

## Causal assessment of surrogacy for time-to-event endpoints using meta-analytic data

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**Abstract:** Surrogate endpoints can be required to carry out trials that would be unfeasible if based on true endpoint but must have been statistically validated prior to their use (Burzykowski, 2006). In this work we propose a new approach for surrogate validation when both the surrogate and the true endpoint are time-to-event. This approach is based on the causal framework of mediation analysis and is developed for meta-analytic data. It uses a joint regression model for the hazard functions of both endpoints (Rondeau, 2007). The meta-analytic nature of the data is taken into account by using shared random effects at both the individual and trial levels. The mediation analysis enables one to study the decomposition of the total effect of the treatment on the true endpoint into a direct effect and an indirect effect through the surrogate (Tchetgen, 2011). The indirect effect of the treatment on the true endpoint through the surrogate is allowed as the composition of a direct effect of the treatment on the surrogate and a direct effect of the surrogate on the true endpoint. A measure of surrogacy is taken as the ratio of indirect effect over total effect. We applied this method for the assessment of the disease-free survival as a surrogate of the overall survival for adjuvant chemotherapy in the context of resectable gastric cancers.

**Key words:** Surrogacy; Mediation Analysis; Joint Modeling; Meta-analysis

**Burzykowski T, Molenberghs G, and Buyse M (Eds.)** (2006). The evaluation of surrogate endpoints. Springer Science & Business Media.

**Rondeau V, et al.** (2007). Joint frailty models for recurring events and death using maximum penalized likelihood estimation: application on cancer events. *Biostatistics*, 8(4), 708-721.

**Tchetgen, E. J. T** (2011). On causal mediation analysis with a survival outcome. *The international journal of biostatistics*, 7(1).