Improving interim decisions in adaptive enrichment designs using short-term or surrogate endpoint data

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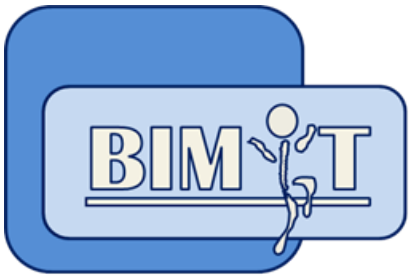

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Outline

- Introduction
- Normal endpoints
- Time-to-event endpoints
- Conclusion

Setup

- Two-stage adaptive enrichment design
- Primary endpoint: e.g. overall survival (OS)
- Surrogate endpoint: e.g. progression free survival (PFS)
- Several biomarker defined subgroups
- Subgroup selection at interim analysis

Interim decision

For each subgroup:

Drop subgroup or continue with recruitment?

Decision can be based on data from

- primary endpoint only
- surrogate endpoint only
- combination of primary and surrogate endpoint

Surrogate variables - normal data

- Primary endpoint Y
- Surrogate variable X
- (X, Y) bivariate normal
- Treatment effects: e_X, e_Y
- Measure of surrogacy (Buyse & Molenberghs 1998):
  - Individual level: $\rho = Corr(X, Y)$
  - Trial level: relative effect $RE = \frac{e_Y}{e_X}$ $(e_X > 0)$

Surrogate variables - normal data

Example (Engel / Walstra 1991: “double regression”):

$$X = a + bZ + \epsilon_1$$
$$Y = \alpha + \beta Z + \gamma X + \epsilon_2$$

- $\epsilon_i \sim N(0, \sigma_i^2)$ $(i = 1, 2)$
- X is observed for N patients, Y only for $n \leq N$
- MLEs from joint likelihood of (X, Y): $\delta_1 = \hat{\beta} + \hat{\gamma}\hat{b}$
- Marginal model for $Y = A + BT + \tilde{\epsilon_2}$
- MLE: $\delta_2 = \hat{B}$
- Relative efficiency:

$$\frac{Var(\delta_2)}{Var(\delta_1)} \approx \frac{1}{1 - (1 - n/N)\rho^2}$$

Sensitivity / Specificity

- Two scenarios:
  - $S-: e_- < e_-^0 \rightarrow$ correct decision = drop subgroup
  - $S+: e_+ > e_+^0 \rightarrow$ correct decision = keep subgroup
- Assessement of decision rules:
  - Sensitivity (true positives) = $P(\hat{e} > c | e_+) = 1 - \Phi\left(\frac{c - e_+}{\sigma_+}\right)$
  - Specificity (true negatives) = $P(\hat{e} < c | e_-) = \Phi\left(\frac{c - e_-}{\sigma_-}\right)$

ROC curve

- ROC curve: sensitivity vs. 1-specificity for all thresholds c

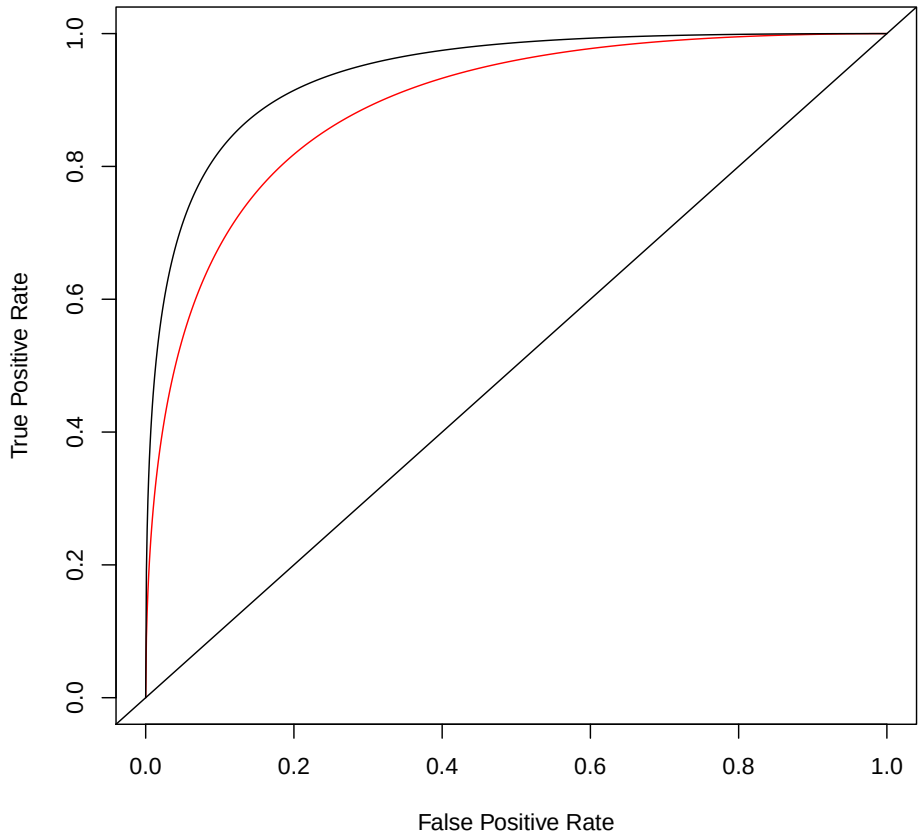
$$C_P(s) = \Phi\left(\frac{e_+ - e_-}{\sigma_+} - \frac{\sigma_-}{\sigma_+}\Phi^{-1}(1-s)\right)$$

- AUC = area under the ROC curve

$$AUC = \int_0^1 C_P(s)ds = \Phi\left(\frac{e_+ - e_-}{\sqrt{\sigma_+^2 + \sigma_-^2}}\right)$$

$\Rightarrow$ comparison of decision rules independent of the treshold

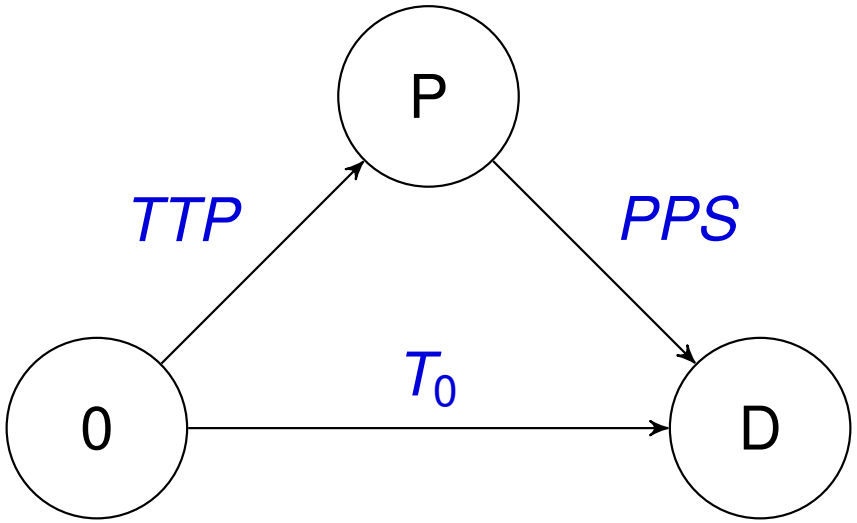
ROC curve - Example



$$n = 25,\ N = 100,\ \rho \approx 0.5,\ e_- = 0,\ e_+ = 1$$

$$Var(\delta_1) = 0.37,\ Var(\delta_2) = 0.52$$

Time-to-event endpoints



- Progression free survival (PFS) = time to progression (P) or death (D)

$$PFS = min(TTP, T_0)$$

- Overall survival (OS) = time to death from any cause

$$OS = \begin{cases} T_0 & for \quad T_0 \leq TTP \\ TTP + PPS & for \quad T_0 > TTP \end{cases}$$

Time-to-event endpoints

- Lagakos (1977), Cook& Lawless (2001):
  - Parametric multistate model: constant transition hazards
  - Estimate OS survival function based on MLEs
  - Substantial reduction in variance possible
- Full parametric modelling may be too restrictive in survival context
- Non-parametric:
  - Estimate OS survival function using Aalen-Johansen estimator
  - Only small improvements possible over Kaplan-Meier estimator

Semi-parametric model

- Cox proportional hazards model for each transition

$$\alpha_{ij}(t) = \alpha_{0,ij}(t) exp(\beta_{ij} Z)$$

- Partial likelihood factorizes (e.g. Hsieh (1993))

$$\mathcal{L} = \prod_i \prod_j L_{ij}$$

$\Rightarrow$ each Cox model can be estimated separately (other events treated as censoring)

- Estimators / test statistics are asymptotically independent

Log-rank / Score tests

- Score

$$U_{ij} = \left[\frac{\partial L_{ij}(\beta_{ij})}{\partial \beta_{ij}} \right]_{\beta_{ij}=0}$$

- observed Fisher information

$$I_{ij} = - \left[\frac{\partial^2 \log L_{ij}(\beta_{ij})}{\partial \beta_{ij}^2} \right]_{\beta_{ij}=0}$$

- U_{ij} are asymptotically independent and approx.

$$U_{ij} \sim N(\log(\lambda_{ij})\sqrt{I_{ij}}, I_{ij})$$

Multistate log-rank test

- Weights $w = (w_{ij})$, $w_{ij} \in [-1, 1]$, $\sum_{i,j} w_{ij}^2 = 1$
- $U = \sum_{i,j} w_{ij} U_{ij}$
- $I = \sum_{i,j} w_{ij}^2 I_{ij}$
- Under $H_0 : \beta_{ij} = 0 \quad \forall i, j$ with $w_{ij} \neq 0$:

$$Z_{MS} = \frac{U}{\sqrt{I}} \sim N(0, 1)$$

- Weights control sensitivity to specific alternative hypotheses
- U inherits independent increments property from U_{ij}

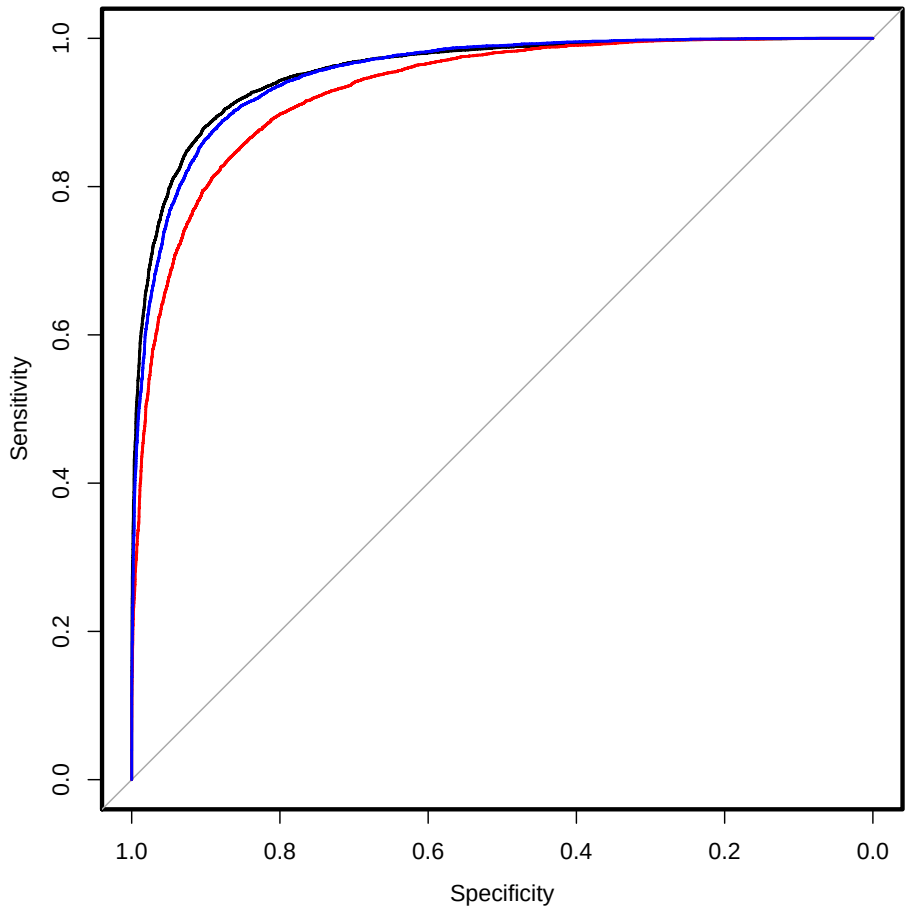
Simulation setup

- Total number of patients: 200 (each scenario)
- Censoring: approx. 50% (OS), 30% (PFS)
- Exponential transition times
- Selection based on LR_{PFS}, LR_{OS} or LR_{MS}

$S_{-}OS = 1, PFS = 1$, $S_{+}: OS = 0.67, PFS = 0.67$, $RE = 1$

$w^2_{0P} = 1/3$, $w^2_{0D} = 1/3$, $w^2_{PD} = 1/3$

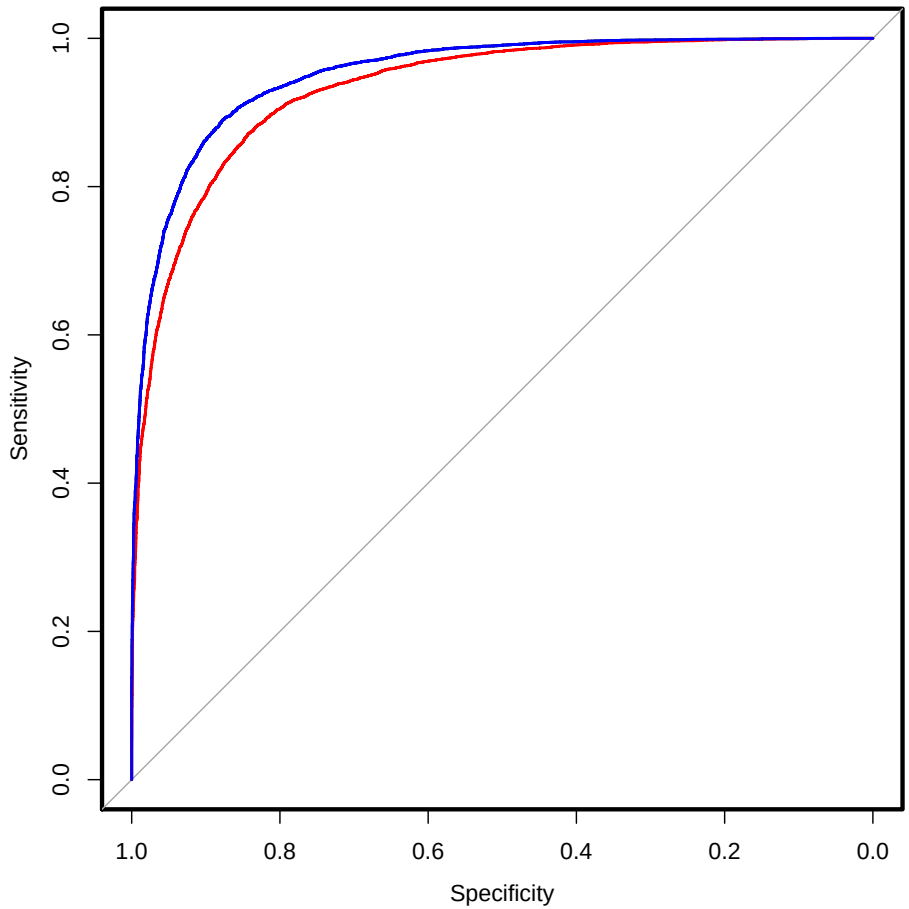
$\beta_{0P} = \beta_{0D} = \beta_{PD} = 0.67$



$S_{-}OS = 1, PFS = 1$, $S_{+}: OS = 0.67, PFS = 0.67$, $RE = 1$

$w^2_{0P} = 1/2$, $w^2_{0D} = 1/2$, $w^2_{PD} = 0$

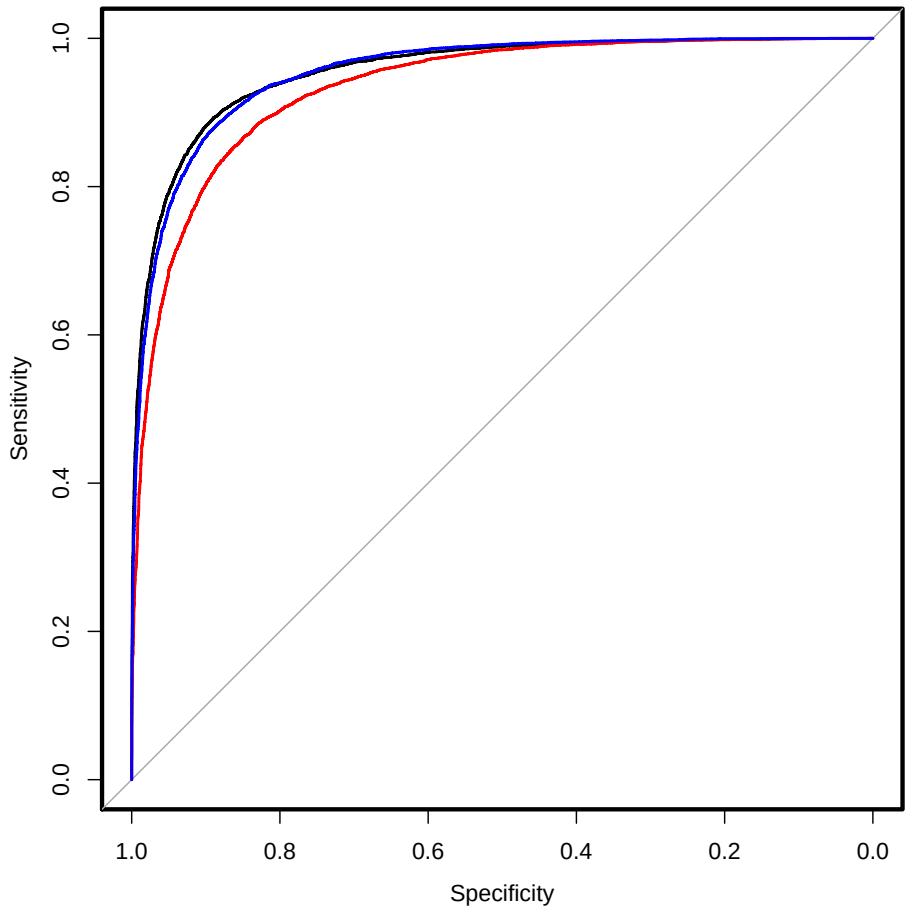
$\beta_{0P} = \beta_{0D} = \beta_{PD} = 0.67$



$S_{-}OS = 1, PFS = 1$, $S_{+}: OS = 0.67, PFS = 0.67$, $RE = 1$

$w^2_{0P} = 0.2$, $w^2_{0D} = 0.4$, $w^2_{PD} = 0.4$

$\beta_{0P} = \beta_{0D} = \beta_{PD} = 0.67$



Conclusion

- Improvement over both OS and PFS possible even when PFS is perfect surrogate
- Weights control how much OS or PFS data is used
- Multistate Log-rank test
  - Easily implemented with existing software
  - Independent increments
  - Sample size calculation possible (non-centrality parameter easy to calulate)

References

- B. Engel and P. Walstra. Increasing Precision or Reducing Expense in Regression Experiments by Using Information from a Concomitant Variable. *Biometrics*, 1991
- S. W. Lagakos. Using auxiliary variables for improved estimates of survival time. *Biometrics*, 33(2):399–404, June 1977.
- R. J. Cook and J. F. Lawless. Some comments on efficiency gains from auxiliary information for right-censored data. *Journal of Statistical Planning and Inference*, 96(1):191–202, June 2001.
- Hsieh, F. Y. and Crowley, John and Tormey, Douglass C. Some test statistics for use in multistate survival analysis. *Biometrika*, 1983