Restricted mean survival vs hazard ratios in oncology randomized controlled trials

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Background

• Survival outcomes are most common in cancer trials (OS, PFS, ...)
• The hazard ratio (HR) is the preferred measure of the treatment effect on those outcomes
• HRs have been challenged as relevant measures of survival benefit
  – Relative rather than absolute measure of treatment effect
  – Not so easy to interpret for non-statisticians (≠ RR for instance)
  – May not be constant in time (non-proportional hazards)
• Often used in conjunction with e.g. the median to characterize absolute effects
RMST

- Censoring usually precludes estimation of mean survival
- Restricted mean survival time (RMST) has been advocated as an alternative summary for survival curves
- Direct interpretation: RMST_{t*} is the life expectancy at horizon t*
- Treatment effect
  - Difference in RMST (RMSTD)
  - Ratio of RMST (RMSTR)
  - Difference (ratio) of restricted mean time loss (t* – RMST_{t*})
- Difference in means more relevant than difference in medians

Karrison Controlled Clinical Trials 2007
Royston & Parmar Statistics in Medicine 2011
Royston & Parmar BMC Medical Research Methodology 2013

Difference in RMST

2nd line EGFR wild-type NSCLC

Docetaxel v erlotinib

$t^* = \text{minimum}(t^*_\text{doc}, t^*_\text{erl}) = 7.3$ mo.
RMSTD: $+0.6$ (0.02 to 1.3)
HR: 0.71 (0.54 to 0.96)
Median PFS
Docetaxel: 2.9 mo. (2.4 to 3.8)
Erlotinib: 2.4 mo. (2.1 to 2.6)

Garassino et al. Lancet Oncology 2013
Objective

- To obtain empirical evidence on the comparison of treatment effects measured as HR or RMSTD/R in recent oncology randomized trials

Methods

- Systematic review of phase III parallel-group randomized trials in oncology published last 6 mo. of 2014 in selected high impact journals
- Reconstruction of individual patients data (IPD) from published survival curves
- For the primary outcome whenever possible
  - Priority given to PFS or EFS if co-primary outcomes
- Reanalysis of each trial → HR, RMSTD, RMSTR
Selection of Trials

- Oncology randomized controlled trials
- Published last 6 months of 2014 in
  - New England Journal of Medicine
  - Lancet Oncology
  - Lancet
  - Journal of Clinical Oncology
  - Journal of the American Medical Association

- Search MEDLINE using Cochrane highly sensitive strategy
- Inclusion criteria
  - Superiority and noninferiority parallel group RCTs
  - Kaplan-Meier curve for a primary or secondary time-to-event outcome
- Exclusion criteria
  - Phase I, II, IV; > 2 arms; meta-analyses; reports of secondary, subgroup, or follow-up analyses;
  - Supportive care, palliative care, or prevention trials;
  - Specific designs (eg. Cluster RCT, cross-over ...)

Reconstruction of IPD

- Extraction of times and survival probabilities on KM curves using DigitizeIt software

- Use of an iterative algorithm* to reconstruct individual patient data for each arms using
  - Reconstructed curves
  - Total number of events (when available)
  - Numbers of patients at risk (when available)

* Guyot et al. BMC Medical Research Methodology 2012
Estimation of Treatment Effects

- **HR**
  - Cox proportional hazards regression model
  - Grambsch-Therneau test for the non-proportional hazards
  - Log-rank test of null treatment effect

- **RMST**
  - t*: minimum of the largest observed event time in each group
  - RMST as area under the KM curve
  - Difference and ratio in RMST
  - Test for null treatment effect: compare RMSTD/SE to a standard normal distribution (same for RMSTR)

Comparison of Treatment Effects

- Comparison of HR and RMSTR (same scale)
- Assess whether a measure is systematically further from the null
- For each trial: ratio HR/RMSTR
- Variance of HR/RMSTR obtained by bootstrap
- Coding so that HR/RMSTR>1 → HR more optimistic than RMSTR
- Meta-analysis of the individual trial ratios
- Subgroup analyses
  - Type of outcome (OS v others)
  - (Non-)proportionality of hazards
Characteristics of the Selected RCTs

- 54 trials
- Selected outcome
  - PFS: 23 (43%)
  - OS: 21 (39%)
  - RFS, FFS, DFS, EFS: 10 (18%)

Treatment Effect Estimates: HR

- Median HR (Q₁ to Q₃): 0.84 (0.67 to 0.996)
  - Range from 0.19 to 1.37

- Proportional hazards
  - Reported as checked (and OK) in 5 (9%) trials
  - We found evidence of NPH in 13 (24%) other trials

- Significant difference in 24 (44%) trials (always in favor of experimental)
Treatment Effect Estimates: RMST

- Median $t^*$ 28.3 mo. (range 11 mo. to 10 y)
- Differences in RMST
  - Range from -2.9 to +10.1 mo.
  - Median ($Q_1$ to $Q_3$): +1.1 mo. (0.2 to 2.8)
- Ratios of RMST
  - Range from 0.90 to 1.87
  - Median ($Q_1$ to $Q_3$): 1.10 (1.01 to 1.20)
- Significant difference for 25 (46%) of trials

Comparison of Treatment Effects

![Graphs showing comparison of treatment effects](attachment:image.png)
HRs and RMSTRs with 95% CIs

Meta-analysis of HR/RMSTR
Subgroup analyses

- By type of outcome
  - 1.04 [1.00; 1.07] for OS (n=21 trials) \( P = .08 \)
  - 1.17 [1.10; 1.23] for others (n=33 trials)

- By evidence of non-proportional hazards
  - 1.12 [1.06; 1.19] for NPH (n=13 trials) \( P = .55 \)
  - 1.10 [1.06; 1.15] without NPH (n=41 trials)

- No difference according to sample-size or f-up duration either (post-hoc)

Discussion

- HR and RMST-based measures in agreement overall

- But RMST yielded more conservative estimates
  - For any time-to-event outcome
  - Whatever the evidence for NPH

- Example: dabrafenib + trametinib v vemurafenib in metastatic melanoma with a BRAF V600 mutation
  - HR 0.71 (0.55 to 0.93) i.e 1/HR 1.41 (1.08 to 1.82)
  - RMSTD 1.1 mo. (0.3 to 2.0) at \( t^* = 18.1 \) mo.
  - RMSTR 1.08 (1.02 to 1.15)
RMST-based vs other measures

- RMST-based measures do not rely on specific assumptions such as PH
- And are quite easily interpreted
- Differences in survival probabilities at a specific time point or in median survival times can also be used
  - Interpretable but summarize a curve by one single point
  - In addition the median survival time may be unestimable (16 [30%] in our sample)
- Limitation of RMST is the choice of t*
  - May be predefined in a protocol according to expected data maturity
  - Curves of RMSTD over time have also been proposed but to not provide a single estimate of the benefit

Limitations of our study

- We used reconstructed IPD
  - Less reliable than the true IPD
  - Unable to perform adjustment / stratification as in some original trials
  - Good reproducibility + agreement with published HRs anyway

- Choice of t*
  - Common strategy for all RCTs without further investigation
  - RMST obtained by KM-integration may become unstable at the right tail
  - Other approaches may be more robust in specific cases (e.g. using flexible models)

- Restricted to trials published in high-impact journals
Reliability of estimation after IPD reconstruction

- 6 randomly studies were extracted by 2 reviewers and survival probabilities were estimated at 5 time points in each group
  - Over the 60 points, the mean reproducibility error was 0.2% (0.01 to 0.4)
- Bland-Altman analysis for the 27 studies reporting non-adjusted HRs
  - Mean difference of logHR was -0.002 (-0.008 to 0.004)