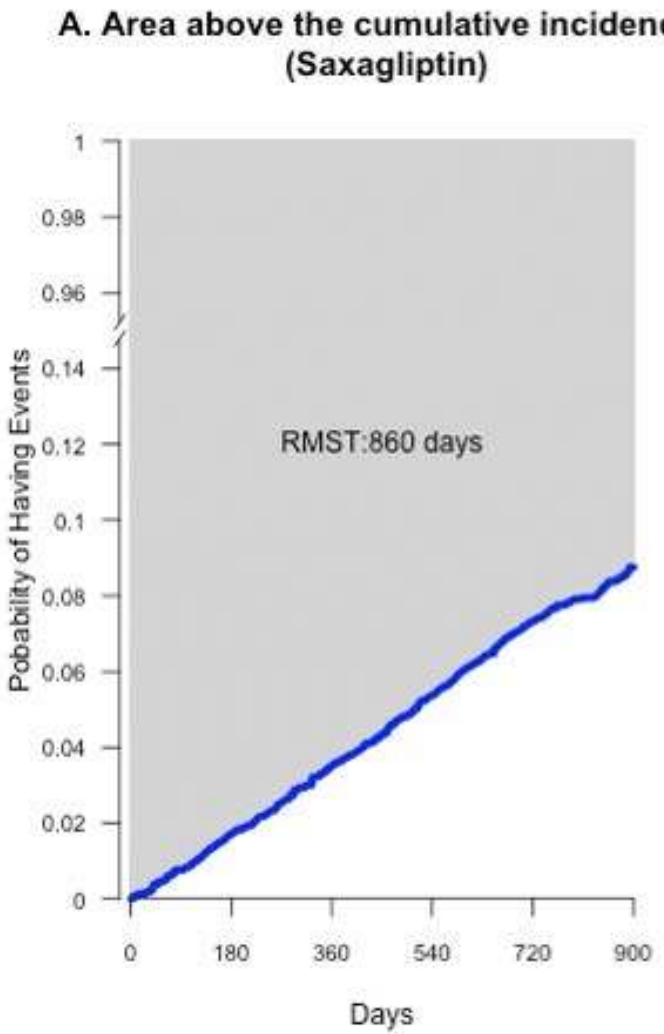
SAVOR-TIMI 53 trial: Primary Endpoint

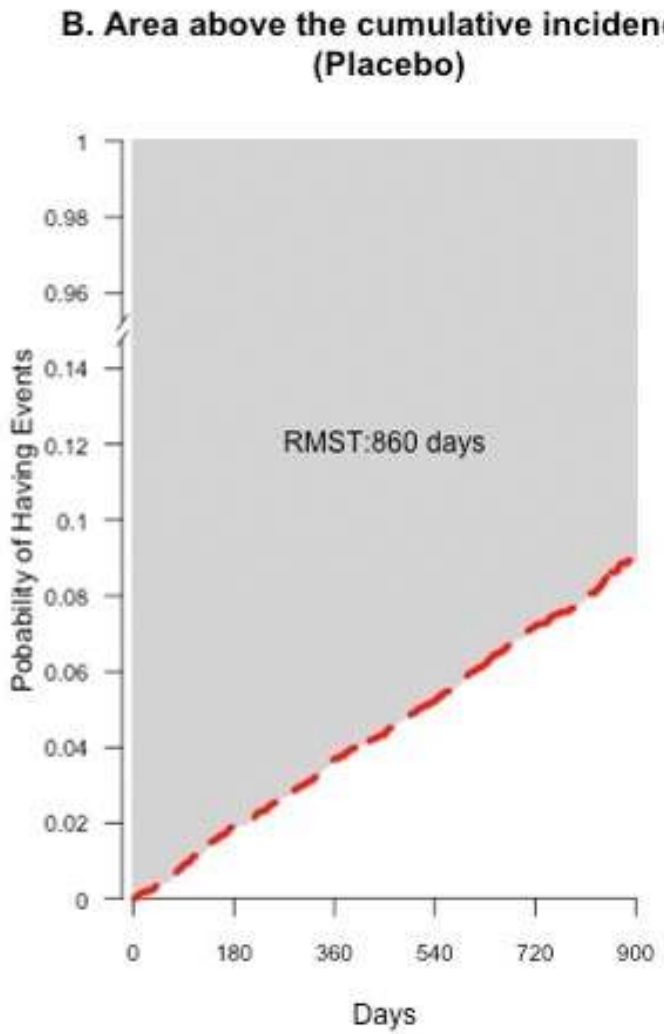


No. at Risk						
Placebo	8212	7983	7761	7267	4855	851
Saxagliptin	8280	8071	7836	7313	4920	847

Uno et al. (2015)

SAVOR-TIMI 53 trial: RMST





SAVOR-TIMI 53 trial: Impacts to Sample Size

- Three methods comapred
  - Hazard Ratio (HR)
  - Difference in event rate at Day 900 ($\Delta\hat{S}(900)$)
  - Difference in RMST at Day 900 ($\Delta\hat{\mu}(900)$)

	Estimate	All Data	25%	20%	15%
		N=16,492	N=4123	N=3298	N=2427
HR	1.00	(0.89, 1.12)	(0.80, 1.26)	(0.78, 1.28)	(0.76,1.36)
$\Delta\hat{S}(900)$	0%	(-1.2,0.9)	(-2.3,2.0)	(-2.6,2.2)	(-2.9,2.6)
$\Delta\hat{\mu}(900)$	0 day	(-5,4)	(-9,9)	(-11,10)	(-12,12)

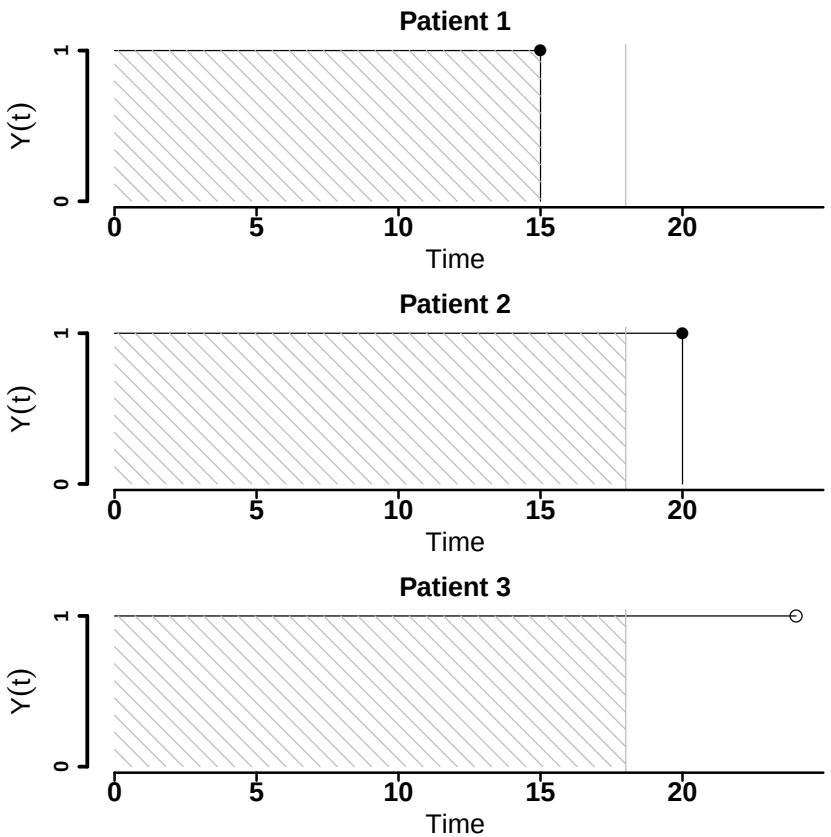
Uno et al. (2015)

Design NI or Safety Trial with RMST

- The standard approach using HR requires a practically infeasible size of a safety study when the event rate is very low (e.g., annual event rate 1% - 1.5%)
- Difference of RMST provides a CI tight enough to make a decision about safety of the new therapy with much smaller study
- The clinical interpretation is crucial for a safety or superiority study

Construction of RMST

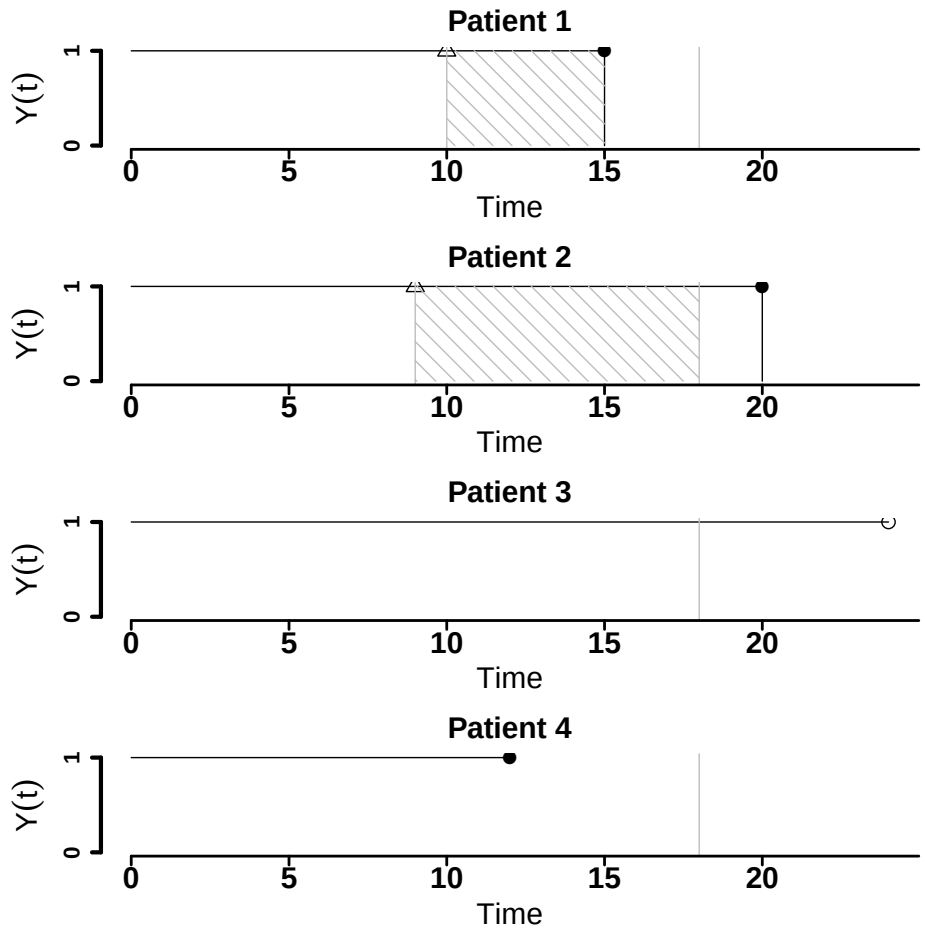
- Restricted Mean Survival Time (RMST), for $0 \leq t \leq \tau$
  - $m(t) = E\{\min(D, t)\} = \int_0^t S_D(u)du$
  - $m(t) = E\{\int_0^t I(D \geq u)du\}$
  - $\int_0^t I(D \geq u)du$: cumulative at-risk process, e.g., area under at-risk process



Analysis of Duration of Response (DOR)

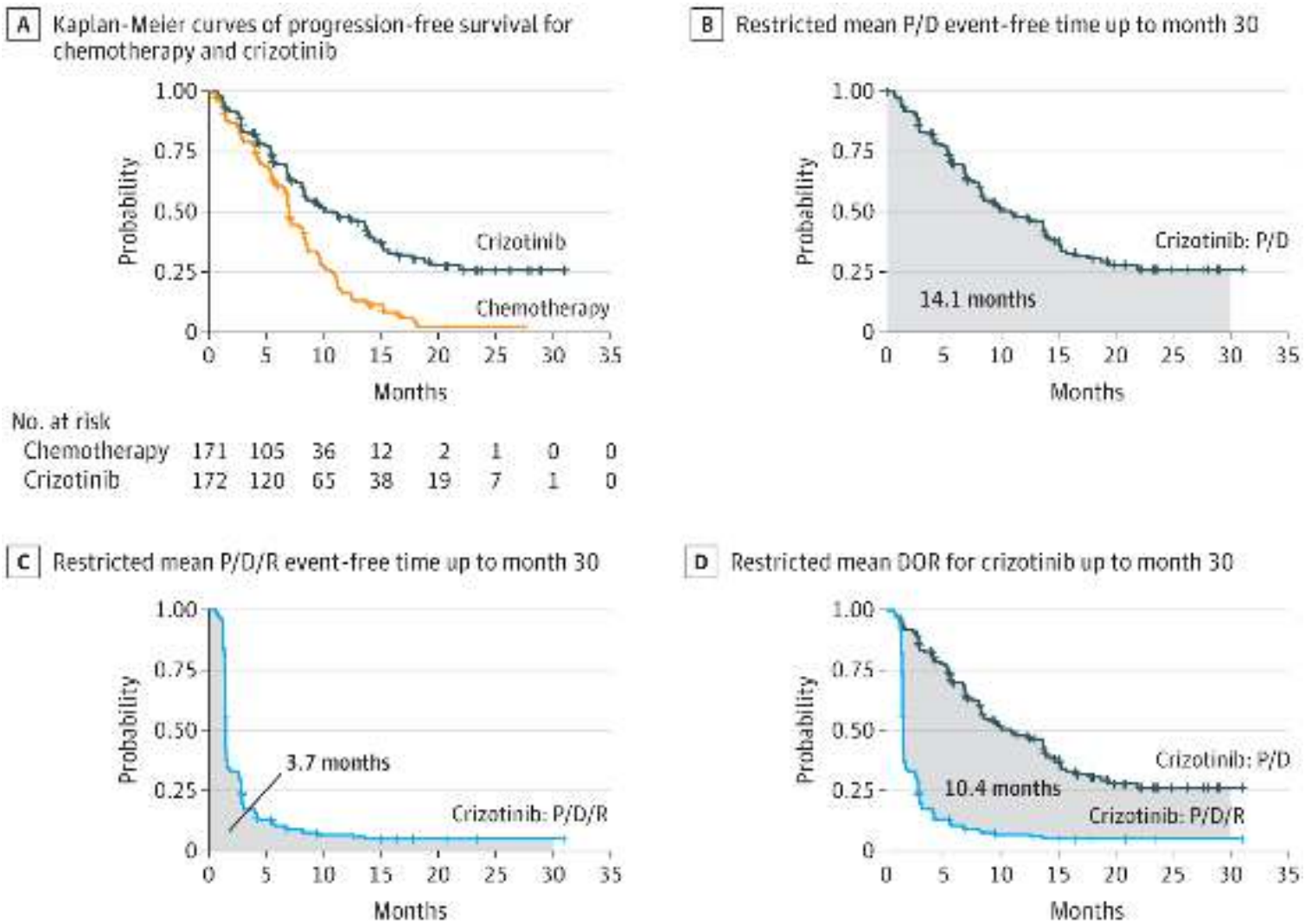
- Duration of response: time from response (R) to progression/death (P/D)
- Clinically meaning, yet challenging to summarize due to its post-randomization nature
- Kaplan-Meier is often used for descriptive summary
- Huang et al. (2018) reported the marginal RMST of DOR

Analysis of Duration of Response (DOR),cont.



- $\mu_{\tau,R}$: RMST for $\min(R, P, D)$
- $\mu_{\tau,PD}$: RMST for $\min(P, D)$
- $\mu_{\tau,DOR} = \mu_{\tau,PD} - \mu_{\tau,R}$

Analysis of Duration of Response (DOR), cont.



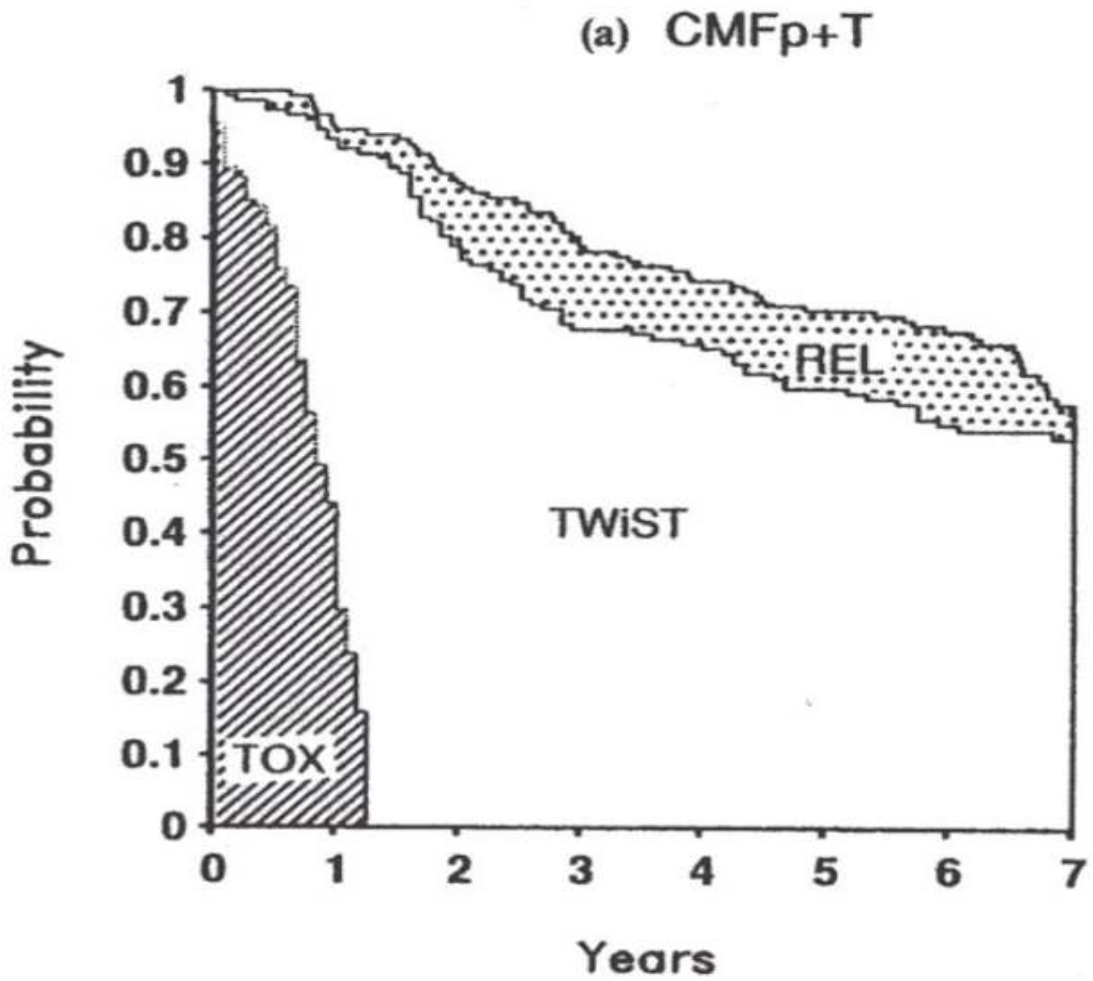
- $\Delta\mu(30)$=7.4 months (95% CI, 6.0-8.8 months; P $<$ .001).

Huang et al. (2018)

Survival Partition for Quality-Adjusted Survival

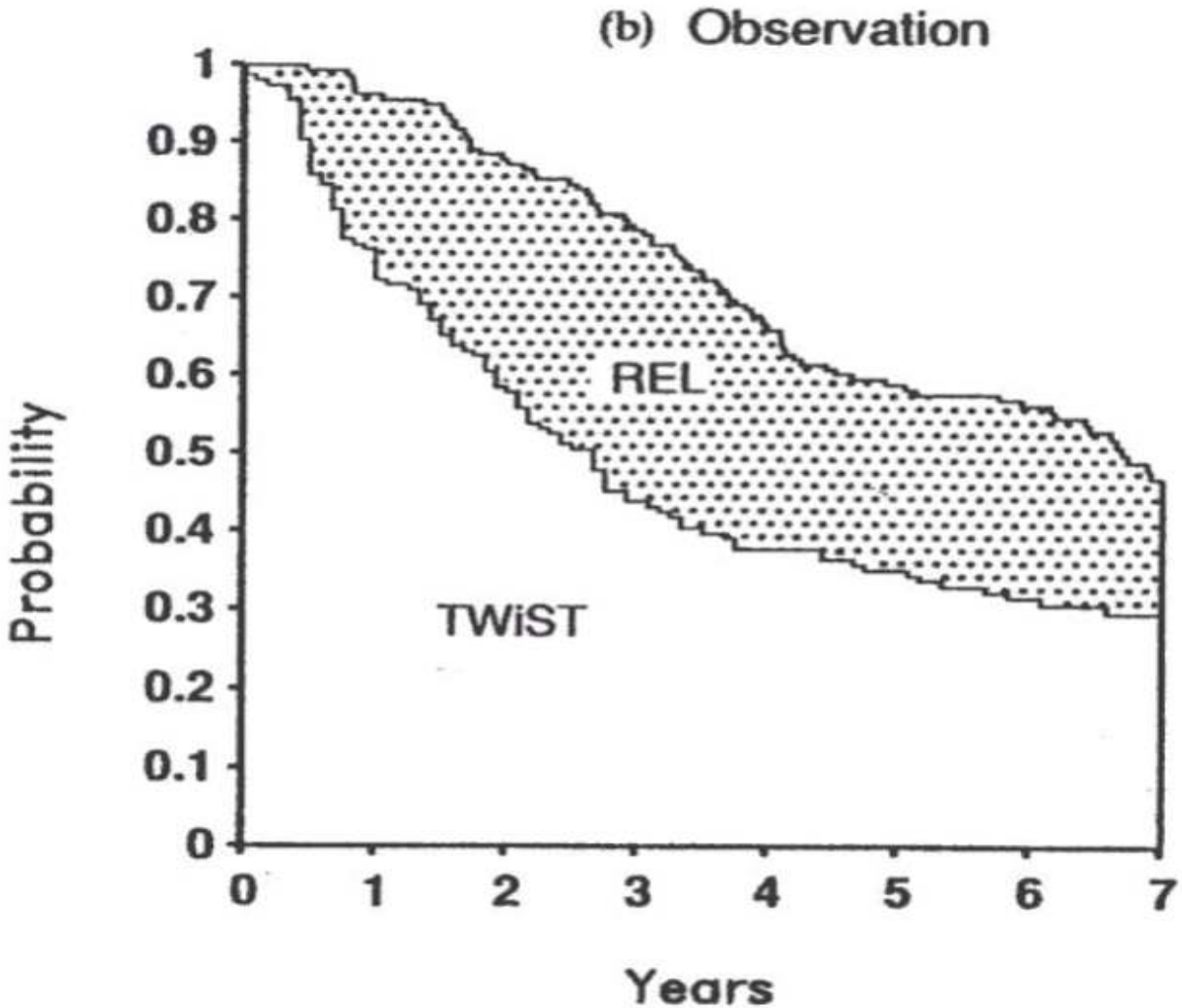
- Glasziou et al. (1990) analyzed the Ludwig III randomized clinical trial of adjuvant Pt-based chemotherapy vs. observation in nodal-invasive breast cancer using restricted mean life.
- The landmark time reflected patient followup: 7 years.
- Survival states: Toxicity, Health (Time Without Symptoms and Toxicity, TWiST), Relapse, Death.

Survival Partition for Quality-Adjusted Survival, cont.



Glasziou et al. (1990)

Survival Partition for Quality-Adjusted Survival, cont.

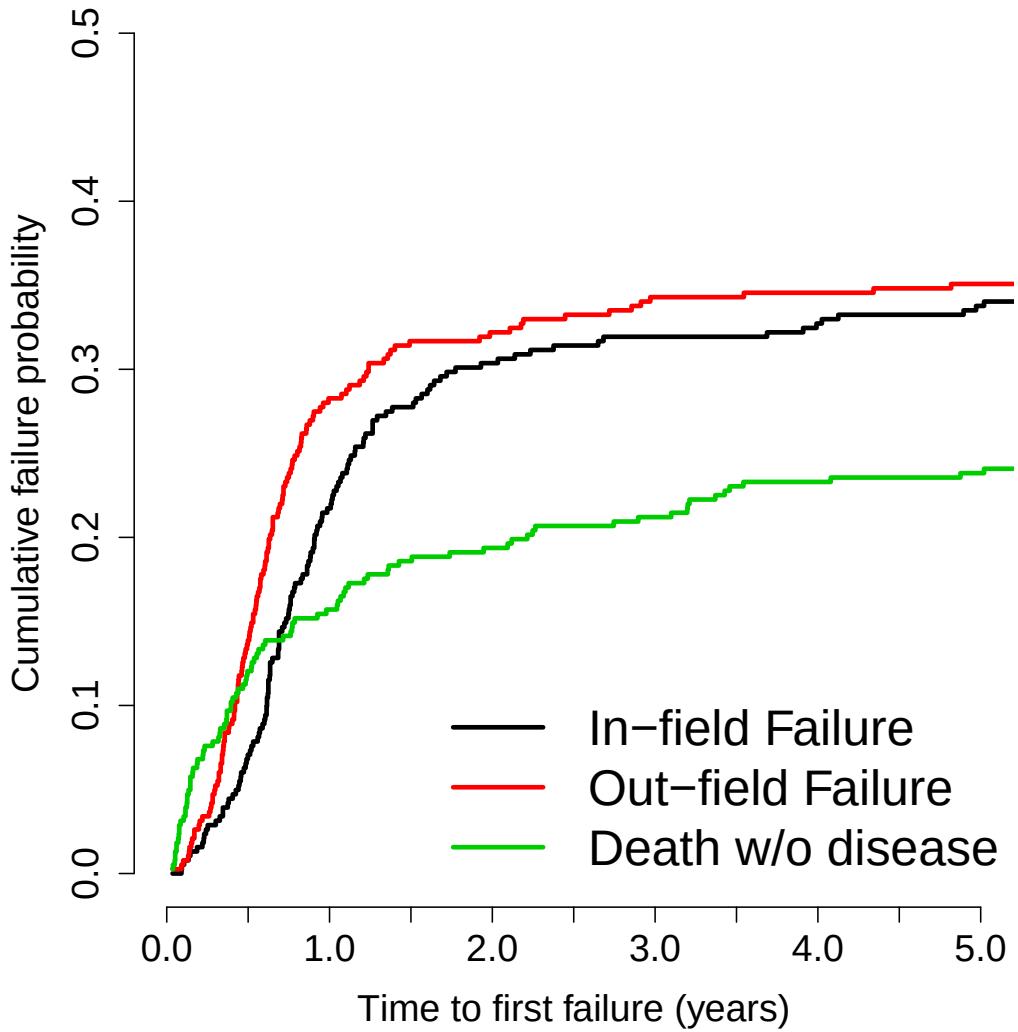


Glasziou et al. (1990)

Restricted Mean Time Loss (RMTL): Competing Risks

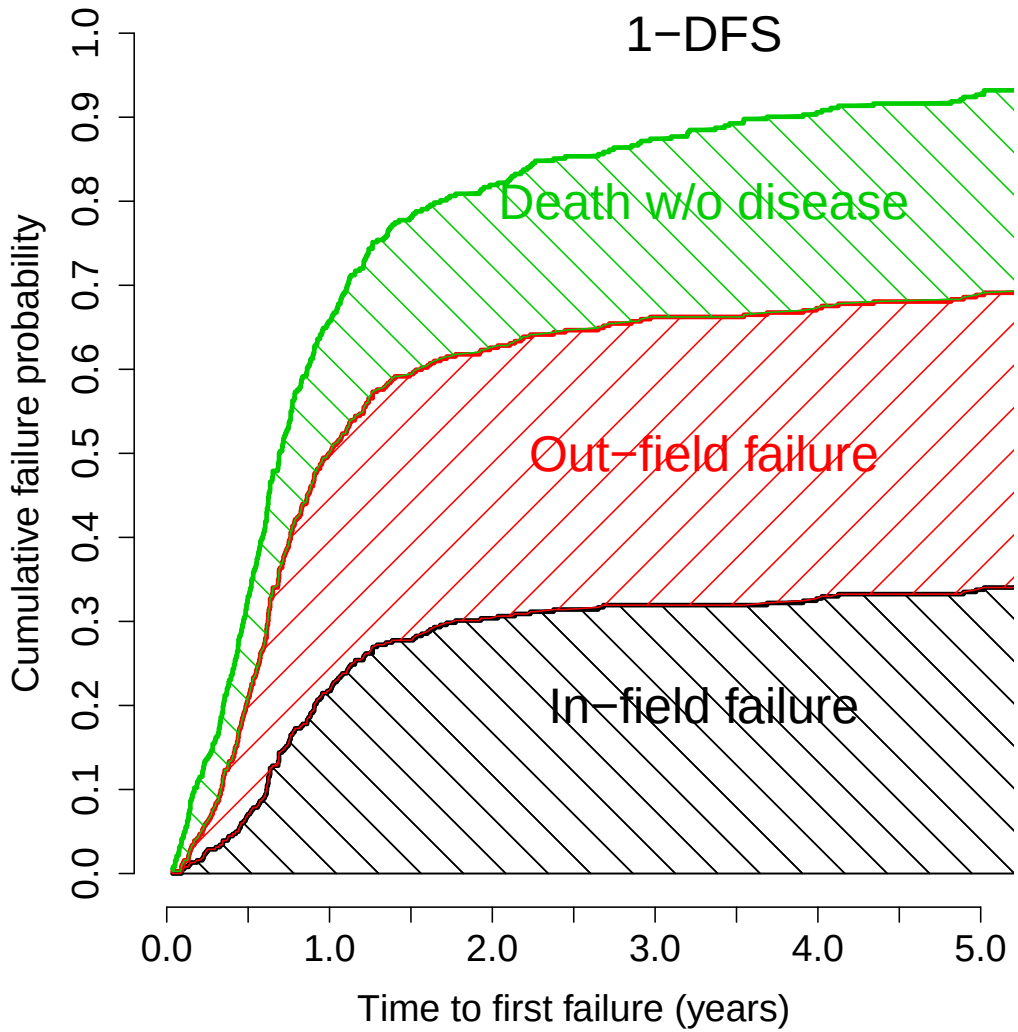
- Competing risks are often of interest when localized therapy, e.g., surgery or radiotherapy is under investigation
- Failure time T^*
- Mutually exclusive event types $D^* \in \{1, \cdots, K\}$:
  takes the value k if it is a type k failure $(k = 1, \cdots, K)$
- Right censoring time C
- Observed data $T = \min(T^*, C), \delta = I(T^* < C), D = I(\delta = 1)D^*$
- For example, in lung cancer trial
  - T: time to first failure (subject to censoring)
  - δ: event indicator, 1 =event, 0 =censoring
  - $D = 1$: in-field failure;
    $D = 2$ out-field failure;
    $D = 3$ death without cancer recurrence

Cumulative Incidence Function (CIF)



- Area under CIF is Restricted Mean Time Loss (RMTL) to the specific failure cause

Cumulative Incidence Functions and Event-free Survival

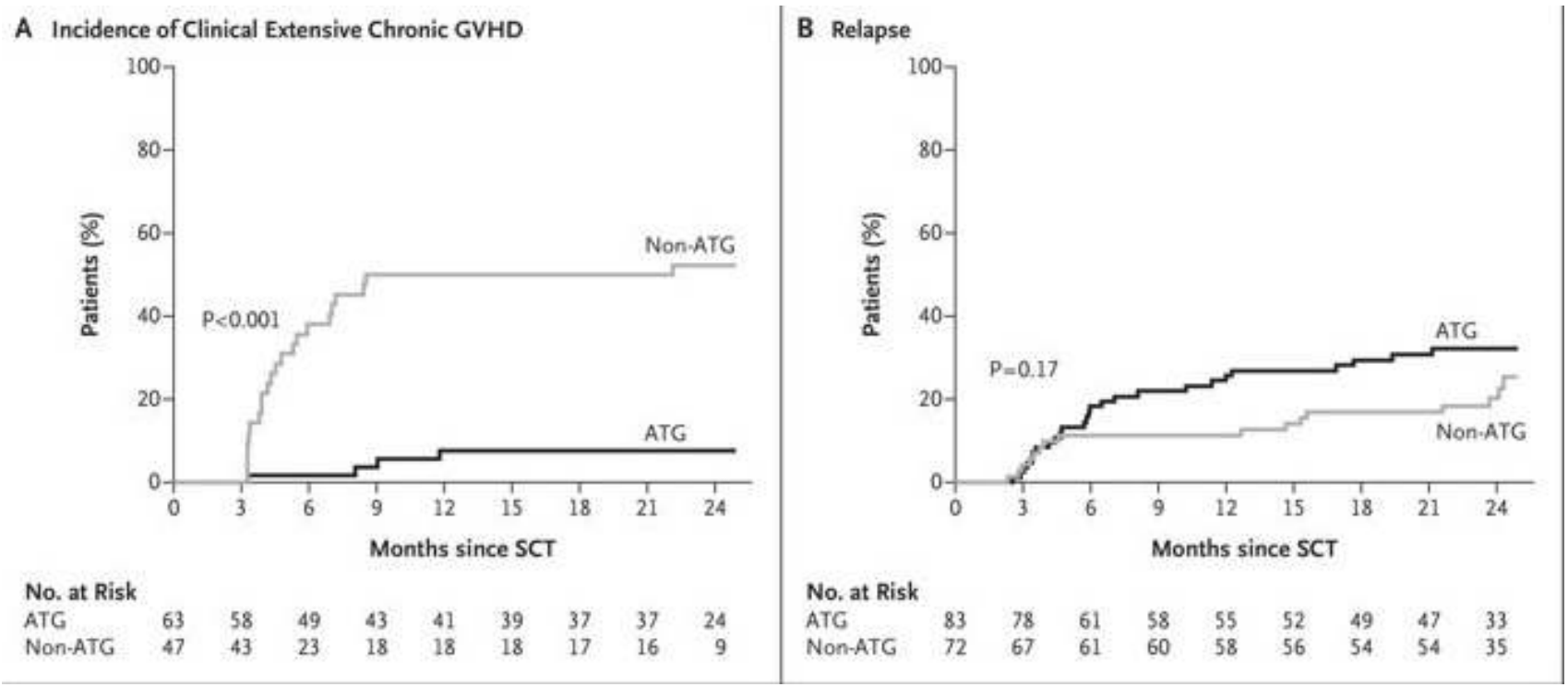


- Zhao et al. (2018) argued analysis using RMTL should be included when reporting competing risks

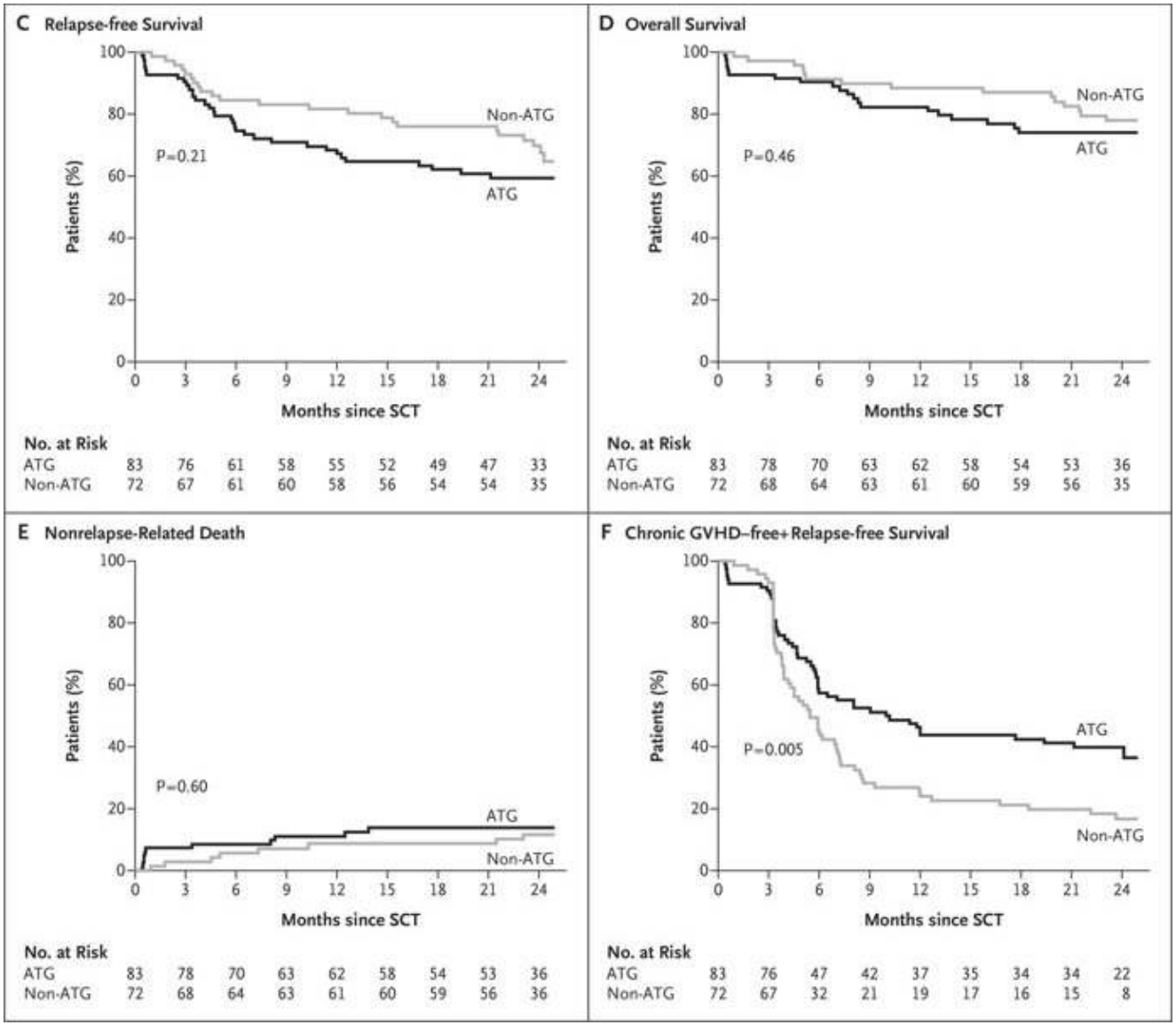
Benefit Risk Assessment

- Treatment effects on different endpoints may point to different directions, creating challenges and difficulties to clinicians
- Allogeneic bone marrow transplantation (BMT) is widely used to re-establish the damaged hematopoietic function in treating acute and chronic leukemia and other hematological malignancies
- Multiple types of events can occur in Post-BMT
  - Relapse
  - Graft-versus-host disease (GVHD)
  - Death
- Evaluating different treatment options is challenging, especially when treatment can have heterogeneous effects or even qualitatively differing impacts on different events

Example in BMT: ATG Trial



Other Results from ATG Trial



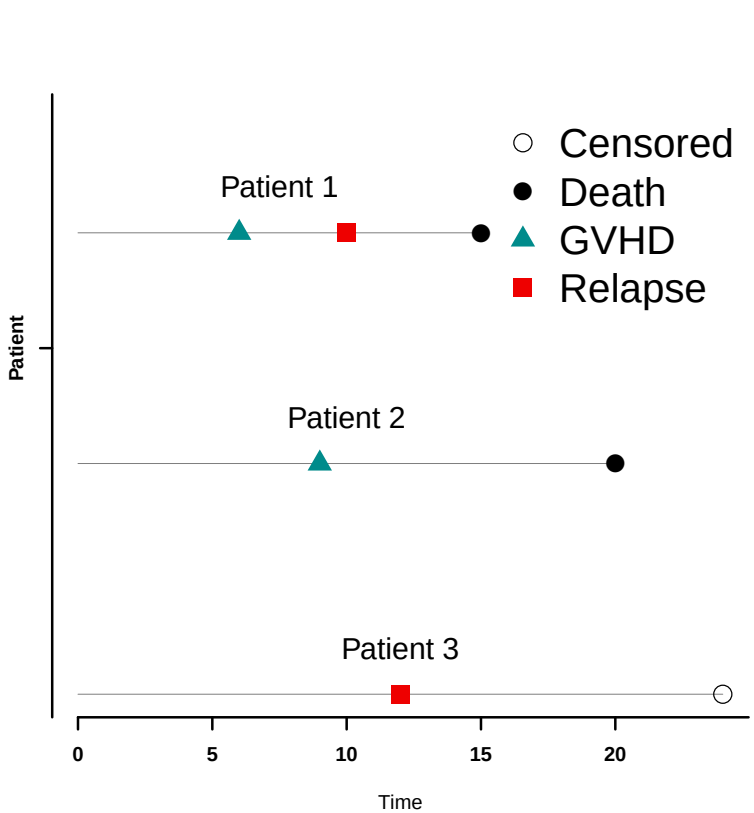
Interpretations of ATG Trial

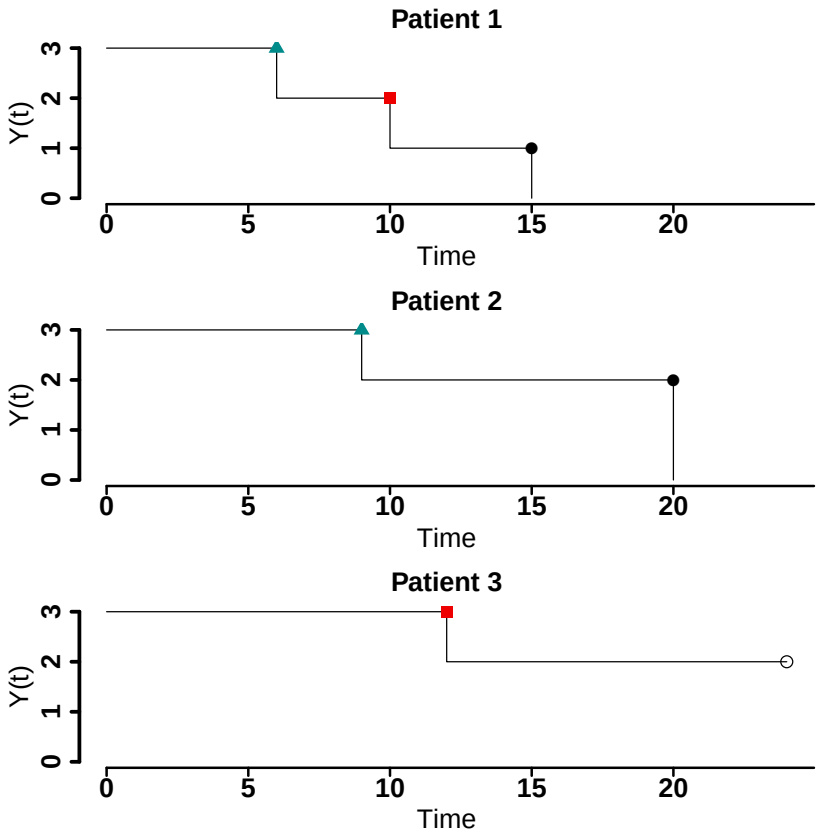
- ATG substantially decreased incidence of chronic GVHD (panel A)
- ATG also increased the incidence of relapse (panel B)?
- RFS (panel C) and OS (panel D) are slightly better for non-ATG?
- Confusions remain among clinicians

Reverse Counting Process

- Proposed by Prof. L.J. Wei (Claggett et al. (2018))
- D: time to terminal event
- $Y(t) = \sum_{k=1}^{K} I(T_k \geq t) + I(D \geq t)$, reverse counting process with K distinct morbidity events
  - T_i time to morbidity i, such as GVHD or relapse
  - reflects individual's disease burden and health condition over time
  - $Y(\cdot)$ after D is not defined

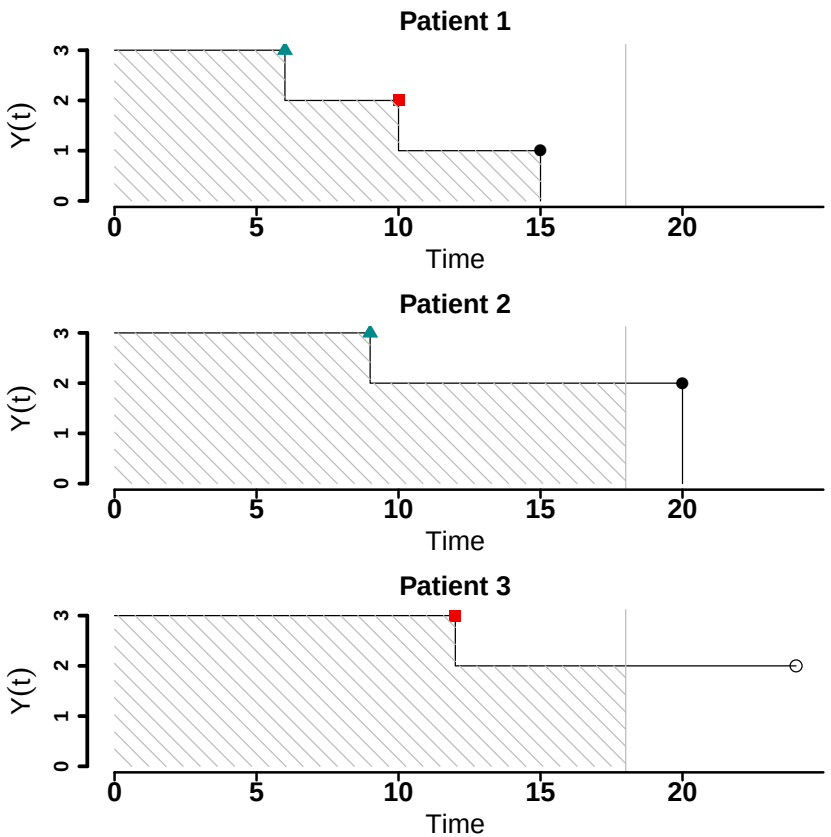
Reverse Counting Process Illustration



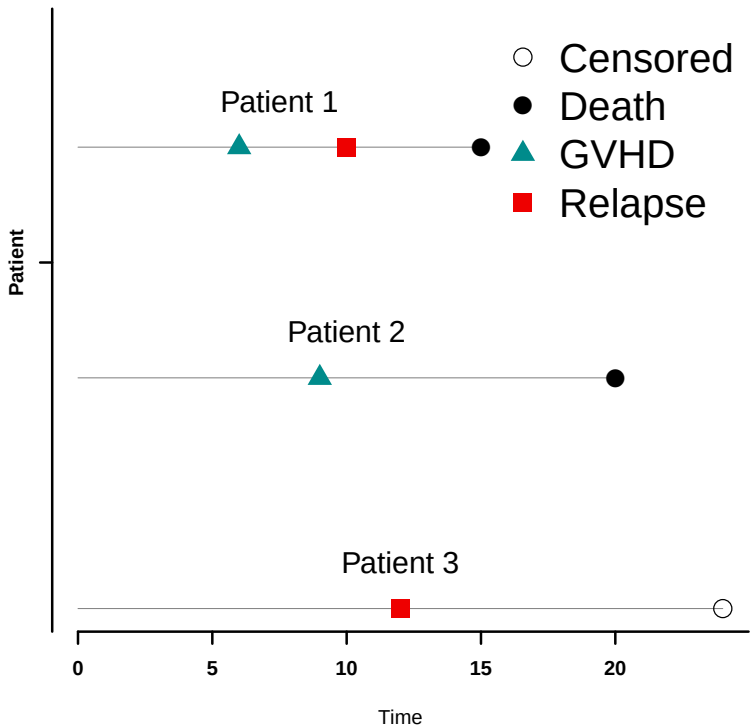


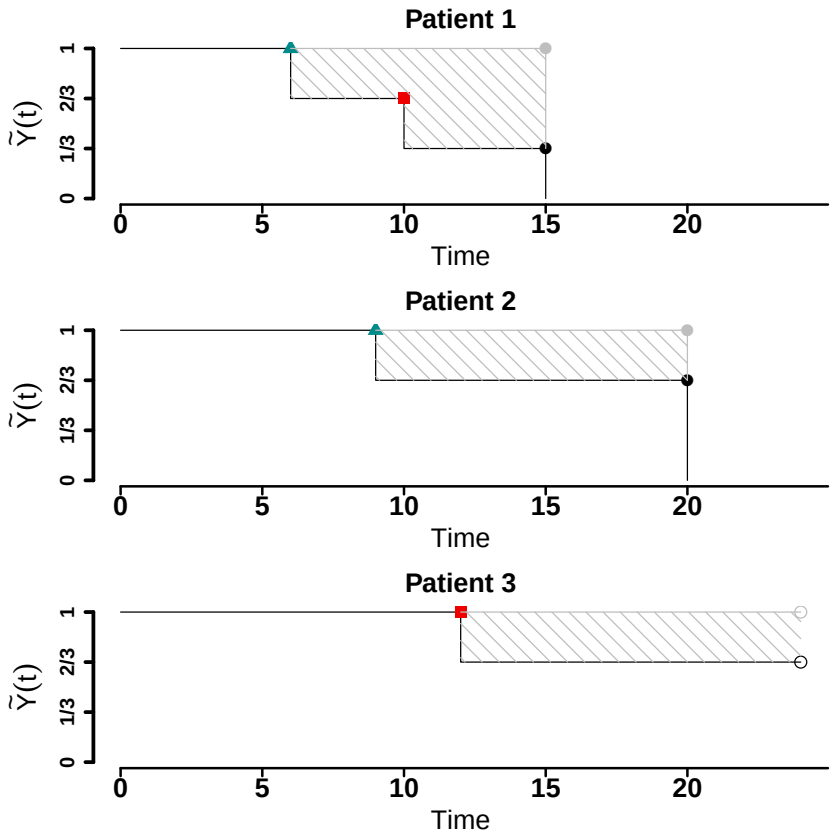
Cumulative Marker Process in Presence of Terminal Event

- $M(t) = \int_0^t Y^*(u)I(D \geq u)du$, cumulative marker process
  - $Y^*(u)I(D \geq u)$ takes 0 after terminal event occurs
  - Area under marker trajectory
- Cumulative Mean $\mu(t) = E\{M(t)\} = \int_0^t E\{Y^*(u)I(D \geq u)du\}$
  - Ideal treatment: prolong survival and maintain high marker value



Standardized Summary Metric: "Morbidity"-Adjusted RMST





A Summary Metric Based on Cumulative Marker Process

- For the non-standardized case, $Y^*(t) = \sum_{k=1}^{K} I(T_k \geq t) + 1$, Claggett et al. (2018) considered

$$\begin{aligned}\mu(t) &= \int_0^t E\{Y^*(u) I(D \geq u) du\} \\ &= \int_0^t E\{Y(u) du\} \\ &= E\{\sum_{k=1}^{K} \min(T_k, D, t) + \min(D, t)\}\end{aligned}$$

  - *sum* of (restricted) mean event-free survival times up to t

Nonparametric Estimation

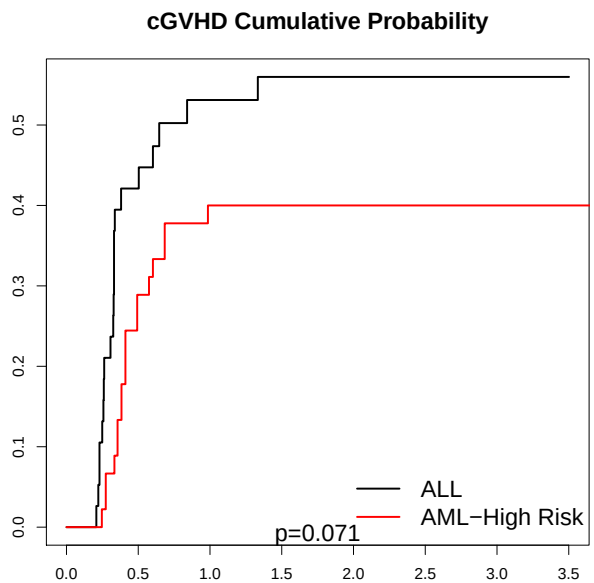
- Induced informative censoring of $M(\cdot)$
- Consider the framework proposed by Sun et al. (2017) for benefit-risk assessment in general
- Notice
  $\mu(t) = \int_0^t E\{Y^*(u)I(D \geq u)\}du = \int_0^t S_D(u)E\{Y^*(u)|D \geq u\}du$
- Moment-type estimator

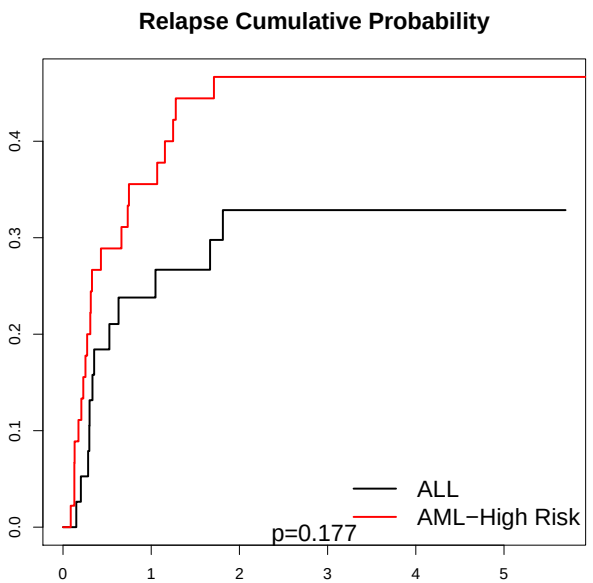
$$\hat{\mu}(t) = \int_0^t \hat{S}_D(u)\frac{\sum_{i=1}^n Y_i^*(u)I(X_i \geq u)}{\sum_{i=1}^n I(X_i \geq u)}du$$

  where $\hat{S}_D(u)$ is K-M estimator of $S_D(u)$, the survivor function of D
- Theorems (Sun et al. (2017))
  - Consistency of $\hat{\mu}$
  - Week convergence of $\sqrt{n}\{\hat{\mu}(t) - \mu(t)\}(0 \leq t \leq \tau)$
- Weights can/should be flexibly incorporated to reflect individual preferences for morbidities
  - Different weights can be used as personalized decision making tools

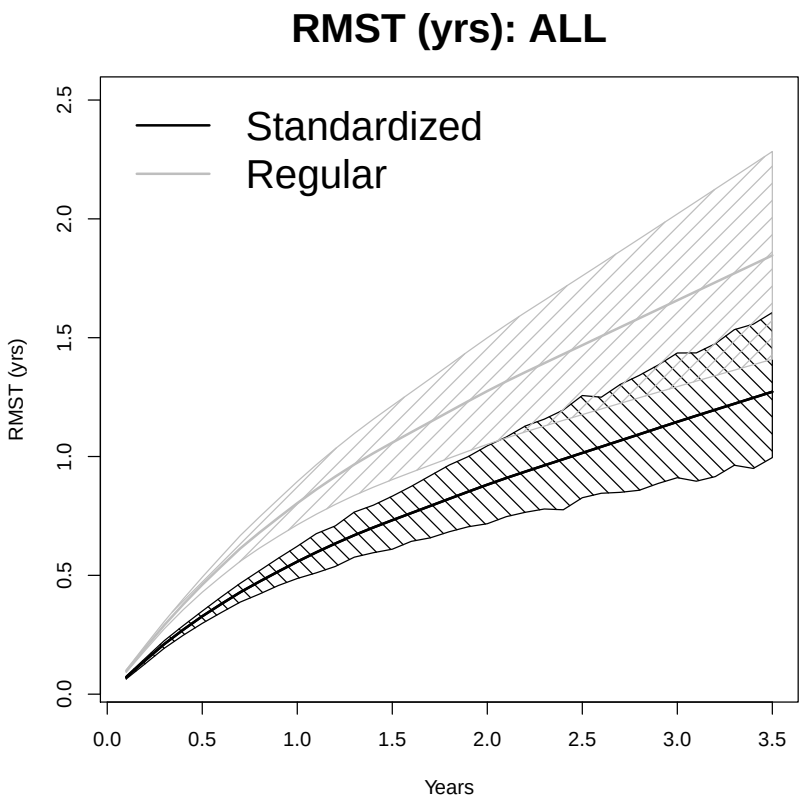
Bone Marrow Transplant Data Analysis

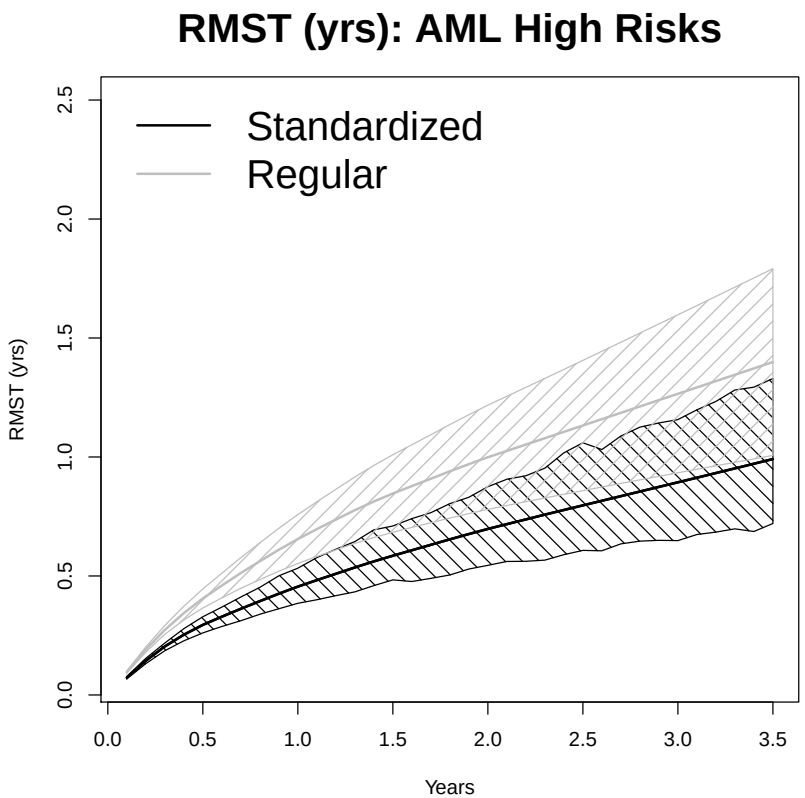
- A multi-center, non-comparative trial of patients prepared for allogeneic marrow transplants with a radiation-free conditioning regimen for patients with acute myeloctic leukemia (AML) and acute lymphoblastic leukemia (ALL) (Copelan et al. (1991))
- Here we analyze and "compare" ALL and High-risk AML patients for illustration purpose solely



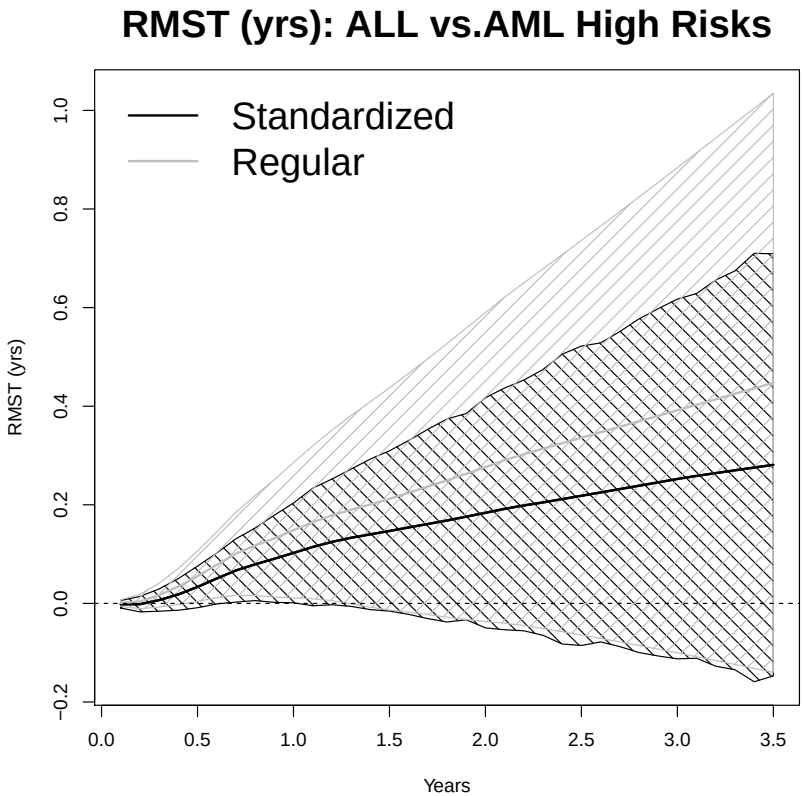


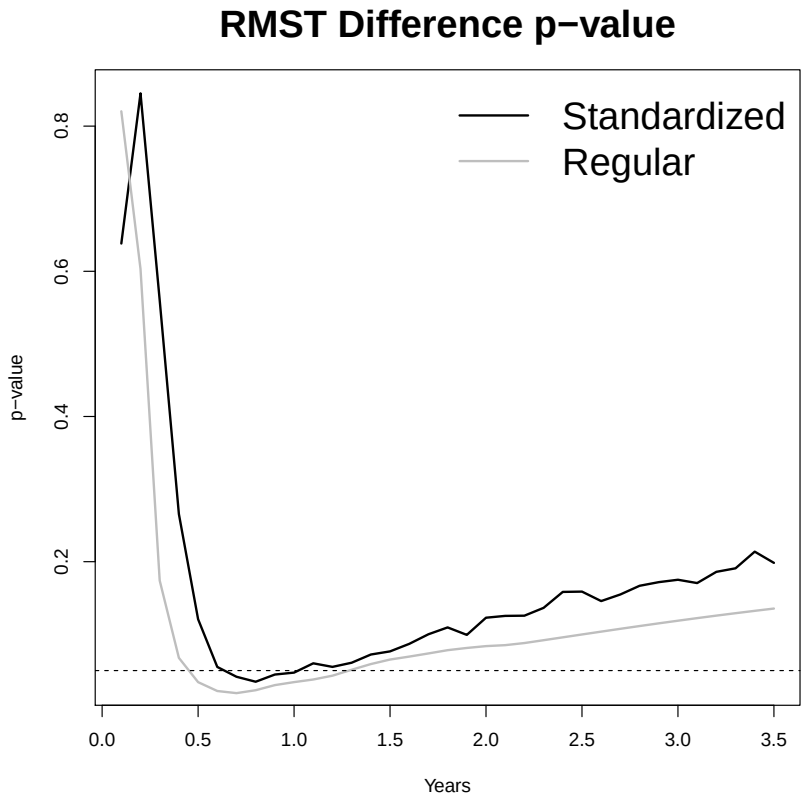
Regular and Standardized RMST





Regular and Standardized RMST Differences





Covariate Adjustment

- Linear models
  - Adjusting for covariates associated with outcome Y increases the precision of the treatment effect estimate
- Logistic regression and Cox PH regression
  - SE of the treatment effect increases (or at best does not decrease)
  - Maybe still want to adjust (for prognostic covariates) because unadjusted estimate is biased towards the null
  - Such "bias" is inherent due to the fact that the unadjusted and adjusted model estimates different measures of treatment effect
- Covariate-adjusted RMST?
  - Gains in precision is not granted

Covariate-adjusted RMST Difference

- Karrison (1987) incorporated covariates Z by fitting a piecewise exponential model, e.g.,

$$\lambda_g(t|Z) = \lambda_{gk} \exp(Z\beta), \ t \in (t_{k-1}, t_k], g = 1, 2$$

  - hazard functions are piecewise constant on $t \in (t_{k-1}, t_k]$
  - non-PH is allowed for treatment effect; PH is assumed for covariates Z
- Zucker (1998) considered

$$\lambda_g(t|Z) = \lambda_{0g}(t) \exp(Z\beta), \ g = 1, 2$$

  - Baseline hazard λ_{0g} completely unspecified, no need to specify the intervals $(t_{k-1}, t_k]$
  - $\hat{\mu}_{\tau,g}$ can be estimated by integrating $\hat{S}_g(t|Z) = \exp[-e^{Z\beta}\hat{\Lambda}_{0g}(t)]$
  - Average $S_g(t)$ over the entire covariate distribution in both arms
- Covariate-adjusted RMST has similar results as linear model (Karrison and Kocherginsky (2018)), e.g., covariate adjustment offers unbiased and more precision estimation of treatment effect

Covariate-adjusted RMST Difference, cont.

- Tian et al. (2014) considered a regression model with link function $\eta(\mu_\tau(X)) = \alpha + \beta X$
- With logic link, β of the treatment indicator becomes

$$\log\{\frac{\mu_{\tau,1}(\tau - \mu_{\tau,2})}{\mu_{\tau,2}(\tau - \mu_{\tau,1})}\}$$

  an odds-ratio like summary for the group contrast
- From the IPCW expression, we have the estimating equation

$$S_n(\beta) = \sum_{i=1}^{n} \frac{\Delta_i^\tau}{\hat{G}(Y_i^\tau)} X_i\{Y_i^\tau - \eta^{-1}(\beta X_i)\}$$

  True parameter β_0 can be estimated by solving $S_n(\beta) = 0$. It can be shown $\hat{\beta}$ is consistent
- Inference can be obtained through perturbation-resampling method (Tian et al. (2005))

Choice of the truncation time point, τ

- In a confirmatory study, τ should be pre-specified
  - Often if not always difficult
- The choice would depend on
  - clinical motivation or interest (short-term? Long-term?)
  - Follow-up time of the study
  - Precision at the tail part of the KM curves
- When choosing τ a posteriori, objective rules like "effective sample size" (Karrison (1987)) can be useful
  - e.g., choose the largest t such that $\hat{N}_{\text{Eff}}(t) > \frac{2}{3}N$, where $\hat{N}_{\text{Eff}}(t) = \frac{\hat{S}(t)(1-\hat{S}(t))}{\hat{V}\{\hat{S}(t)\}}$

Final Notes

- Collective efforts to change the culture of reporting and interpreting HR alone
- Model-free and clinically interpretable metrics like RMST should be appreciated and better interpreted
- A lot of potential (and fun) to exploit the additivity of RMST

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Thank You!