A Model-Independent Method to Determine Restricted Mean Survival Time in the Analysis of Survival Curves

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Abstract
The restricted mean survival time (RMST) is a relatively new parameter proposed to improve the analysis of survival curves. As opposed to the median, the RMST has the advantage of capturing the overall shape of the survival curve, including the so-called “right tail.” One limitation of RMST lies in the mathematical complexity of its calculation (model-dependent analysis). In the present report, we describe a model-independent method that simplifies the calculation of RMST. The estimation approach (trapezoidal rule) is the same as that commonly employed in pharmacokinetics. In the analysis of 6 survival curves, the performance of the model-independent method was virtually the same as that of model-dependent methods.

Keywords Survival · Kaplan-Meier · Median · Mean survival time · Trapezoidal rule · Model-independent methods · Area under the curve · Pharmacokinetics

Viewpoint
For many decades, in comparative trials, the literature on anti-cancer treatments has presented the outcome for the two treatments under comparison according to the median overall survival (OS), (and/or progression-free survival, PFS), and the hazard ratio (HR) for OS and/or PFS. In addition, a more sophisticated approach has been proposed, which is based on the estimation of restricted mean survival time (RMST) [1, 2].

In survival analyses, the usefulness of RMST is well-recognized [1]. Its main advantage lies in its ability to capture the overall shape of the survival curve over time (in comparison with the median that performs a punctiform time-length estimation generating 50% of residual survival). The typical approach for determining RMST is based on complex mathematical models that describe the hazard to which patients are exposed over time [2]. The model based on proportional hazards is the most widely used, but other approaches have been proposed as well [2]. Therefore, estimating RMST is extremely complex, irrespective of whether the individual survival information is available or the estimation is performed from aggregate information. The most typical approach reconstructs, from the graph, the individual survival times and the individual outcomes, selects a survival-vs-time mathematical model (e.g., the proportion hazards model), performs a least-squares fitting of the individual data to the model, and finally integrates the best-fit survival-vs-time curve to estimate the area under the survival curve (AUC).

The proposal described herein is to carry out a model-independent analysis for estimating the RMST based on a much simpler procedure. This approach is drawn from pharmacokinetics, a field where model-independent methods have been available for many years [3, 4].

The survival curves based on the Kaplan-Meier method represent the typical material from which the mean survival time (MST) is estimated [1, 2, 5]. The MST is identical to the AUC, and can therefore be evaluated from time zero to infinity or from time zero to a certain time-point of the follow-up (t*). In this latter case, survival is restricted to t*, and so the RMST is the AUC evaluated from time zero to t*.

In both survival analysis and pharmacokinetic analysis, the AUC of model-dependent methods is calculated as the...
Fig. 1 Values of RMST for 6 survival curves estimated by model-independent [7] and model-dependent methods [3, 4]. Panels a through c show the survival curves for the three randomized trials (RE01, GOG111, and IPASS, respectively). The numerical values shown in the figure are the following (model-dependent estimate vs model-independent estimate): RE01 experimental arm, 1.243 vs 1.246; controls, 0.929 vs 0.927; GOG111 experimental arm, 3.46 vs 3.468; controls, 2.68 vs 2.749; IPASS experimental arm, 7.08 vs 7.30; controls, 6.17 vs 6.05. Although Royston and Parmar [4] provided 3 estimates of RMST for each curve, we considered only the intermediate value among the 3 available. The units of time have been kept the same as those reported in the paper by Royston and Parmar (i.e., years for RE01 and GOG111, months for IPASS). The survival curves shown in panels a, b, and c have been modified from the articles where they were originally published [6-10]; in panel b, the dashed lines reflect the best-fit curves estimated by the authors.

64 integral of the mathematical function [1]. In particular, when model-independent analysis is adopted, the AUC is calculated according to the trapezoidal rule, which is widely used in pharmacokinetics [4]. Determining the AUC according to the trapezoidal rule has the advantage of an extreme mathematical simplicity.

67 In the model-independent methodology proposed herein, the RMST is estimated from the survival curve as the value of AUC from time zero to \( t^* \), where AUC is calculated by the trapezoidal rule.

70 Hence:

\[
\text{RMST} = \text{AUC (determined by the trapezoidal rule)}
\]  

71

72  In 2011, Royston and Parmar [4] described the model-dependent calculation of RMST by comparing 3 statistical models with one another (pseudovalues method, Kaplan-Meier method, and flexible parametric method). Their comparison was carried out by examining 6 survival curves derived from 3 randomized trials (RE01, GOG111, and IPASS Pan-Asia Study (IPASS)). The RE01 trial compared interferon-alpha with medroxyprogesterone acetate in metastatic kidney cancer \( (t^* = 4 \text{ years}) \); the GOG111 trial compared paclitaxel + cisplatin vs cyclophosphamide + cisplatin in advanced ovarian cancer \( (t^* = 7 \text{ years}) \); the IPASS trial compared gefitinib vs carboplatin + paclitaxel in advanced pulmonary adenocarcinoma \( (t^* = 18 \text{ months}) \). All these survival curves have been published previously [6-8]. References 6 to 8 provide information for identifying the original clinical trials.

84 In the present analysis, the model-independent values of RMST were determined according to the AUC calculation previously described [5]. Briefly, this procedure retrieves the
published graphs of the survival curves, then estimates the survival percentage-vs-time data points with a digitizer 
(WebPlotDigitizer: https://automeris.io/WebPlotDigitizer). And finally determines the model-independent values of 
RMST (according to Eq. 1). An Excel datasheet can be used to 
apply the trapezoidal rule (e.g., "Find the area under a curve 
in Excel"). https://www.youtube.com/watch?v=
U6EWNesdR5A), and also the numerous tools developed 
for pharmacokinetics are suitable for this purpose.

Figure 1 shows the estimates of RMST for these 6 curves 
determined by model-dependent and model-independent 
methods. Each estimation of RMST from the Kaplan-Meier 
graph required less than 5 min. Our results show that the 
correlation between model-independent and model-
dependent estimates is strong ($R^2 = 0.9983$).

There are some advantages and disadvantages in 
implementing the model-independent approach. The advantage 
ecessarily lies in the remarkable simplification of 
mathematics; furthermore, the absence of a pre-specified model 
eliminates the need to choose the "best" mathematical function 
for each data set. The main disadvantage is that no 
variability is estimated for the individual values of AUC. However, 
when multiple data sets are evaluated to compare the same 
two treatments, the issue of variability can be addressed by 
determining between-study variability of AUC (weighted ac-
cording to numerosity) instead of intra-study variability.

In conclusion, using a model-independent version of 
RMST can contribute to increase the use of this important 
survival parameter. Although RMST can improve the analysis 
of survival curves as opposed to medians (e.g., when long-
term survivors are present), its applicability is still very limited 
mainly because of its extreme technical complexity. The previous 
experiences of pharmacokineticists in handling the area 
under the concentration-time curve through simplified 
methods can be transferred to the field of oncology, where 
the AUC can supplement the information provided by med-
ians. The current literature in oncology has not yet ade-
quately employed the RMST, but expanding the use of this param-
eter could be worthwhile, particularly when immunotherapies 
resulting in long-term survival are concerned.
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