# Evaluation of Progression Free Survival as a Surrogate for Overall Survival for prostate cancer treatment: Software development

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## INTRODUCTION

In clinical trials, the determination of the true endpoint or the effect of a new therapy on the true endpoint may be difficult, requiring an expensive, invasive or uncomfortable procedure. In some trials, however, the main endpoint of interest (true endpoint), for example death, is rare and/or takes a long time to reach. In such trials, there would be benefit in finding a more proximate endpoint (surrogate endpoint) to determine more quickly the effect of an intervention [1].

The validation and evaluation of a surrogate endpoint needs to be assessed at both the patient and the trial-level [2]. On one hand, the individual-level surrogacy measures the association between the potential surrogate endpoint and the true endpoint after adjusting for treatment effects on both true and surrogate endpoints.

On the other hand, the trial-level surrogacy describes how well one can predict the treatment effect on the true endpoint in a future trial based on the observed association between the treatment effects on the surrogate and true endpoints observed in previous trials [3].

Unfortunately, standard software to perform analysis to validate surrogate endpoints is lacking. To that end, we developed a user friendly SAS macro to automate such an analysis. We demonstrate the usage and capacities of the software implementation using a clinical trial dataset with two failure time endpoints.

## METHODS

In validation of a possible surrogate, two major branches have been developed, methods in single-trial settings and meta-analytical evaluation methods. The second one has been applied in our analysis.

Firstly, a bivariate copula model was used to measure association between failure time endpoints. It was assumed that the joint survival function for $(S_{ij}, T_{ij})$ could be written as:

$$F(s,t) = P(S_{ij} \geq s, T_{ij} \geq t) = C_\theta \{F_{S_{ij}}(s), F_{T_{ij}}(t)\} \quad s,t \geq 0,$$

where $F_{Sij}$ and $F_{Tij}$ denote the marginal survival functions for both endpoints [3]. $C_\theta$ is a copula, a bivariate distribution function on $[0,1]^2$. The marginal distribution were given by the following equations:

$$F_{S_{ij}}(s) = \exp\{-\int_0^s \lambda_{Si}(x)\exp(\alpha_i Z_{ij})dx\},$$

$$F_{T_{ij}}(t) = \exp\{-\int_0^t \lambda_{Ti}(x)\exp(\beta_i Z_{ij})dx\},$$

where $\lambda_{Si}$ and $\lambda_{Ti}$ are trial specific marginal baseline hazard function, and $\alpha_i, \beta_i$ are trial specific effects of treatment $Z$ on the endpoint in trial $i$.

At the second stage it is assumed that:

$$\begin{pmatrix} \alpha_i \\ \beta_i \end{pmatrix} = \begin{pmatrix} \alpha \\ \beta \end{pmatrix} + \begin{pmatrix} a_i \\ b_i \end{pmatrix},$$

where the second term on the right hand side is assumed to follow a zero mean normal distribution with dispersion matrix:

$$D_r = \begin{pmatrix} d_{aa} & d_{ab} \\ & d_{bb} \end{pmatrix}.$$

Trial level surrogacy is assessed based on the coefficient of determination:

$$R^2_{trial} = \frac{d^2_{ab}}{d_{aa}d_{bb}}.$$

Individual level surrogacy is assessed based on Kendall's $\tau$, as it depends only on the copula function but not the marginal distribution of $S_{ij}$ and $T_{ij}$.

$$\tau = 4\int_0^1\int_0^1 C_\theta(F_{S_{ij}}, F_{T_{ij}})C_\theta(dF_S, dF_T) - 1$$

Unfortunately, there is no standard software to perform this validation. A SAS macro has been developed to perform the analysis.

## SAS MACRO CALL

```
%macro cont(data=,true=,trueind=,surr=,surrind=,trt=, center=);

Data: is the dataset containing one record for each subject, with
   the following variables:
True: variable representing the true endpoint,
Trueind: censoring indicator (1=event, 0= censoring),
Surr: variable containing the surrogate endpoint,
Surrind: censoring indicator (1=event, 0=censoring),
Trt: treatment indicator (0 or 1),
Center: unique id (continuous) for units for which treatment
   effects are estimated,
Trial: unique id (continuous) for the group of unit, for which
common baselines are to be used,
```

## Dataset

The data that are analyzed come from a multicenter trial conducted in 13 countries.
Patients were randomized to an active treatment and on a control treatment. Some centers were having only patients on one treatment arm. The true endpoint was overall survival and the surrogate was progression free survival. The median survival time was 485 days on OS and 88 days on PFS for active group (340 and 85 respectively for control group). Figure 1 shows the Kaplan Meier survival curves .
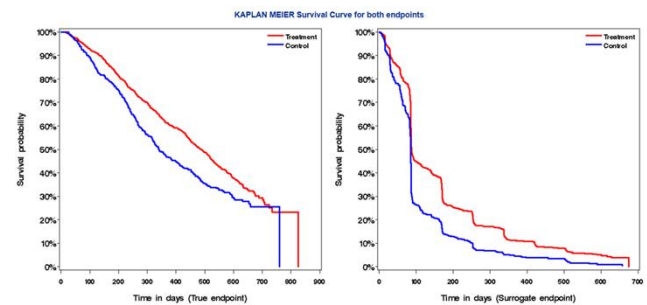


Fig1: Kaplan Meier survival curves for both endpoints stratified by treatment arm

## RESULTS

A trial level surrogacy equal to 0.31 and individual level surrogacy equal to 0.3 were obtained. Figure 2 shows the estimated treatment effect on the true endpoint vs treatment effect obtained on the surrogate from the developed macro. Table 1 summarizes obtained estimates with their confidence interval.
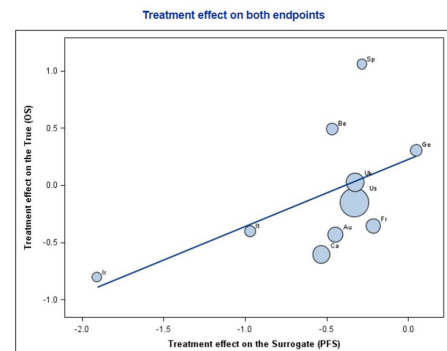


**Fig2**: Treatment effect on overall survival versus Treatment effect on progression free survival (left panel). Point size proportional to the number of subjects in each center. The straight line contains predictions from a weighted linear regression.

### SURROGACY MEASURES

| INDIVIDUAL | | | TRIAL | | |
|---|---|---|---|---|---|
| LOWER | TAU | UPPER | LOWER | R square | UPPER |
| 0.2635 | 0.3039 | 0.3442 | -0.1592 | 0.3175 | 0.7942 |

**Table1**: Estimated individual level and trial level surrogacy measures

## DISCUSSION AND CONCLUSIONS

• The obtained individual and trial level surrogacy values show relatively low association between overall survival and progression free survival.
•For a good surrogate, obtained estimates should be close to one, with short confidence intervals.
• For this dataset progression free survival may not be a good surrogate for overall survival.

## REFERENCES

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