Meta-analysis and validation of surrogate endpoints

Tomasz Burzykowski

International Drug Development Institute (IDDI), Belgium

tomasz.burzykowski@iddi.com

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Outline

- Definitions/reminders
- The meta-analytic approach
- Examples of applications
- Adjustment for estimation error
- Conclusions

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Definitions

- *Clinical endpoint*: a characteristic or variable that reflects how a patient feels, functions, or survives
- *Biomarker*: objectively measured and evaluated indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention
- *Surrogate endpoint*: a biomarker that is intended to substitute for a clinical endpoint

*Ref: Biomarkers Definition Working Group, Clin Pharmacol Ther 2001;**69**:89*

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Statistical validation of surrogate endpoints

"The effect of treatment on a surrogate endpoint must be reasonably likely to predict clinical benefit"

*Ref: Biomarkers Definition Working Group, Clin Pharmacol Ther 2001;**69**:89*

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Important implications

- A prediction model is needed
  - not in the approaches by Prentice (1989), Freedman et al. (1992), ...
- Validity of a surrogate ≈ quality of prediction
- Model extrapolated to a new treatment (mechanism)
  - validation across a range of classes of treatments
  - a “leap of faith”; biological argumentation in addition to the statistical

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A Meta-analytic approach

- First-stage: a joint model:

$$S_{ij} = \mu_{S_i} + \alpha_i Z_{ij} + \varepsilon_{S_{ij}}$$
$$T_{ij} = \mu_{T_i} + \beta_i Z_{ij} + \varepsilon_{T_{ij}}$$

- Error Structure:

$$\begin{pmatrix} \varepsilon_{S_{ij}} \\ \varepsilon_{T_{ij}} \end{pmatrix} = N\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \sigma_{SS} & \sigma_{ST} \\ & \sigma_{TT} \end{pmatrix} \right)$$

- Second stage: a linear model for trial-specific effects:

$$\begin{pmatrix} \mu_{S_i} \\ \mu_{T_i} \\ \alpha_i \\ \beta_i \end{pmatrix} = N\left(\begin{pmatrix} \mu_S \\ \mu_T \\ \alpha \\ \beta \end{pmatrix}, \begin{pmatrix} d_{SS} & d_{ST} & d_{Sa} & d_{Sb} \\ & d_{TT} & d_{Ta} & d_{Tb} \\ & & d_{aa} & d_{ab} \\ & & & d_{bb} \end{pmatrix} \right)$$

*Ref: Buyse et al, Biostatistics 2000;**1**:49.*

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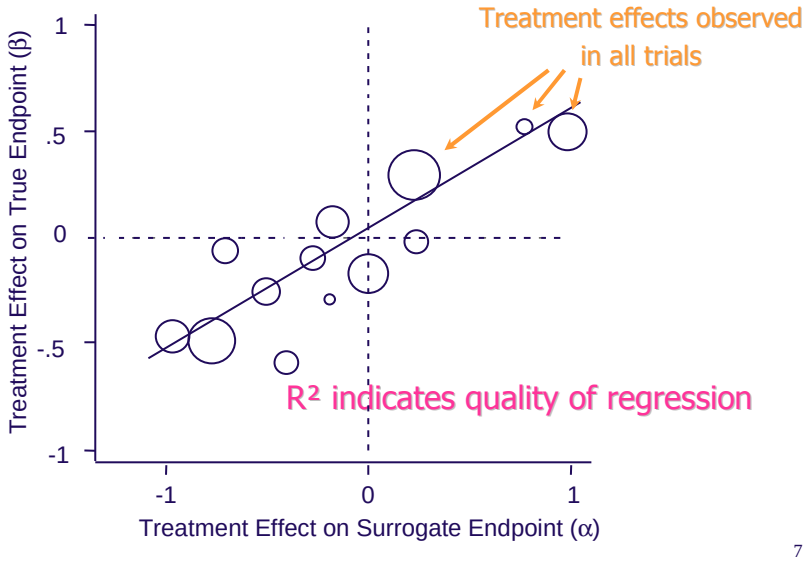
Prediction of treatment effect: several trials



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Validation of surrogate endpoints: the meta-analytic approach

Based on a two-stage model

First stage: a joint model for individual observations on surrogate and true endpoints

- (individual-level) association between endpoints
- (trial-specific) effects of treatment on surrogate/true endpoint

Second stage: a linear model for the trial-specific treatment effects

- $R^2_{trial} \approx 1$: surrogate "valid at the trial-level"

*Ref: Buyse et al, Biostatistics 2000;**1**:49; Burzykowski, Molenberghs, Buyse (2005), Springer*

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Is it feasible?

- The approach requires replicated trials
  - previous trials with the surrogate and true endpoints observed
  - for various classes of treatments
- Need strong, consistent relationships between changes in surrogate and true endpoint
  - at both individual patient level and group level
- Models for various combinations of endpoints needed
  - continuous binary, categorical, survival, longitudinal ...

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Examples in oncology: candidate surrogates for overall survival

- Colorectal ca: tumor response, DFS, PFS
  - Buyse et al., *Lancet* 2000; Sargent et al., *JCO* 2005; Buyse et al., *JCO* 2007, *Stat Meth Med Res* 2008; Burzykowski et al., *Lifetime Data Analysis* 2008
- Metastatic prostate ca: PSA
  - Collette et al., *JCO* 2005
- Metastatic breast ca: response, disease control, TTP, PFS
  - Burzykowski et al., *JCO* 2008
- Locally advanced head & neck ca: LRC and EFS
  - Michiels et al., *Lancet Oncology* 2009
- Curatively resected stomach ca: DFS (?)
  - GASTRIC, *ASCO Meeting* 2009, *abstract* 4517

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Colorectal cancer

Sargent et al., JCO 2005

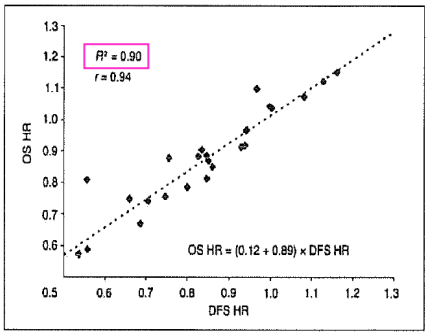

Fig 2. Disease-free survival (DFS) versus overall survival (OS) hazard ratios (HR) by trial.

Buyse et al., JCO 2007

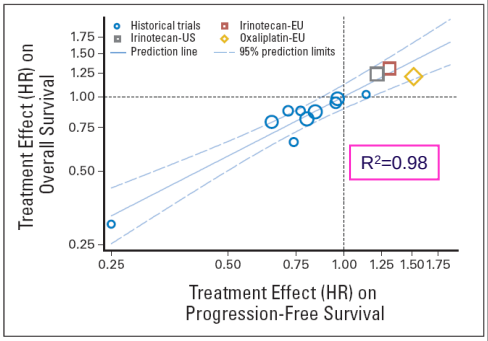

Fig 4. Correlation between treatment effects on progression-free and on overall survival in historical trials (circles), in irinotecan trials (squares), and in oxaliplatin trial (diamond). A logarithmic scale is used for both axes. Symbol size is proportional to the number of patients. HR, hazard ratio; EU, European Union.

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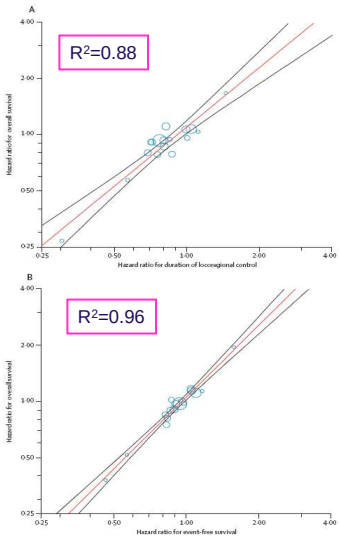
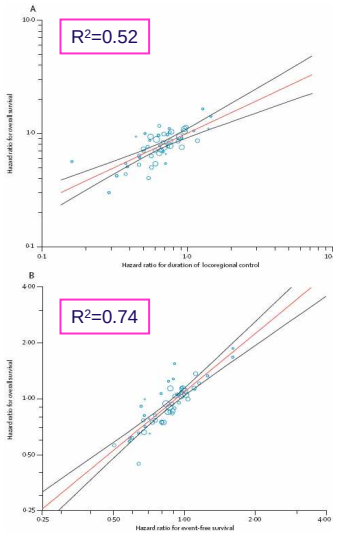
Head and neck cancer (Michiels et al., 2009)

Radiotherapy trials



Concomitant chemotherapy trials



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Sample correlation may be biased

- Treatment effects are estimated
- κ = (estimation error variance) / (treatment effects variance)
  - reliability ratio
- $\rho_{estimation}$ = Corr(estimation error for α_i and β_i)

$$\hat{R}_{trial} = \frac{R_{trial}}{\sqrt{(1+\kappa_S)(1+\kappa_T)}} + \frac{\rho_{estimation}}{\sqrt{\left(1+\frac{1}{\kappa_S}\right)\left(1+\frac{1}{\kappa_T}\right)}}$$

Ref: *Schaalje & Butts, Biometrics 1993;**49**:1262*
Burzykowski, Molenberghs, Buyse (2005), Chap. 11,

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Example: sample correlation & rare events

- For a rare event, κ_T can be large even for large trials. Then

$$\hat{R}_{trial} = \frac{R_{trial}}{\sqrt{(1+\kappa_S)(1+\kappa_T)}} + \frac{\rho_{estimation}}{\sqrt{\left(1+\frac{1}{\kappa_S}\right)\left(1+\frac{1}{\kappa_T}\right)}} \approx \frac{\rho_{estimation}}{\sqrt{\left(1+\frac{1}{\kappa_S}\right)}}$$

- If κ_S small, we get an estimate of $\rho_{estimation}$, not of R_{trial}

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Correlation adjusted for estimation error (1)

- Assume the following model

$$\begin{pmatrix}\hat{\alpha}\\ \hat{\beta}\end{pmatrix}=\begin{pmatrix}\alpha_i\\ \beta_i\end{pmatrix}+\begin{pmatrix}\omega_{Si}\\ \omega_{Ti}\end{pmatrix}=\begin{pmatrix}\alpha\\ \beta\end{pmatrix}+\begin{pmatrix}a_i\\ b_i\end{pmatrix}+\begin{pmatrix}\omega_{Si}\\ \omega_{Ti}\end{pmatrix}$$

$$\begin{pmatrix}a_i\\ b_i\end{pmatrix}\sim N\left(\begin{pmatrix}0\\ 0\end{pmatrix},\begin{pmatrix}d_{aa} & d_{ab}\\ d_{ab} & d_{bb}\end{pmatrix}\right),\quad \begin{pmatrix}\omega_{Si}\\ \omega_{Ti}\end{pmatrix}\sim N\left(\begin{pmatrix}0\\ 0\end{pmatrix},\begin{pmatrix}\tau_{SS,i} & \tau_{ST,i}\\ \tau_{ST,i} & \tau_{TT,i}\end{pmatrix}\right)$$

- Fix τ_{SS}, τ_{ST}, τ_{TT} at the estimated values
- Estimate d_{aa}, d_{ab}, d_{bb}
  - SAS: PROC MIXED with PARMS statement

Ref: *Burzykowski, Molenberghs, Buyse (2005), Chap. 11,*

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Correlation adjusted for estimation error (2)

- Consider a measurement error model:

$$\beta_i=\gamma_0+\gamma_1\alpha_i+\xi_i,\quad \xi_i\sim N(0,\sigma_\xi)$$
$$\begin{pmatrix}\hat{\alpha}_i\\ \hat{\beta}_i\end{pmatrix}=\begin{pmatrix}\alpha_i\\ \beta_i\end{pmatrix}+\begin{pmatrix}\omega_{Si}\\ \omega_{Ti}\end{pmatrix}$$

- Estimate γ_0, γ_1, σ_ξ by the method of moments
- Use the estimates to compute R^2_{trial}

Ref: *Burzykowski, Molenberghs, Buyse (2005), Chap. 11*

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Computing the adjusted correlation: issue

- If within-trial (estimation) variability is larger than the between-trial variability, computation of the adjusted correlation is difficult
  - non-convergence issues
- Between-trial variability of treatment effects is needed
  - in contrast to the “usual” meta-analysis
- Center-level validation problematic

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Advanced Colorectal Cancer: PFS as Surrogate for Survival

- 13 trials, 4,352 pts
- 10 “historical” trials: 5FU+LV vs. 5FU alone (1744 pts.) or with raltitrexed (1345 pts.)
- 3 “validation” trials (1263 pts.)
  - 5FU+LV vs. 5FU+LV+CPT11 (2 trials, 843 pts.)
  - 5FU+LV vs. 5FU+LV+oxaliplatin (1 trial, 420 pts.)

Ref:

- *MAGIC, J Clin Oncol 2004;22:3766; Cunningham et al, Ann Oncol 1996;7:961; Pazdur et al, Proc ASCO 1997;16:abstr 801; Cocconi et al, J Clin Oncol 1998;16:2943*
- *Douillard et al, Lancet 2000;355:1041; Saltz et al, NEJM 1997;343:905*
- *de Gramont et al, J Clin Oncol 2000;18:2938*
- *Buyse et al, JCO 2007;25;5218*

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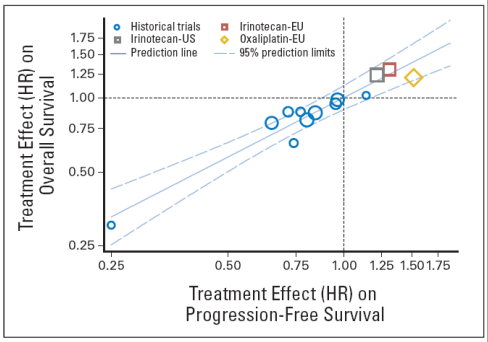
Advanced colorectal cancer

- Treatment effects: Hougaard copula, Weibull model

s.size	-ln HR_{OS}	SE	-ln HR_{PFS}	SE	Corr
434	0.01821	0.10352	0.03771	0.09761	0.77911
422	0.23657	0.10595	0.42860	0.10081	0.77151
489	0.20910	0.11126	0.21977	0.09986	0.74560
148	1.19428	0.18364	1.38815	0.18884	0.82291
185	0.42637	0.14584	0.29840	0.14401	0.81114
309	0.05526	0.11230	0.04843	0.11244	0.85020
135	-0.02290	0.19239	-0.13199	0.18229	0.80360
206	0.13203	0.14480	0.25794	0.14626	0.80232
271	0.13120	0.12653	0.33098	0.12660	0.79163
490	0.14124	0.09791	0.17039	0.09541	0.78403



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Advanced colorectal trial

- Analysis unadjusted for the estimation error:

$$\hat{R}_{trial} = 0.962 \ (\mathrm{SE} = 0.023),\ \hat{R}^2{}_{trial} = 0.926$$
$$\ln(\mathrm{HR}_{\mathrm{OS}}) = 0.012 + 0.823 \times \ln(\mathrm{HR}_{\mathrm{PFS}})$$

- Analysis adjusted for the estimation error:

$$\hat{R}_{trial} = 0.989 \ (\mathrm{SE} = 0.025),\ \hat{R}^2{}_{trial} = 0.978$$
$$\ln(\mathrm{HR}_{\mathrm{OS}}) = -0.003 + 0.807 \times \ln(\mathrm{HR}_{\mathrm{PFS}})$$

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Conclusions

- Meta-analysis-based validation of surrogate endpoints differs from the “classic” meta-analysis
  - Bivariate outcome
  - Focus on association between the treatment effects
  - Broader trial-inclusion criteria (various classes of treatments)
  - Random treatment effects assumed
  - Between-trial heterogeneity necessary
- Simple regression/sample correlation may be prone to bias
  - adjustment for the estimation error needed
  - more efficient methods to be developed

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