

Statistical validation of surrogate outcome measures

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Surrogate outcome measures?

Lagakos SW, Hoth DF. Surrogate markers in AIDS: Where are we? Where are we going? *Ann Intern Med* 1992; 116: 599.

Fleming TR, DeMets DL. Surrogate end points in clinical trials: are we being misled? *Ann Intern Med* 1996; 125: 605.

DeGruttola V, Fleming TR, Lin DY, Coombs R. Validating surrogate markers – are we being naive? *J Infectious Dis* 1997; 175: 237.

Baker SJ. Surrogate endpoints: wishful thinking or reality? *J Natl Cancer Inst* 2006; 98 : 502.

Berger VW. Does the Prentice criterion validate surrogate endpoints? *Statist in Med* 2004; 23: 1571.

Burzykowski T. Surrogate endpoints: wishful thinking or reality? *Statist Meth Med Res* 2008; 917: 463.

Surrogate outcome measures?

The researches of many commentators have already thrown much darkness on this subject, and it is probable that if they continue, we shall soon know nothing at all about it.

Mark Twain

*For the
mathematically
inclined...*

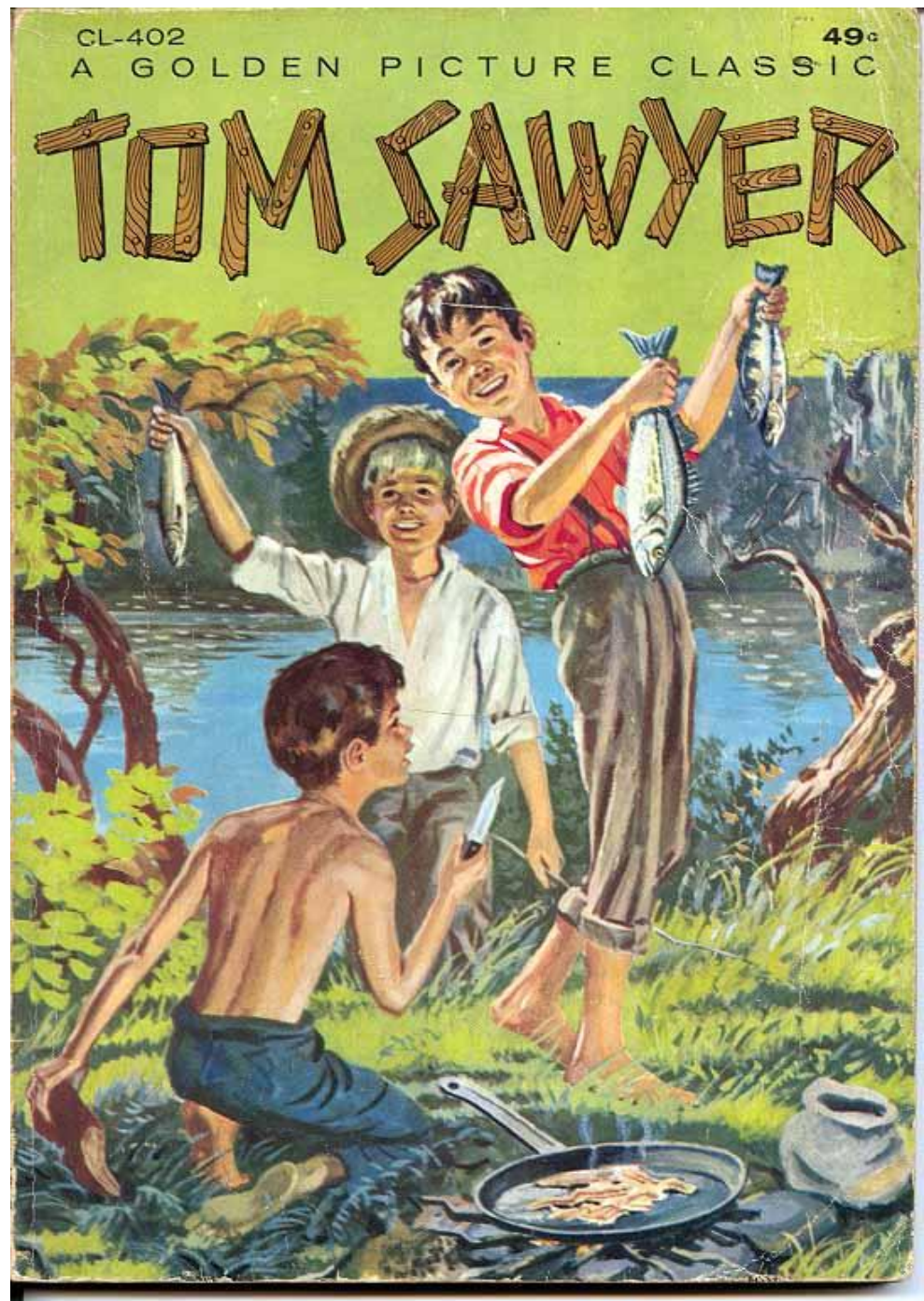
Statistics for Biology and Health

**Tomasz Burzykowski
Geert Molenberghs
Marc Buyse**
Editors

**The Evaluation
of Surrogate
Endpoints**

 Springer

*For the
others...*



Interest in surrogate endpoints / markers

- Feasibility / practicality of trials:
 - Shorter duration
 - Smaller sample size
 - Lower cost
- Availability of biomarkers that are potential surrogates:
 - Countless tissue, cellular, and hormonal factors
 - Advanced imaging techniques
 - Genomics, proteomics, metabolomics, other-ics

Outline

1. Capture of effect in a single randomized trial
2. Association measures in meta-analyses
3. Prediction
4. Causal inference
5. Conclusions

1. Capture of effect in a single randomized trial
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The single trial framework

Randomized
treatment



Biomarker or intermediate
endpoint, potential surrogate

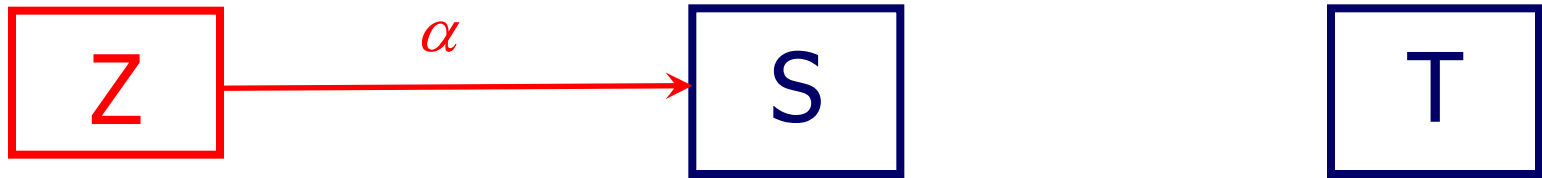


True clinical
endpoint

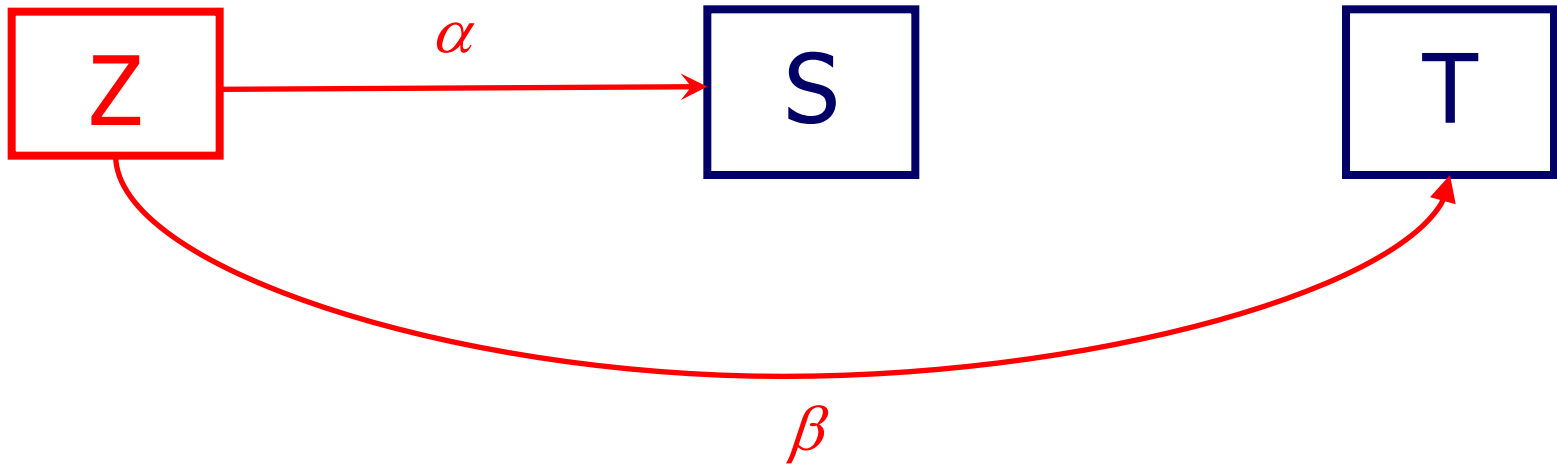


Parameters of interest

Effect of treatment on surrogate

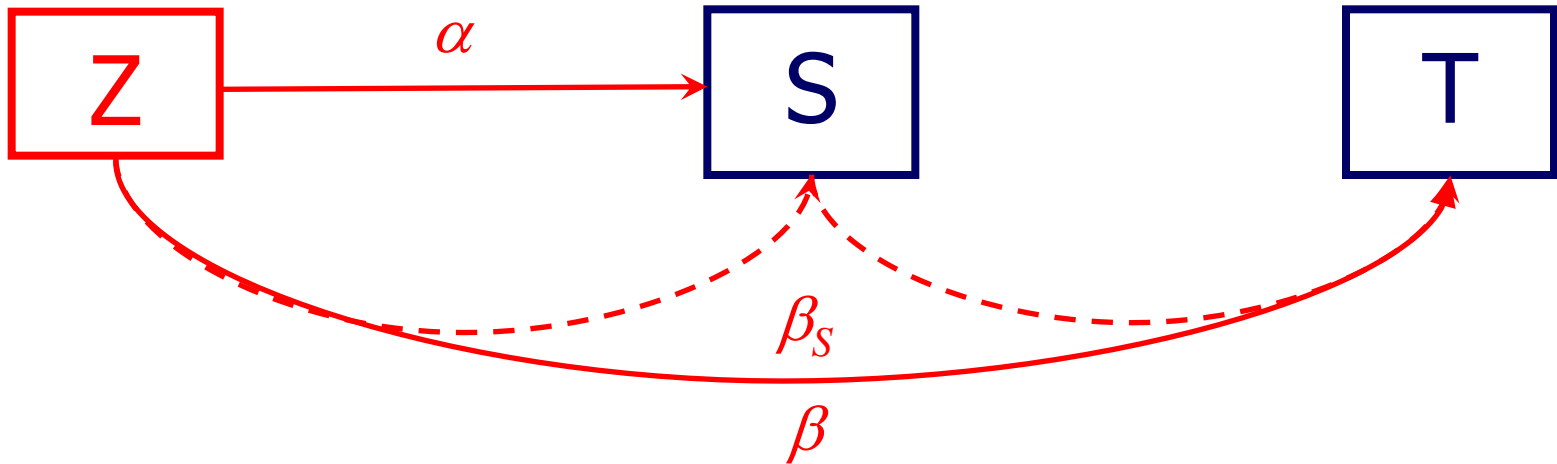


Parameters of interest



Effect of treatment on true endpoint

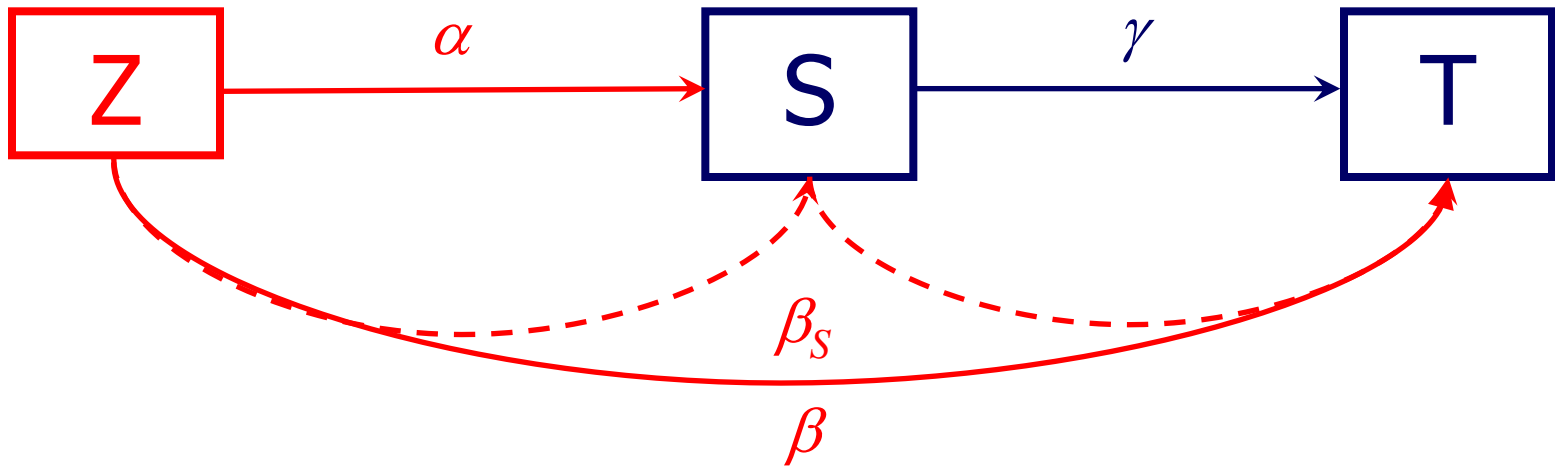
Parameters of interest



Effect of treatment on true endpoint,
adjusted for the surrogate

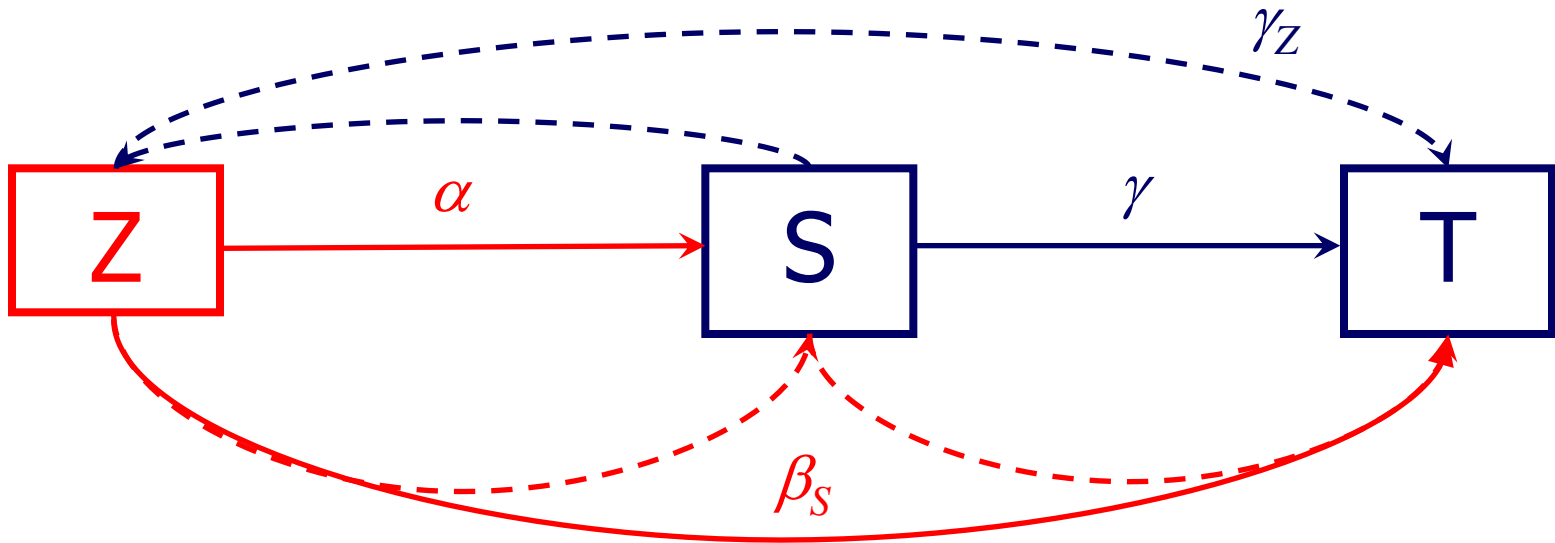
Parameters of interest

Effect of surrogate on true endpoint



Parameters of interest

Effect of surrogate on true endpoint,
adjusted for treatment



Correlation of endpoints is not enough

Key point: *“A correlate does not a surrogate make”*

⇒ A test of

$$H_0: \gamma_Z = 0$$

is not sufficient to establish validity

Refs: Fleming and DeMets, *Ann Intern Med* 1996, 125: 605
Biomarkers Definition Working Group, *Clin Pharmacol Ther* 2001, 69: 89.

A first set of criteria

A marker or endpoint can be used as a surrogate if

- it predicts the final endpoint:

$$H_0: \gamma_Z = 0$$

- it **fully captures** the effect of treatment upon the final endpoint:

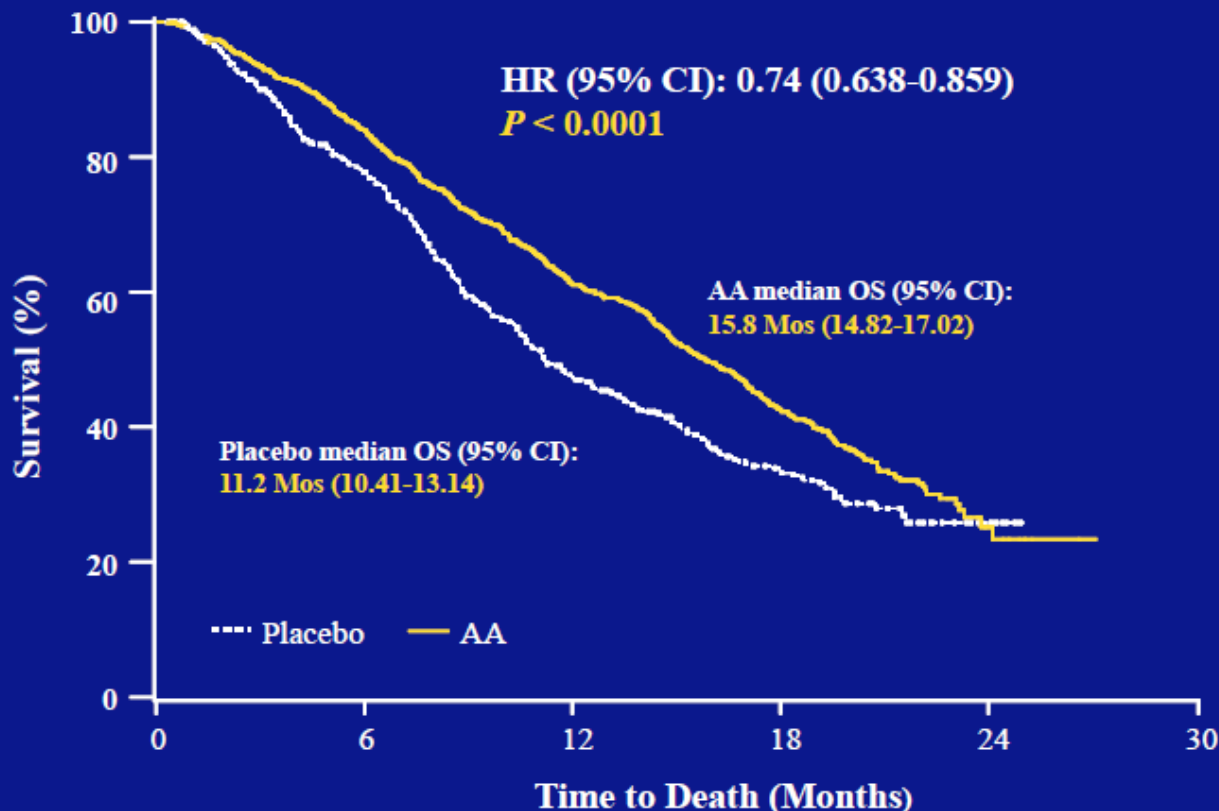
$$H_0: \beta = 0 \text{ and } H_0: \beta_S \neq 0$$

An example of Prentice's approach

- Circulating tumor cells were measured among patients with metastatic castration-resistant prostate cancer.
- Patients randomized between abiraterone prednisone and placebo prednisone after failure of chemotherapy.
- CTC counts were taken at baseline, 4, 8 and 12 weeks after starting therapy.
- CTC conversion refers to a baseline count ≥ 5 cells and a count under treatment < 5 cells.

Phase III trial in metastatic prostate cancer

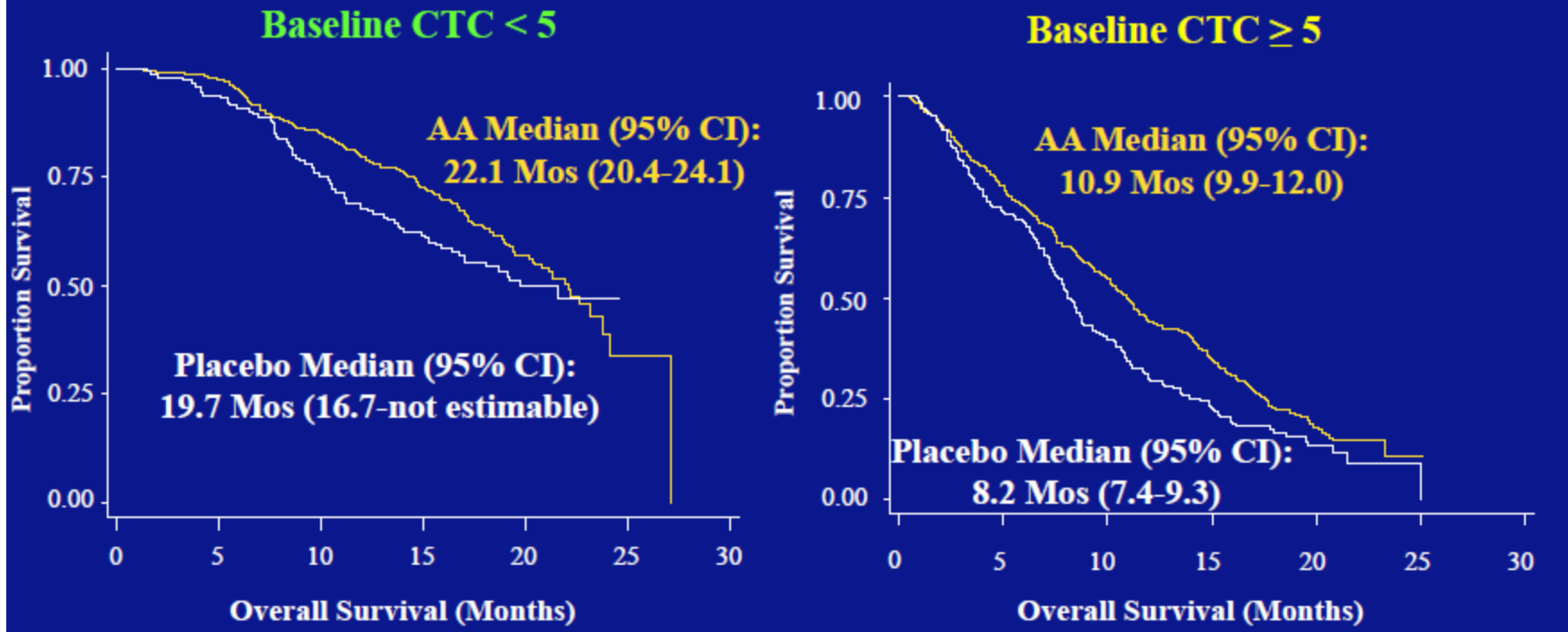
Second/Preplanned Analysis (775 Events): the Median OS Benefit of AA Increased From 3.9 to 4.6 Months



AA	797	657	473	273	15	0
Placebo	398	306	183	100	6	0

CTC counts are prognostic but not predictive

AA Improves Overall Survival in Patients with Favorable and Unfavorable CTC Counts at Baseline



Model for treatment effect on overall survival

Treatment, Baseline LDH and CTC Count Were Prognostic for Survival in the Multivariate Model While PSA Was Not

	Baseline (n = 949, CPE = 0.70 [SE = 0.008])	
Biomarker	HR (95% CI)	p Value
Treatment	0.70 (0.59, 0.828)	< 0.0001
LDH	2.98 (2.496, 3.565)	< 0.0001
CTC count	1.19 (1.137, 1.245)	< 0.0001
Hgb	0.95 (0.891, 1.001)	0.0574
ALP	0.98 (0.874, 1.097)	0.7218
PSA	1.04 (0.983, 1.093)	0.1797

PSA, prostate-specific antigen; Hgb, hemoglobin; LDH, lactase dehydrogenase; ALP, alkaline phosphatase.

Is CTC conversion a surrogate endpoint?

Indication That The Treatment Effect on Survival Is Well Explained by the Biomarker Panel with CTC and LDH

Baseline CTC ≥ 5		
	Week 12 (n = 321, CPE = 0.71 [SE = 0.014])	
Model Factors	HR (95% CI)	p Value
Treatment	1.030 (0.773, 1.372)	0.8371
LDH_FC	1.252 (1.047, 1.497)	0.0135
LDH_BL	3.036 (2.276, 4.048)	<0.0001
CTC Conversion	0.386 (0.284, 0.527)	<0.0001
CTC_BL	1.135 (0.987, 1.306)	0.0747

Landmark analysis;
BL, Baseline;

CTC Conversion: Baseline ≥ 5 and post-baseline < 5 ;
FC, Fold change defined as post-baseline/baseline value.

Is CTC conversion a surrogate endpoint?

The Prentice criteria are fulfilled by CTC conversion:

- Highly significant prognostic impact of CTC conversion on OS:

$$\gamma_Z = \log(0.386) = -0.95 \quad (P < 0.0001)$$

- Highly significant treatment effect on OS:

$$\beta = \log(0.7) = -0.36 \quad (P < 0.0001)$$

- No treatment effect on OS after adjustment for CTC conversion:

$$\beta_S = \log(1.03) = 0.03 \quad (P = 0.83)$$

Yet, do these results provide convincing evidence that CTC conversion is a valid surrogate for OS?

Problems with Prentice's approach

- Requires significant treatment effects on surrogate and true endpoints
- Rooted in hypothesis testing (impossible to prove the null $H_0: \beta_S \neq 0$ in finite samples)
- Does not quantify the predictive ability of a surrogate

The proportion explained

The proportion explained is defined as

$$PE = 1 - \frac{\beta_S}{\beta}$$

For a good surrogate, $PE \cong 1$

Problems with the proportion explained

- Confidence limits for PE are wide
- PE is not a proportion
- PE can lie anywhere on the real line !

*Refs: Lin et al, Stat in Med 1997, 16: 1515;
Buyse and Molenberghs, Biometrics 1998, 54: 1014.*

Beyond the proportion explained

The proportion explained can be re-expressed as

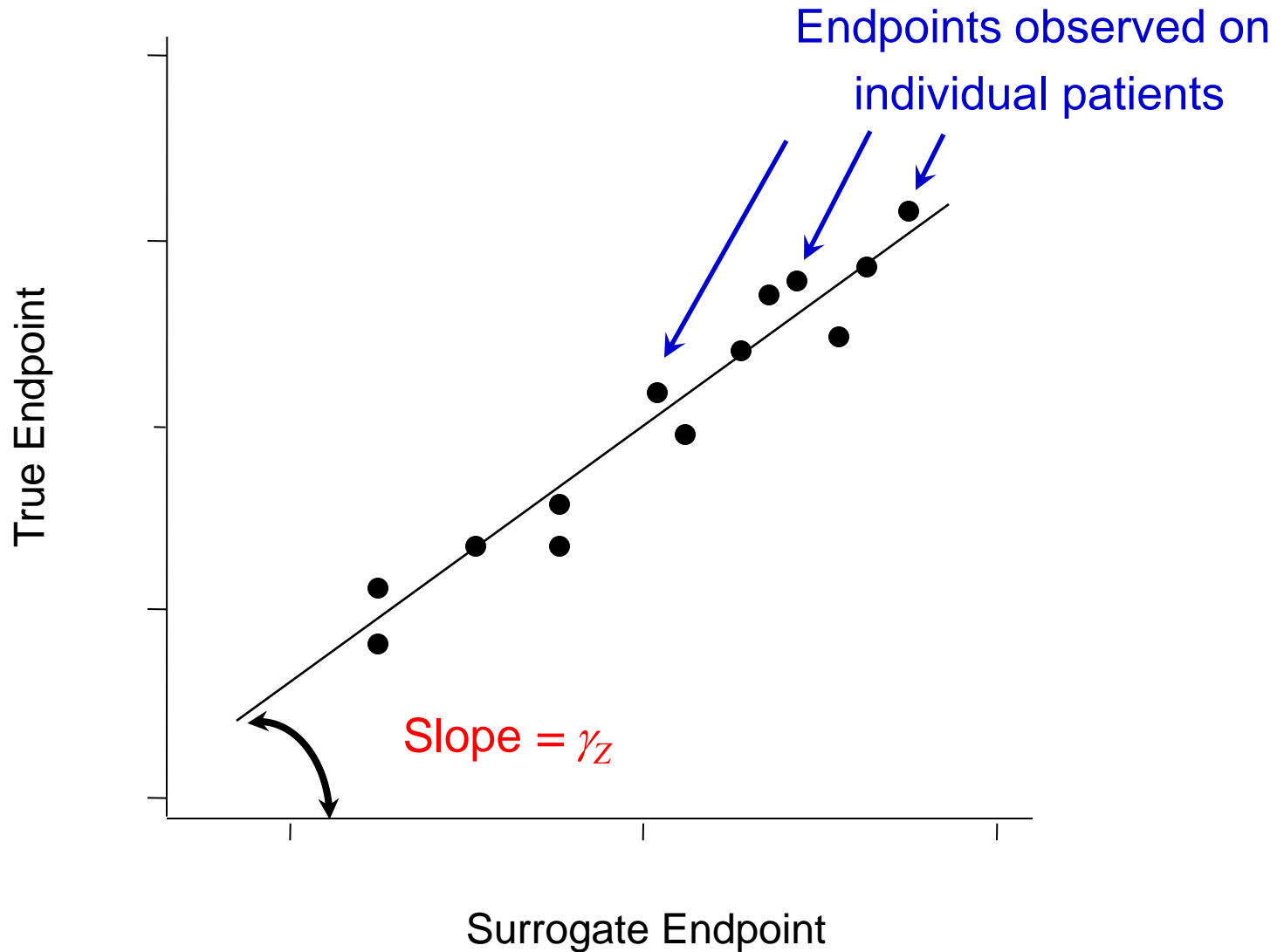
$$PE = \lambda \cdot \frac{\gamma_Z}{RE}$$

where RE is the relative effect and λ^2 a ratio of variances

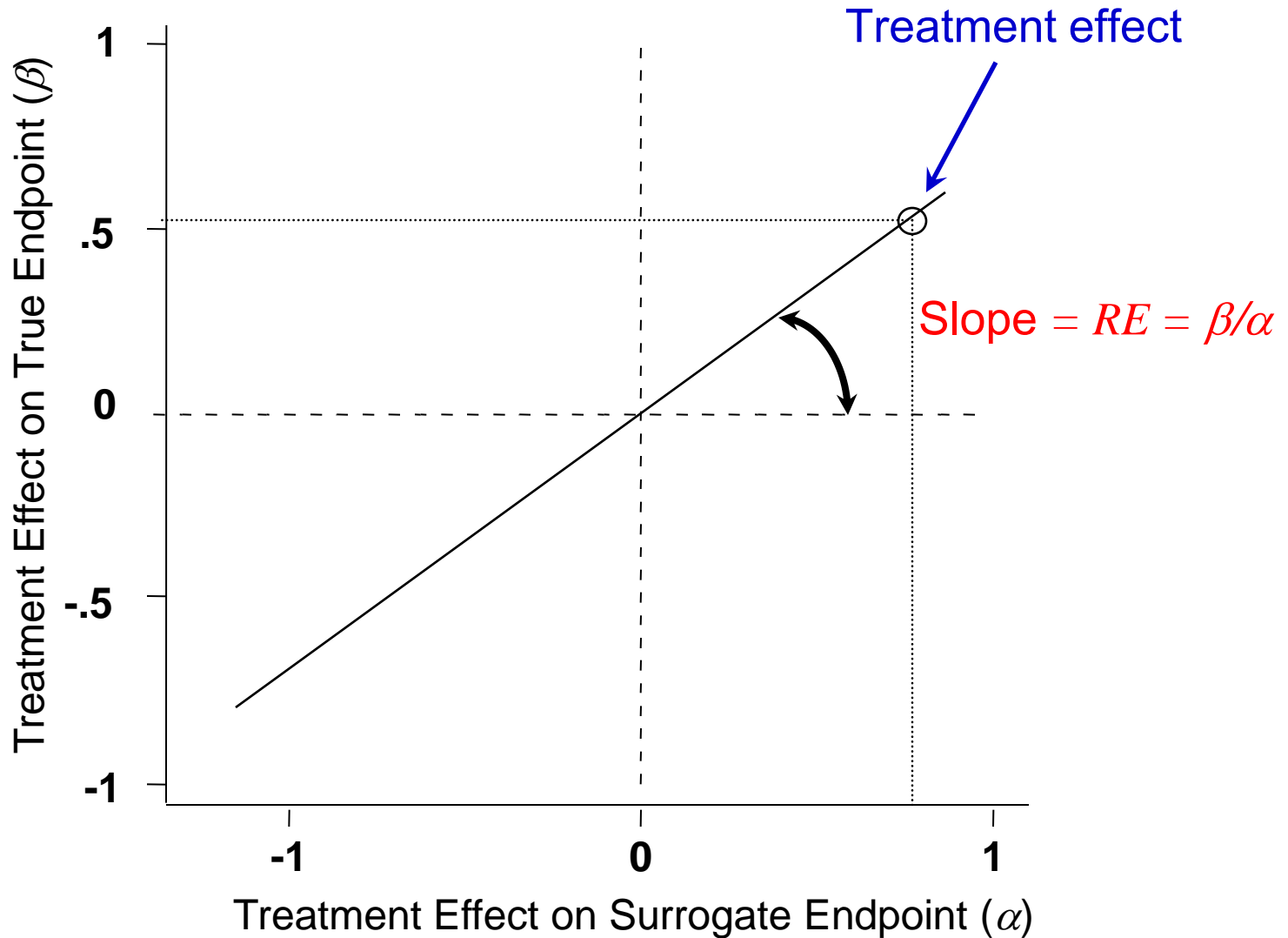
$$RE = \frac{\beta}{\alpha}$$

$$\lambda^2 = \frac{\sigma_{TT}}{\sigma_{SS}}$$

Prediction of true endpoint from surrogate endpoint



Prediction of treatment effect (regression through the origin !)



Need for multiple trials

For a marker to be used as a surrogate, we need
*“repeated demonstrations of a strong correlation
between the marker and the clinical outcome”*.

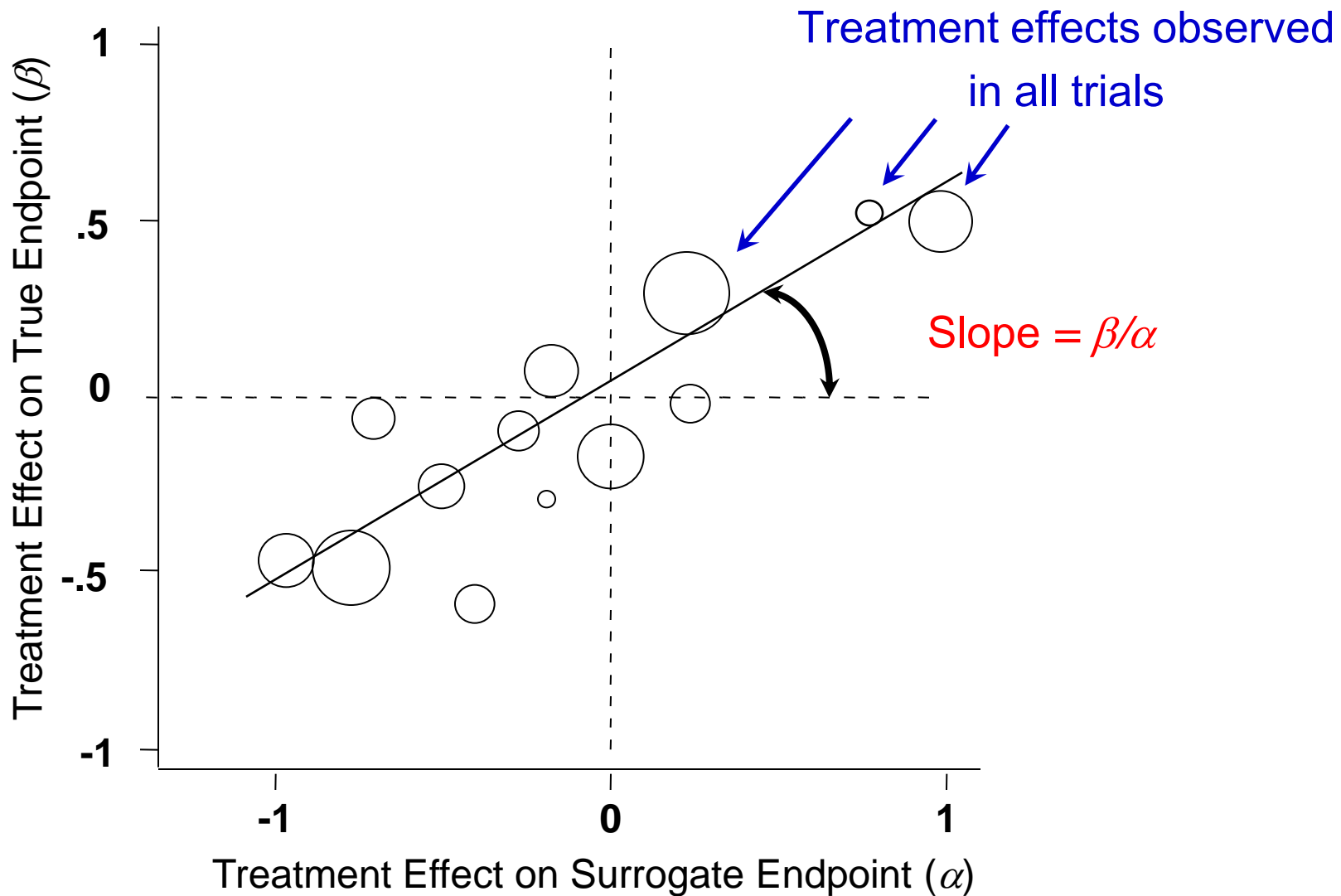
And,

*“there has been little work on alternative statistical
approaches. A meta-analysis approach seems
desirable to reduce variability”*.

Refs: Holland, 9th EUFEPS Conference on “Optimising Drug Development:
Use of Biomarkers”, Basel, 2001;
Albert et al, Stat in Med 1998, 17: 2435.

1. Capture of effect in a single randomized trial
2. **Association measures in meta-analyses**
3. Prediction
4. Causal inference

Prediction of treatment effect: multiple trials



Measures of association at two levels

At the individual level, correlation between the endpoints (generalizes γ_Z)

$$R_{\text{indiv}}^2$$

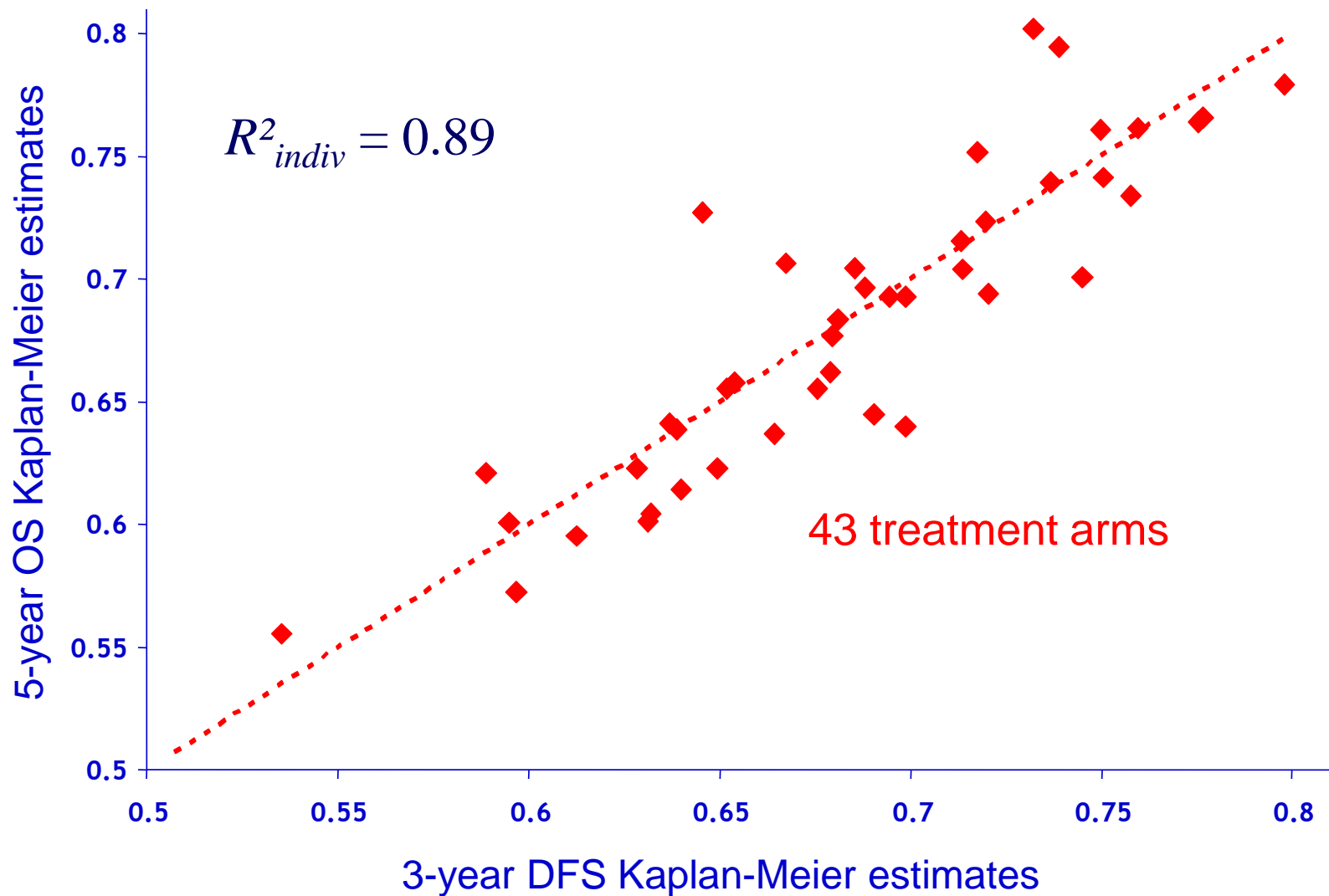
At the trial level, correlation between the treatment effects on the endpoints

$$R_{\text{trial}}^2$$

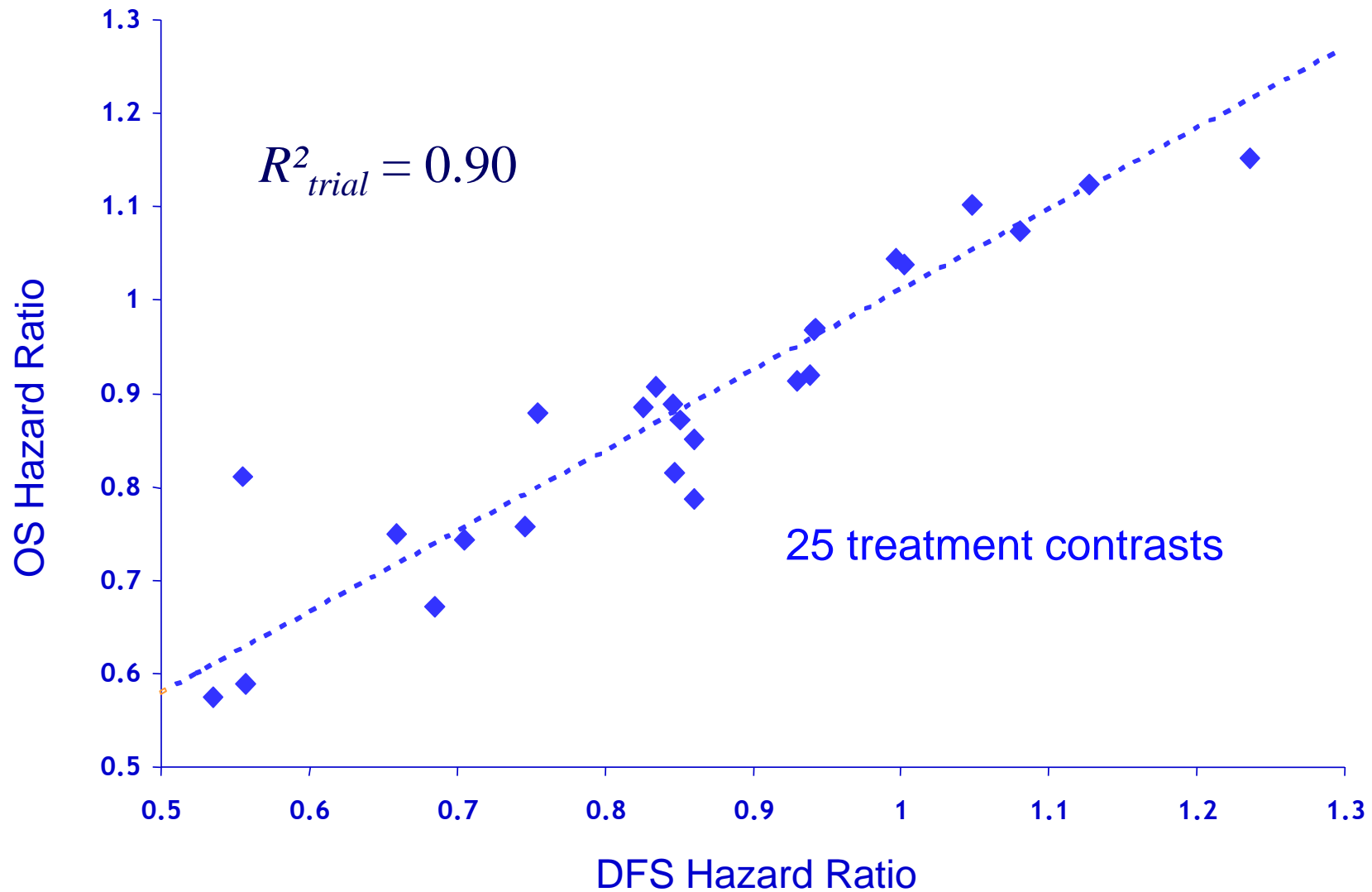
Early colorectal cancer : DFS as a surrogate for OS

- Patients with early colorectal cancer, after resection of primary tumor
- Units of analysis : 20,898 patients in 18 randomized trials (25 treatment contrasts)
- Treatments: 5FU-based therapy vs. control or another 5FU-based therapy (43 treatment arms)
- Surrogate endpoint: disease-free survival (DFS)
- True endpoint: survival (OS)

Correlation between endpoints



Correlation between treatment effects



1. Capture of effect in a single randomized trial
2. Association measures in meta-analyses
- 3. Prediction**
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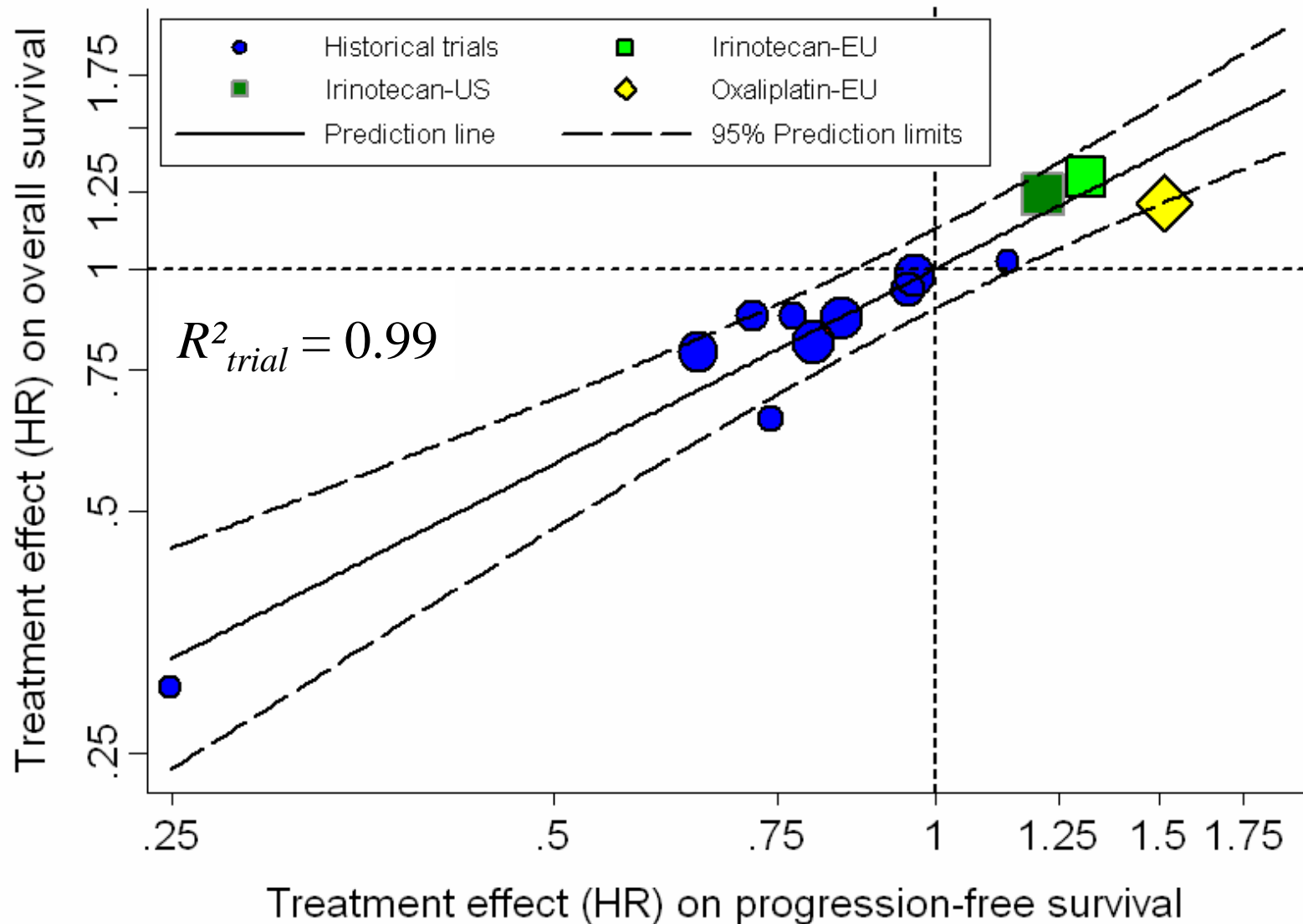
The “Surrogate Threshold Effect” (STE)

The “Surrogate Threshold Effect” is the treatment effect on the surrogate that would predict a statistically significant treatment effect on the true endpoint.

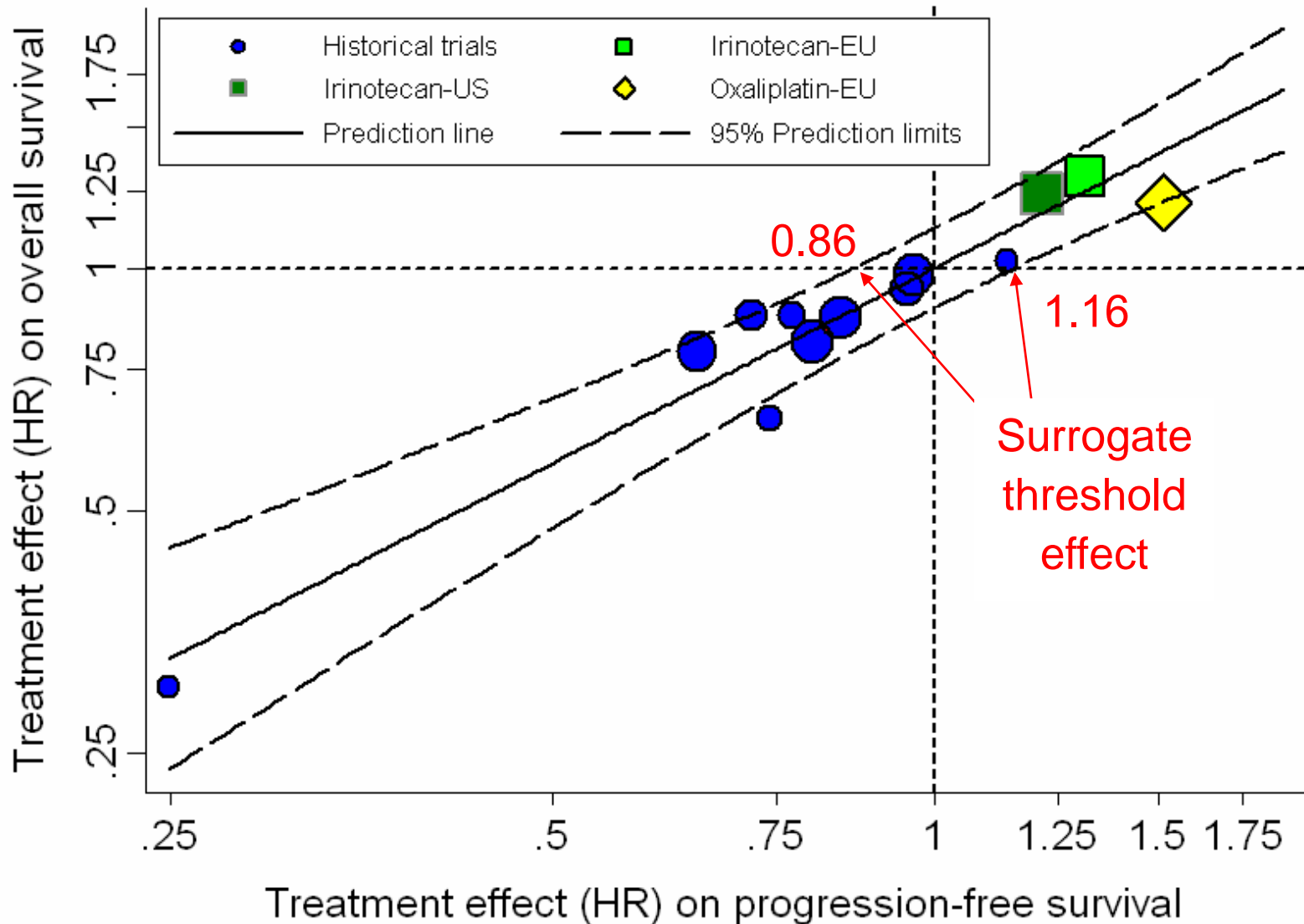
Advanced colorectal cancer: PFS as a surrogate for OS

- Patients with advanced (metastatic) colorectal cancer
- Units of analysis: 4,352 patients in 13 trials
- Treatments (5FU/LV common arm):
 - 10 historical trials
5FU vs. 5FU/L
 - 3 validation trials
oxaliplatin or irinotecan + 5FU/LV vs. 5FU/LV
- Surrogate endpoint: PFS
- True endpoint: OS

Correlation between treatment effects



The “Surrogate Threshold Effect” (STE)



1. Capture of effect in a single randomized trial
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Return to early colorectal cancer

Randomized treatment	Z	0	Control (no treatment or standard chemotherapy)
		1	Experimental chemotherapy
Surrogate endpoint: DFS at 3 years	S	0	Recurrent disease or death within 3 years
		1	Alive without recurrence at 3 years
True endpoint: OS at 5 years	T	0	Dead within 5 years
		1	Alive at 5 years

Counterfactual outcomes

Each subject has four *potential outcomes*, denoted $T_i(0)$ and $T_i(1)$ for the true endpoint, and $S_i(0)$ and $S_i(1)$ for the surrogate endpoint.

Subject	Z	$T(0)$	$T(1)$	$S(0)$	$S(1)$
1	0	1	?	1	?
2	1	?	1	?	1
3	1	?	0	?	0
4	0	0	?	1	?
5	1	?	1	?	1
...					

Counterfactual probabilities

Denote p_{11} to p_{44} the counterfactual probabilities :

	$(T(0), T(1))$			
$(S(0), S(1))$	$(0,0)$	$(0,1)$	$(1,1)$	$(1,0)$
$(0,0)$	p_{11}	p_{12}	p_{13}	p_{14}
$(0,1)$	p_{21}	p_{22}	p_{23}	p_{24}
$(1,1)$	p_{31}	p_{32}	p_{33}	p_{34}
$(1,0)$	p_{41}	p_{42}	p_{43}	p_{44}

Principal stratification

Frangakis and Rubin (*Biometrics* 2002) define the *principal stratification* for the surrogate endpoint:

$(S(0), S(1))$	$(T(0), T(1))$				Principal stratification
	$(0,0)$	$(0,1)$	$(1,1)$	$(1,0)$	
$(0,0)$	p_{11}	p_{12}	p_{13}	p_{14}	Never responders
$(0,1)$	p_{21}	p_{22}	p_{23}	p_{24}	Improved
$(1,1)$	p_{31}	p_{32}	p_{33}	p_{34}	Always responders
$(1,0)$	p_{41}	p_{42}	p_{43}	p_{44}	Harmed

Principal surrogate

For a good surrogate, subjects who are improved (or harmed) on the surrogate must also be improved (or harmed) on the true endpoint

		$(T(0), T(1))$			
$(S(0), S(1))$	(0,0)	(0,1)	(1,1)	(1,0)	Principal stratification
(0,0)	p_{11}	p_{12}	p_{13}	p_{14}	Never responders
(0,1)	p_{21}	p_{22}	p_{23}	p_{24}	Improved
(1,1)	p_{31}	p_{32}	p_{33}	p_{34}	Always responders
(1,0)	p_{41}	p_{42}	p_{43}	p_{44}	Harmed

For a « principal » surrogate, p_{22} / p_{2+} and p_{44} / p_{4+} must be close to 1 (p_{i+} denotes the number of subjects in principal stratum i).

Associative proportion

Surrogate associative proportion: $(p_{22} + p_{42} - (p_{24} + p_{44})) / (p_{2+} - p_{4+})$

Associative proportion: $(p_{22} + p_{42} - (p_{24} + p_{44})) / (p_{+2} - p_{+4})$

		$(T(0), T(1))$				
$(S(0), S(1))$	$(0,0)$	$(0,1)$	$(1,1)$	$(1,0)$	Principal stratification	
$(0,0)$	p_{11}	p_{12}	p_{13}	p_{14}	Never responders	
$(0,1)$	p_{21}	p_{22}	p_{23}	p_{24}	Improved	
$(1,1)$	p_{31}	p_{32}	p_{33}	p_{34}	Always responders	
$(1,0)$	p_{41}	p_{42}	p_{43}	p_{44}	Harmed	

Associative proportion assuming monotonicity

Surrogate associative proportion: p_{22} / p_{2+}

Associative proportion: p_{22} / p_{+2}

		$(T(0), T(1))$			
$(S(0), S(1))$	$(0,0)$	$(0,1)$	$(1,1)$	$(1,0)$	Principal stratification
$(0,0)$	p_{11}	p_{12}	p_{13}	0	Never responders
$(0,1)$	p_{21}	p_{22}	p_{23}	0	Improved
$(1,1)$	p_{31}	p_{32}	p_{33}	0	Always responders
$(1,0)$	0	0	0	0	Harmed

Note: $p_{i4} = 0 \forall i$ and $p_{4j} = 0 \forall j$

Early colorectal cancer

Surrogate associative proportion = .54 (-1.33; 2.19)

Associative proportion = .83 (-2.02; 3.19)

$(S(0), S(1))$	$(T(0), T(1))$				Principal stratification
	$(0,0)$	$(0,1)$	$(1,1)$	$(1,0)$	
$(0,0)$.259	.001	.026	.001	Never responders
$(0,1)$.001	.011	.021	.000	Improved
$(1,1)$.021	.014	.619	.011	Always responders
$(1,0)$.001	.000	.014	.001	Harmed

Early colorectal cancer with monotonicity

Surrogate associative proportion, $p_{22} / p_{2+} = .10$ (.00 - .50)

Associative proportion, $p_{22} / p_{+2} = .12$ (.00 - .64)

		$(T(0), T(1))$			
$(S(0), S(1))$	(0,0)	(0,1)	(1,1)	(1,0)	Principal stratification
(0,0)	.259	.003	.037	0	Never responders
(0,1)	.003	.002	.012	0	Improved
(1,1)	.029	.008	.647	0	Always responders
(1,0)	0	0	0	0	Harmed

Note: $p_{i4} = 0 \forall i$ and $p_{4j} = 0 \forall j$

Problems with causal inference

- Estimation of counterfactual probabilities through complex model (e.g. Bayesian)
- Results sensitive to restrictive assumptions (e.g. monotonicity)
- Poor estimates (large confidence intervals)
- No agreed upon measure of surrogacy
- Without monotonicity, the net associative proportion is a ratio of differences; its values span $[-\infty, +\infty]$

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Conclusions

- There are no absolute standards for surrogacy
- Even so, some intermediate endpoints (DFS, PFS in colorectal cancer) or biomarkers (CTCs in prostate cancer) have undergone « validation »
- Principal surrogacy is more principled than statistical surrogacy, but causal inference is challenging
- Large sets of randomized data are required (typically, meta-analyses of RCTs)
- If a surrogate is shown valid under specific conditions (treatment / environment), is it still valid under different conditions (e.g. an experimental treatment)?
- Good (let alone perfect) surrogates are hard to find!

Surrogate outcome measures?

Get your facts first, and then you can distort them as much as you please.

Mark Twain