Network meta-analysis for surrogate endpoint evaluation in advanced colorectal cancer: a Bayesian approach

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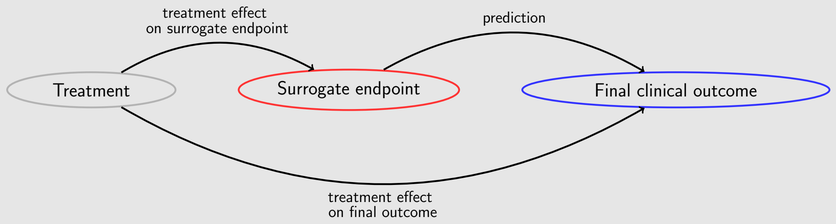
Introduction

- Surrogate endpoints are very important in regulatory and HTA decision-making in healthcare, in particular if they can be measured early compared to the long-term final clinical outcome and act as good predictors of clinical benefit.

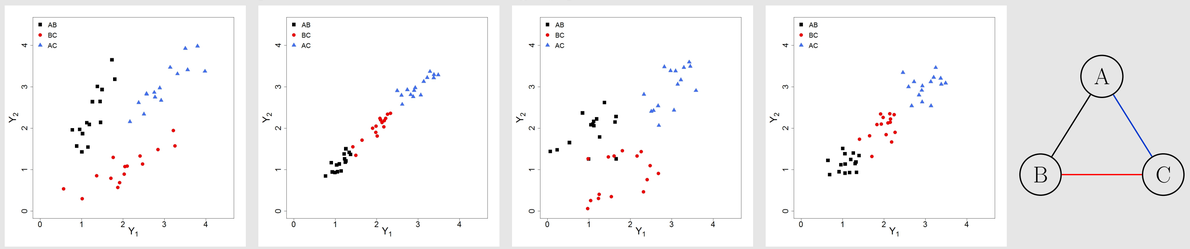


Surrogate outcome (definition): A biomarker that is intended to substitute for a clinical (final) outcome. A surrogate end point is expected to predict clinical benefit. [*Biomarkers Definitions Working Group. Clin Pharmacol Ther 2001*]

- Progression free survival (PFS) and tumour response (TR) have been investigated as surrogate endpoints for overall survival (OS) in advanced colorectal cancer (aCRC).
- Whilst in the past strong surrogate relationship between the treatment effects on TR or PFS and on OS has been found for traditional chemotherapies [*Buyse et al JCO 2007*], in more recent evaluation based on trials investigating modern therapies, the validity of these putative surrogate endpoints has been suboptimal [*Ciani et al JCE 2015*]. We aim to evaluate surrogate endpoints by differentiating between therapies of different mechanisms of action.

Methods

- Multivariate meta-analysis methods, traditionally used to obtain average treatment effects on multiple correlated endpoints [*van Houwelingen et al. 2002, Riley et al. 2007, Wei et al. 2013, Bujkiewicz et al. 2013*], are suitable tools for modelling surrogate endpoints [*Bujkiewicz et al. 2015, Bujkiewicz et al. 2016*]. Bivariate meta-analysis (bvMA) of treatment effects on a surrogate and a final outcome allows for both the validation of a surrogate endpoint and for making predictions of an unobserved treatment effect on the final clinical outcome from observed treatment effects on a surrogate endpoint.
- Whilst bvMA can be used to model surrogate endpoints, it does not differentiate between the treatment options.
- We propose use of bivariate network meta-analysis (bvNMA) as a method for modelling surrogate relationships between treatment effects on a surrogate and a final clinical outcome within treatment contrasts, borrowing information across treatment contrasts through the network structure of evidence base.
- bvNMA takes into account potential differences in surrogacy patterns between treatment contrasts



- We apply this methods to data from randomised controlled trials (RCTs) in aCRC.

Bivariate random-effects meta-analysis (BRMA)

The bivariate random effects meta-analysis (BRMA) model for correlated and normally distributed treatment effects on two outcomes Y_{1i} and Y_{2i} is usually presented in the form described by van Houwelingen *et al.* and Riley *et al.*:

within–study model

$$\begin{pmatrix} Y_{1i} \\ Y_{2i} \end{pmatrix} \sim \text{MVN}\left(\begin{pmatrix} \mu_{1i} \\ \mu_{2i} \end{pmatrix}, \mathbf{\Sigma_i} = \begin{pmatrix} \sigma_{1i}^2 & \sigma_{1i}\sigma_{2i}\rho_{wi} \\ \sigma_{1i}\sigma_{2i}\rho_{wi} & \sigma_{2i}^2 \end{pmatrix}\right),$$

between–study model

$$\begin{pmatrix} \mu_{1i} \\ \mu_{2i} \end{pmatrix} \sim \text{MVN}\left(\begin{pmatrix} \beta_1 \\ \beta_2 \end{pmatrix}, \mathbf{T} = \begin{pmatrix} \tau_1^2 & \tau_1\tau_2\rho \\ \tau_1\tau_2\rho & \tau_2^2 \end{pmatrix}\right).$$

Hierarchical framework:

- Y_{1i}, Y_{2i} – estimates of correlated true treatment effects μ_{1i}, μ_{2i}; $\mathbf{\Sigma_i}$ – within-study covariance matrices of the estimates,
- μ_{1i}, μ_{2i} – true treatment effects in the population; τ_j – between-studies standard deviations, ρ – between-studies correlation,
- (β_1, β_2) – pooled estimates.

In the Bayesian framework, prior distributions are placed on the parameters of the model, for example:

$$\beta_1 \sim N(0, 10^4), \quad \beta_2 \sim N(0, 10^4), \quad \tau_j \sim U(0, 2), \quad \frac{\rho + 1}{2} \sim Beta(1.5, 1.5).$$

Surrogacy criteria: perfect surrogacy means that $\rho = \pm 1$ and $\mu_{1i} = 0 \Leftrightarrow \mu_{2i} = 0$.

- BRMA model is typically used to obtain average effects on two outcomes for studies of the same treatment contrast.
- In the context of surrogate endpoints, BRMA may use data on a range of treatments.
- This model works well for strong surrogate relationships across all treatments.

Bivariate network meta-analysis (bvNMA) for surrogate endpoint evaluation

We use hierarchical bvNMA models to differentiate the association patterns between the treatment contrasts or classes whilst borrowing strength across treatment contrasts. To take into account the network structure of the data, we model the treatment effect differences Y_{jkli} between treatments k and l in study i for outcome $j = 1, 2$, as follows:

$$\begin{pmatrix} Y_{1kli} \\ Y_{2kli} \end{pmatrix} \sim \text{N}\left(\begin{pmatrix} \mu_{1kli} \\ \mu_{2kli} \end{pmatrix}, \mathbf{\Sigma_i}\right), \ \mathbf{\Sigma_i} = \begin{pmatrix} \sigma_{1kli}^2 & \sigma_{1kli}\sigma_{2kli}\rho_{wkli} \\ \sigma_{1kli}\sigma_{2kli}\rho_{wkli} & \sigma_{2kli}^2 \end{pmatrix}$$

$$\begin{pmatrix} \mu_{1kli} \\ \mu_{2kli} \end{pmatrix} \sim \text{N}\left(\begin{pmatrix} d_{1kl} \\ d_{2kl} \end{pmatrix}, \mathbf{T}\right), \ \mathbf{T} = \begin{pmatrix} \tau_{1kl}^2 & \tau_{1kl}\tau_{2kl}\rho_{1kl,2kl} \\ \tau_{1kl}\tau_{2kl}\rho_{1kl,2kl} & \tau_{2kl}^2 \end{pmatrix}$$

- k and l – baseline (control) and experimental treatments respectively in a study i,
- μ_{jkli} – the random true treatment effects (differences between the effects of treatments k and l) on outcome j in study i,
- d_{jkl} – mean treatment effect differences between treatments k and l for each outcome j.

We use the first-order **consistency assumption** [Lu and Ades 2009]: for any three treatments (b, k, l), the treatment differences (μ_{jkli}) satisfy the following consistency equations:

$$\begin{pmatrix} d_{1kl} \\ d_{2kl} \end{pmatrix} = \begin{pmatrix} d_{1bl} - d_{1bk} \\ d_{2bl} - d_{2bk} \end{pmatrix}$$

If $b = 1$ is a common reference treatment in the network, d_{j1k} are the basic parameters for each outcome j, with $d_{j11} = 0$ and prior distributions $d_{j1k} \sim N(0, 10^3)$, $\tau_{jkl} \sim unif(0, 2)$, $\frac{\rho_{1kl,2kl}+1}{2} \sim Beta(1.5, 1.5)$.

Surrogacy criteria: within treatment contrast kl, perfect surrogacy: $\rho_{1kl,2kl} = \pm 1$ and $\mu_{1kli} = 0 \Leftrightarrow \mu_{2kli} = 0$.

Illustrative example: advanced colorectal cancer

- Data were obtained from **four published systematic reviews** of RCTs investigating a range of pharmacological treatments in aCRC [*Chan et al 2017, Wagner et al 2009, Mocellin et al. 2017, Kumachev et al. 2015*], categorised into classes with respect to their mechanism of action:
  - antiangiogenic treatments targeting vascular endothelial growth factor (anti-VEGF)
  - anti epidermal growth factor receptor inhibitors (EGFRi)
  - humanised monoclonal antibody targeting integrin receptors (anti-IgG2)
  - monoclonal antibody targeting the type 1 insulin-like growth factor receptor (anti-IGF1R)
  - chemotherapies compared to the targeted therapies and combinations of these therapies.
- We included **50 randomized controlled trials** (RCTs) investigating use of
  - anti-VEGF with chemotherapy vs. chemotherapy alone (15 RCTs)
  - EGFRi with chemotherapy vs. chemotherapy alone (24 RCTs)
  - EGFRi with chemotherapy vs. anti-VEGF with chemotherapy (4 RCTs)
  - EGFRi with anti-VEGF and chemotherapy vs. anti-VEGF with chemotherapy (4 RCTs)
  - anti-IgG2 with EGFRi and chemotherapy vs. EGFRi with chemotherapy (1RCT, 2 subgroups)
  - anti-IGF1R with chemotherapy vs. chemotherapy alone (1 RCT)
  - EGFRi with anti-VEGF and chemotherapy vs. chemotherapy alone (1 RCT)

  The treatments are summarised in the network diagram of the below figure.

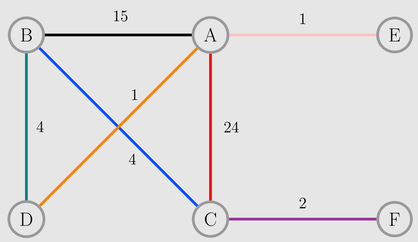


Figure: Network diagram for the aCRC data, A – chemotherapy alone, B – anti-VEGF + chemotherapy, C – EGFRi + chemotherapy, D – EGFRi + anti-VEGF + chemotherapy, E – anti-IGF1R , F – anti-IgG2 + chemotherapy.

- Tumour response (TR) is used as an example of a potential surrogate endpoint to progression free survival (PFS) as a final clinical outcome.
- The models are applied to data representing treatment effect on the two outcomes on log odds ratio (OR) scale for TR and log hazard ratio (HR) scale for PFS.
- The scatter plot in Figure 1 illustrates the association patterns between the treatment effects on the two outcomes for each treatment contrast.
- The within-study correlation between the treatment effects on TR and PFS was obtained from individual participant data of a RCT comparing Bevacizumab (anti-VEGF) with chemotherapy vs. chemotherapy alone. This correlation was assumed to apply to all studies.

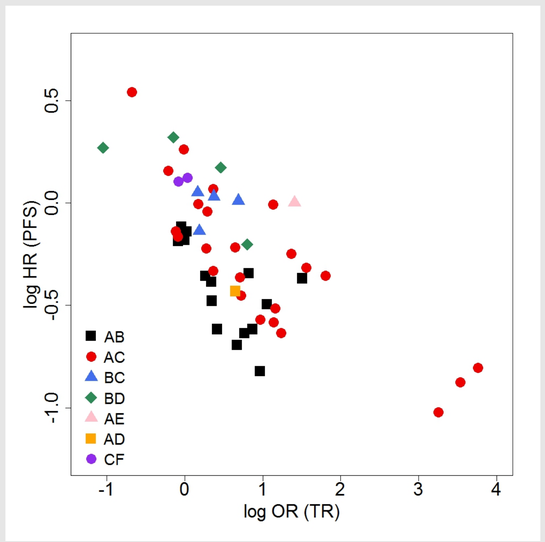


Figure: Scatter plot for the aCRC data, A – chemotherapy alone, B – anti-VEGF + chemotherapy, C – EGFRi + chemotherapy, D – EGFRi + anti-VEGF + chemotherapy, E – anti-IGF1R , F – anti-IgG2 + chemotherapy.

Results

- Both models (bvMA and bvNMA) were applied to evaluate the surrogacy patterns across and within all treatment contrasts. Table below reports the between-studies correlations and variances along with the mean treatment effects.

	treatment contrast			
model	AB	AC	BC	BD
between-studies correlations				
BRMA		-0.67 (-0.85, -0.41)		
bvNMA	-0.43 (-0.84, 0.16)	-0.79 (-0.95, -0.46)	-0.02 (-0.88, 0.88)	-0.28 (-0.94, 0.65)
OR (TR)				
BRMA		1.69 (1.43, 2.03)		
bvNMA	1.62 (1.28, 2.03)	2.20 (1.73, 2.92)	1.38 (1.09, 1.77)	1.19 (0.52, 2.53)
HR (PFS)				
BRMA		0.79 (0.73, 0.86)		
bvNMA	0.70 (0.63, 0.77)	0.74 (0.66, 0.83)	1.06 (0.96, 1.21)	1.08 (0.72, 1.60)
τ^2_{TR}				
BRMA		0.29 (0.15, 0.49)		
bvNMA	0.22 (0.07, 0.56)	0.57 (0.23, 1.22)	0.1 (0, 0.68)	0.76 (0.03, 3.18)
τ^2_{PFS}				
BRMA		0.08 (0.04, 0.13)		
bvNMA	0.03 (0.01, 0.09)	0.1 (0.04, 0.2)	0.03 (0, 0.23)	0.21 (0.01, 1.36)

Table: A – chemotherapy alone, B – anti-VEGF + chemotherapy, C – EGFRi + chemotherapy, D – EGFRi + anti-VEGF + chemotherapy.

- Take-one out cross validation procedure was carried out to evaluate surrogate the treatment effect on TR as predictor of the treatment effect on PFS. In the below table we compare the predictions from the two methods.

	treatment contrast			
model	AB	AC	BC	BD
Number of studies				
	15	24	4	4
mean absolute error				
BRMA	0.2	0.24	0.17	0.30
bvNMA	0.19	0.24	0.09	0.23
% reduction				
bvNMA	16.6	0.24	-28.5	-128.8

Table: Average absolute error and % reduction in the width of the predicted interval from bvNMA compared to BRMA for each treatment contrasts.

Conclusions

- Use of bvNMA allowed for surrogate endpoint evaluation within treatment contrasts in a single analysis.
- The NMA model allowed us to disentangle information on a relatively strong study-level surrogate relationship between treatment effects on TR and PFS for the treatment contrast of EGFRi with chemotherapy vs. chemotherapy alone from a set of treatments with suboptimal overall surrogacy relationship and resulted in more accurate and precise predictions for studies comparing anti VEGF therapies (with chemotherepy) vs. chemotherapy alone.
- In conclusion, bivariate network meta-analysis offers a new meta-analytic approach for surrogate endpoint evaluation that allows modelling of surrogate relationships in greater detail.

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