Surrogate Enpoints Validation in Oncology

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Outline

- Definitions & reminders
- Simple situation (normally distributed endpoints)
- More complex situations
- Case studies in advanced colorectal cancer
  - *Response / survival*
  - *PFS / survival*
- Remarks and conclusions

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; it is expected to predict clinical benefit (or harm or lack of benefit or harm).

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

Endpoints

- Endpoint of interest (*T*): true endpoint
  - Overall survival, myocardial infarction, ...
  - Can be difficult to use in a trial (long follow-up, costly to measure, rare event, …)

- Replacement (*S*): surrogate endpoint
  - Easier/quicker to measure or observe
  - Might reduce the duration, size and/or cost of trial
  - Should be “valid”

*Ref: Fleming and DeMets, Ann Intern Med 1996;**125**:605.*

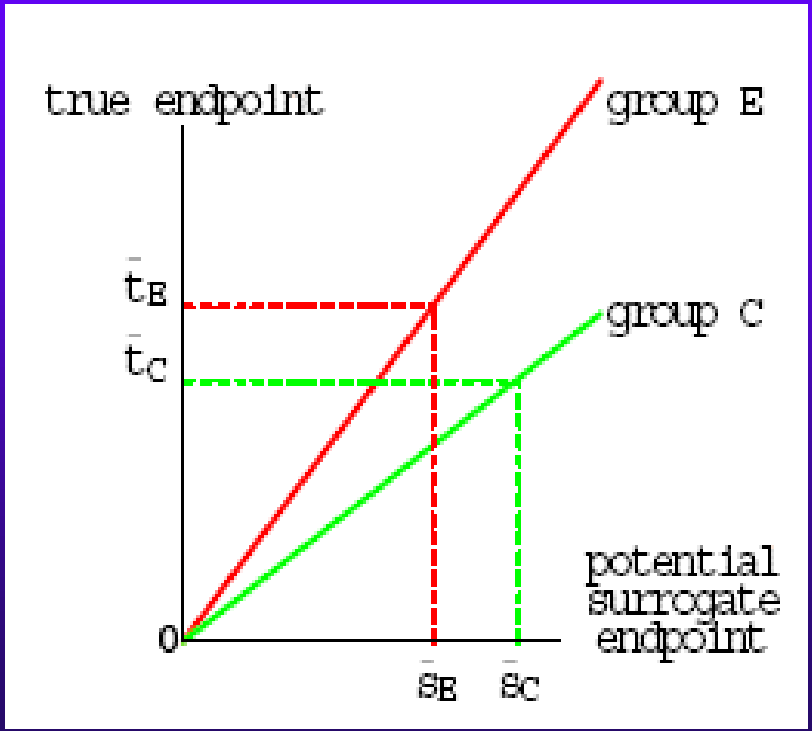
Why To Use Surrogates?

- Practicality of studies:
  - Size
  - Duration
  - Cost
- Availability of biomarkers:
  - Genomics / proteomics
  - Imaging techniques
  - Tissue, cellular, hormonal factors, etc.

*Ref: Schatzkin and Gail, Nature Reviews (Cancer) 2001;**3**:19-27*

When is a Biomarker a Good Surrogate?

- A strong correlation between the biomarker and the clinical endpoint is not sufficient (or even necessary ?).



*Ref: Baker & Kramer, BMC Medical Research Methodology 2003;**3**.*

When is a Biomarker a Good Surrogate?

- There must be evidence that the biomarker predicts the (effect of treatment upon the) clinical endpoint, based on
  - epidemiological
  - pathophysiological
  - biological
  - statistical evidence.

- What kind of *statistical* evidence do we need?

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

Statistical Validation of Surrogate Endpoints

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

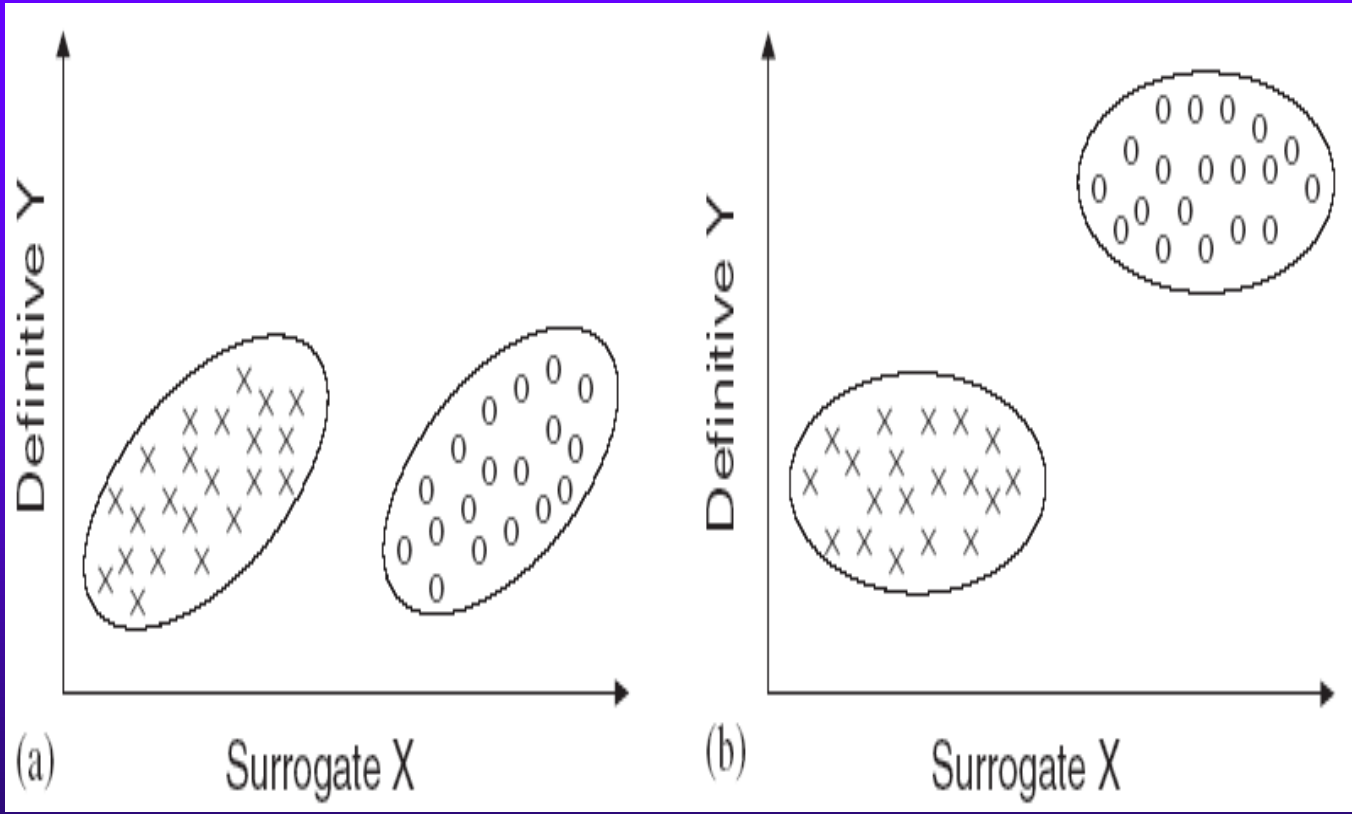
*Ref: Biomarkers Definitions Working Group, Clin Pharmacol Ther 2001;**69**:89.*

Two Levels of Surrogacy

- Individual-level: the biomarker predicts the clinical endpoint
- Trial-level: treatment effect on the biomarker allows reliable prediction of the effect of treatment upon the true endpoint

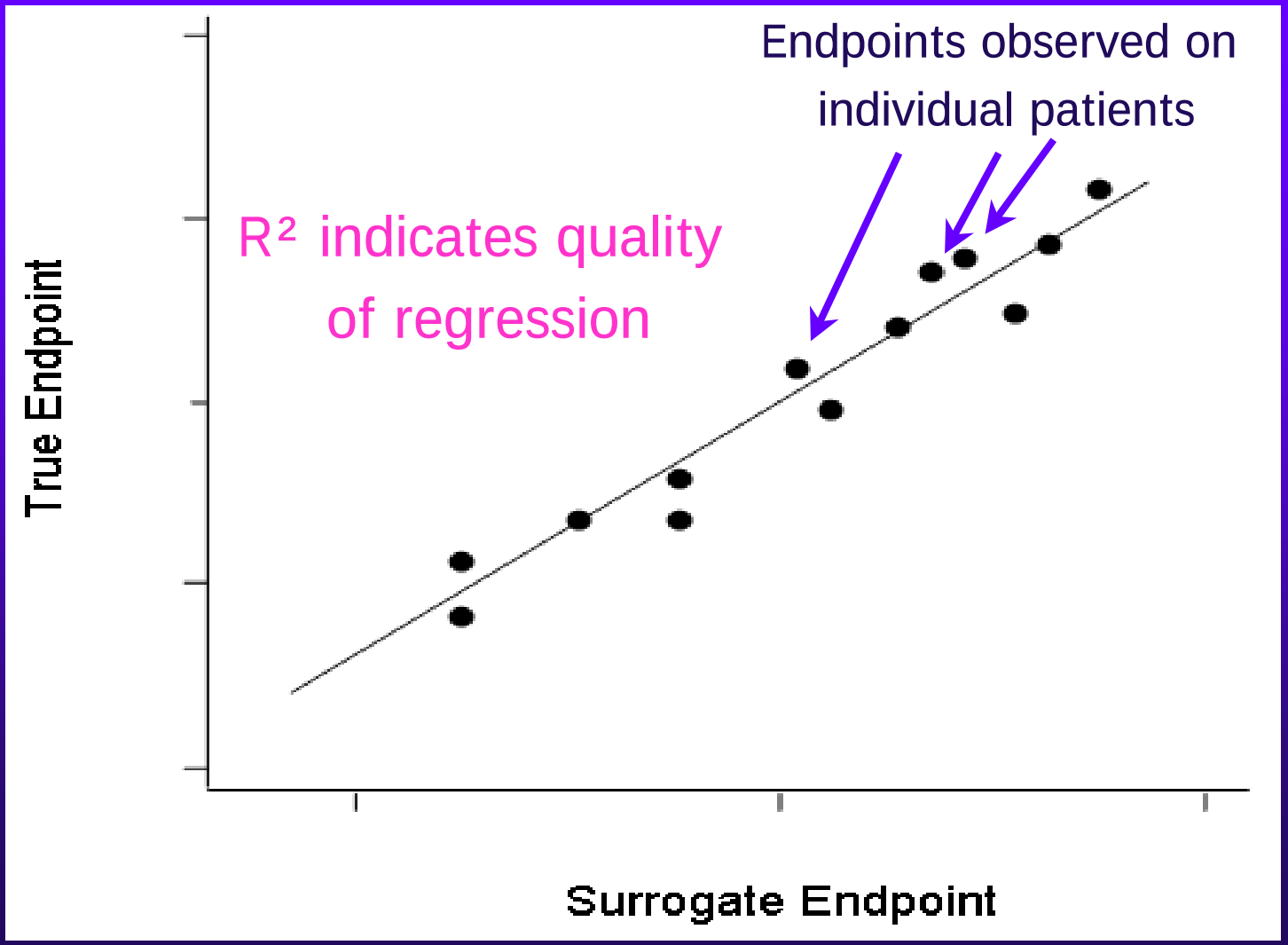
*Ref: Buyse and Molenberghs, Biometrics 1998;**54**:1014.*

Individual- & Trial-Level Surrogacy Can Be Different

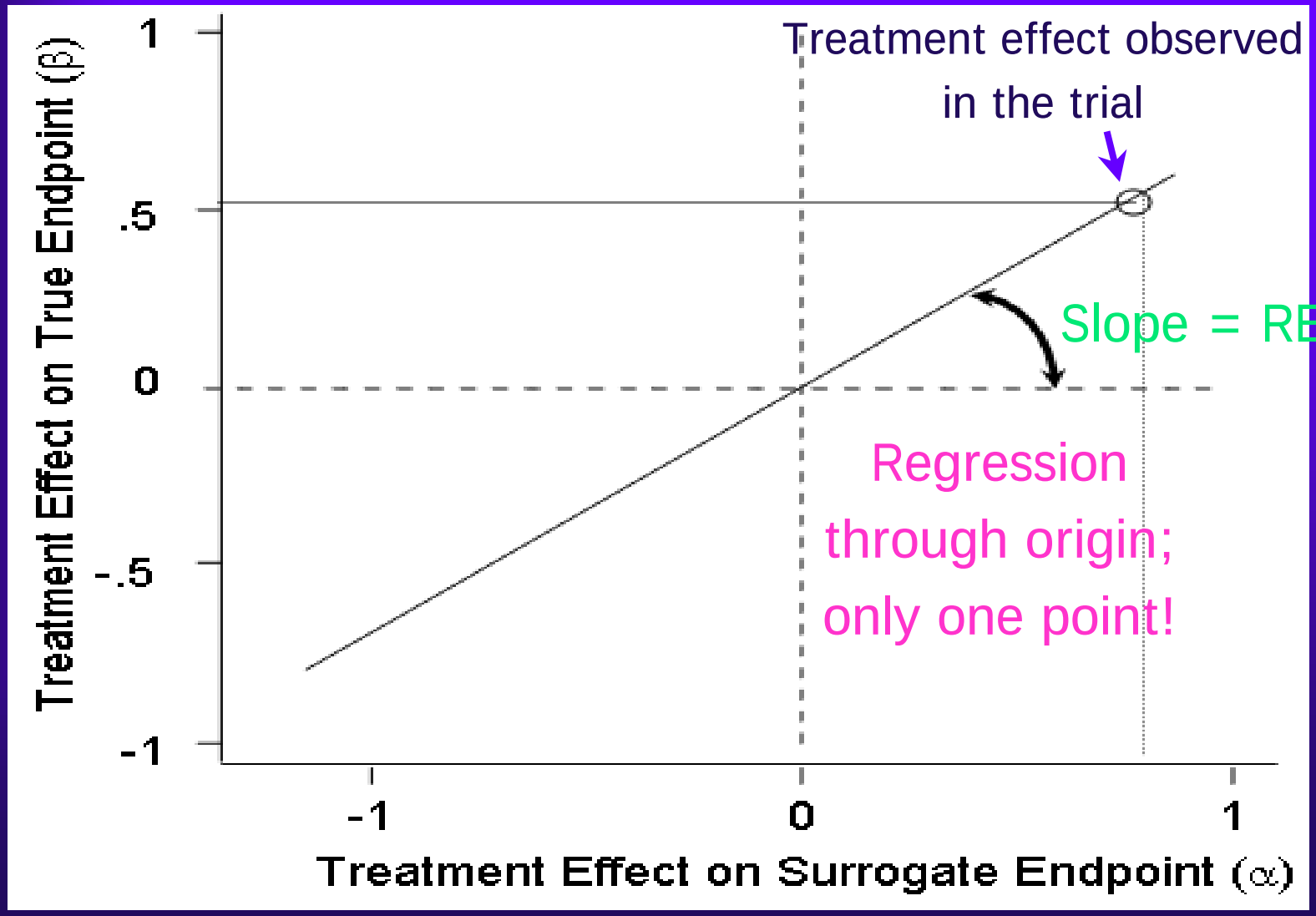


*Ref: Korn, Albert & McShane, Statist Med 2005;**24**:163.*

Prediction of True Endpoint From Surrogate Endpoint



Prediction of Treatment Effect: One Trial

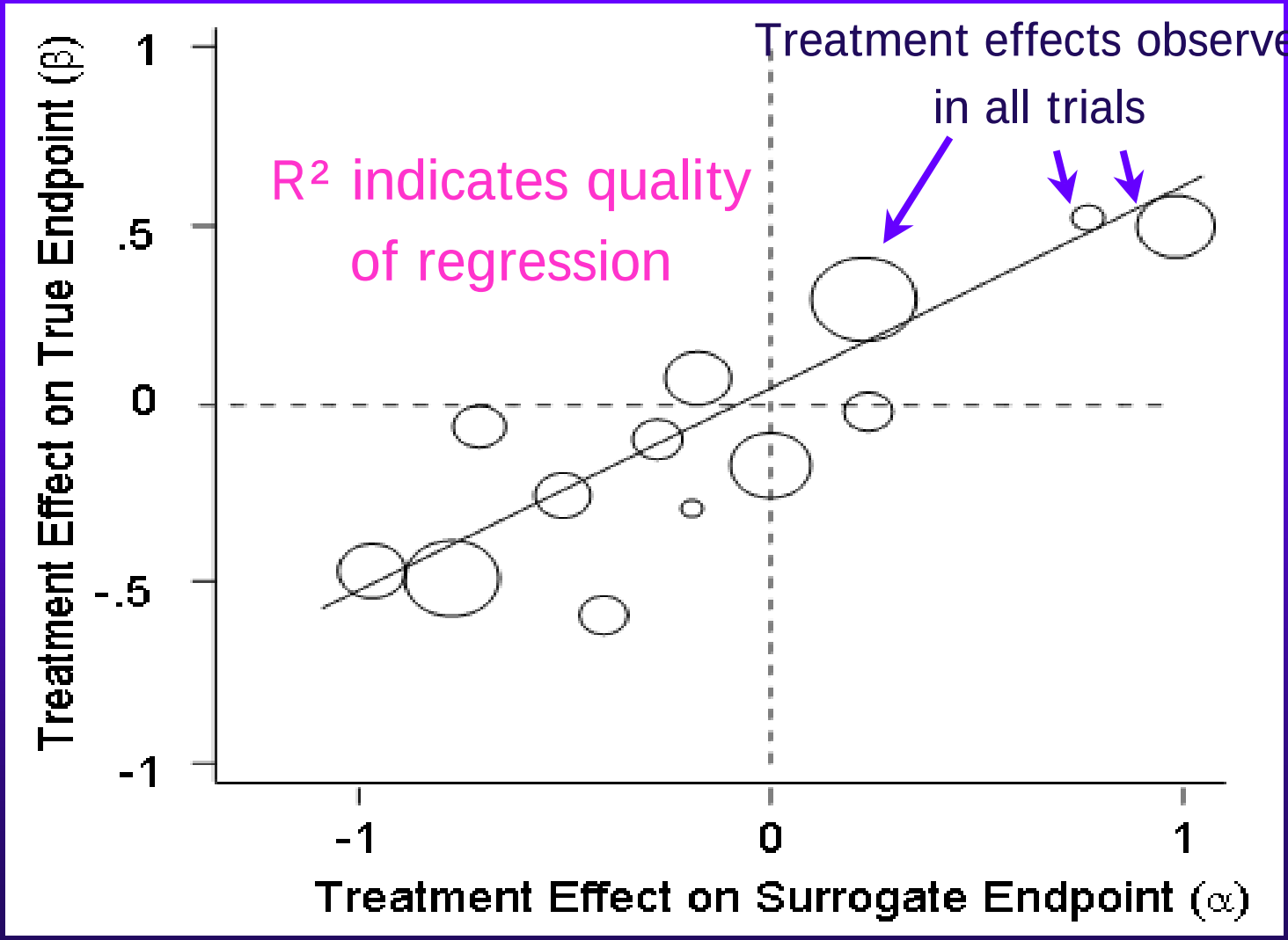


Statistical Validation of Surrogate Endpoints: Several Trials

"A meta-analysis approach seems desirable to reduce variability. Nevertheless, we need to resolve basic problems in the interpretation of measures of surrogacy such as PE as well as questions about the biologic mechanisms of drug action."

*Ref: Albert et al, Statist in Med 1998;**17**:2435.*

Prediction of Treatment Effect: Several Trials



*Ref: Daniels and Hughes, Statist in Med 1997;**16**:1965.*

Formal Statistical Definition of Surrogate Endpoints: Several Trials

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.*

Advanced Colorectal Cancer: Response as Surrogate for Survival

- 4 successive meta-analyses (27 trials & 4,010 patients)
- Treatments:
  - 5FU/LV *vs.* 5FU bolus
  - 5FU/MTX *vs.* 5FU bolus
  - 5FU C.I. *vs.* 5FU bolus
  - HAI FUDR *vs.* 5FU bolus
- Unit of analysis for treatment effects: trial ([26-382] pts. each)

*Ref: Meta-Analysis Group In Cancer, J Clin Oncol 1992;**10**:896; J Clin Oncol 1994;**12**:960; J Natl Cancer Inst 1996;**88**:252; J Natl Cancer Inst 1997;**89**:497; J Clin Oncol 1998;**16**:301; J Clin Oncol 1998;**16**:3537.*

Substantial Response Benefits

Overall response rate

- *with 5FU bolus:*
  219 / 1874 = 11.7%

- *with experimental 5FU:*
  479 / 2136 = 22.4%

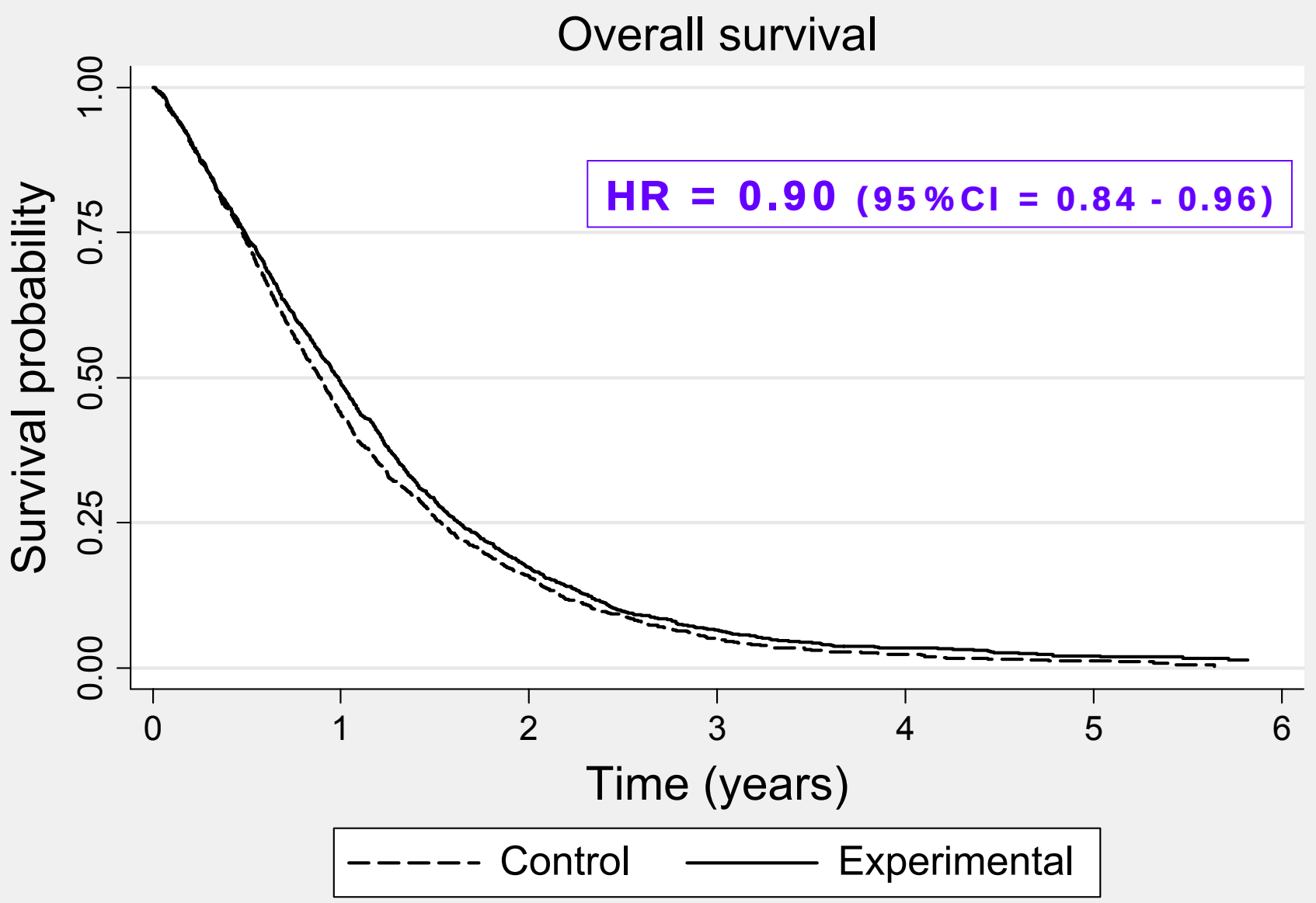
P << 0.0001

Ref:

*Buyse et al, Lancet 2000;**356**:373;*

*Burzykowski et al, JRSS A 2004;**167**:103.*

Small Survival Benefit

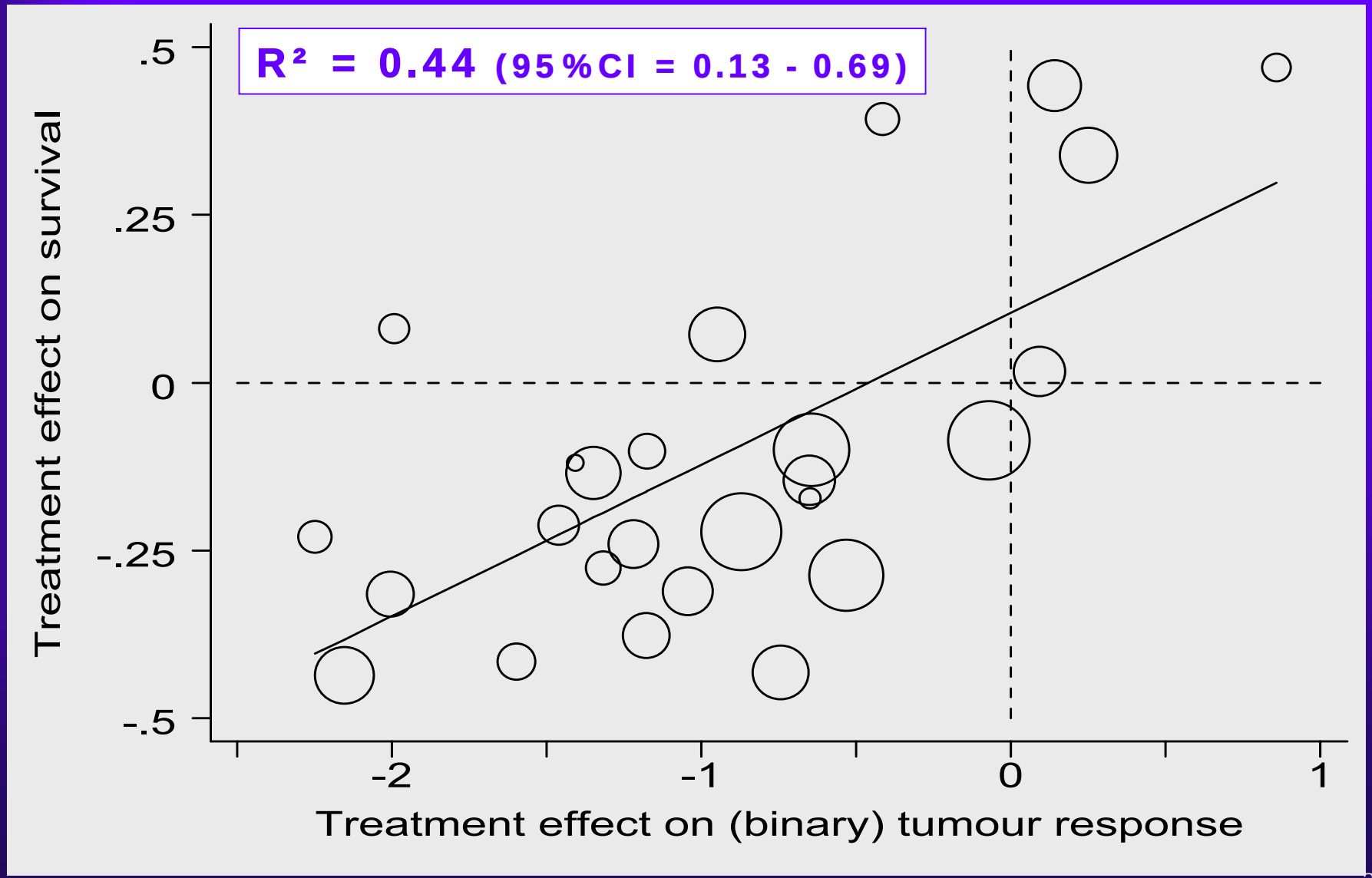


Prediction of Indivdual Outcomes

- Survival odds ratio = 3.62 (95% C.I. = 3.07-4.17)
  - Odds of surviving beyond time *t* for responders are more than three times higher than for non-responders (landmark 3 months)
- Strong association at the individual-level

*Ref: Burzykowski et al, JRSS A 2004;**167**:103.*

Prediction of Treatment Effect



Prediction of Treatment Effect

- *Prediction of treatment effect is poor*

  R^2 = 0.44 (95% C.I. = 0.13 - 0.69)

- Hence, less than a half of the variability in treatment effects upon survival can be explained by the variability in treatment effects upon response
  - response is not a valid surrogate at the trial level

Ref:
*Buyse et al, Lancet 2000;**356**:373;*
*Burzykowski et al, JRSS A 2004;**167**:103.*

Advanced Colorectal Cancer: PFS as Surrogate for Survival

- Analysis of historical trials show that
  - PFS correlates moderately well with OS
  - Treatment effects on PFS correlate extremely well with treatment effects on OS
- Therefore, PFS is an acceptable surrogate for OS

- Validation trials show that
  - Treatment effect on OS is predicted extremely well when patients receive no effective second line therapy
  - Treatment effect on OS < than predicted when all patients receive effective second line therapy, and > than predicted when more patients in the experimental group receive effective second line therapy

Buyse et al, *Proc Am Soc Clin Oncol* 2005;**23**: abstract 3513.

Final Remarks

- *Statistical validation requires the following:*
  - data from randomized trials
  - large numbers of observations
  - replication at the trial or center level
  - range of therapeutic questions
- *Hence:*
  - individual patient data meta-analyses are needed
  - access to such data is a HUGE problem

*Ref: Temple, JAMA 1999;**282**:790.*

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