



# Is PFS a “valid” surrogate for OS in advanced ovarian cancer? A meta-analysis

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# DEFINITIONS

Clinical endpoint: *a characteristic or variable that reflects how a patient feels, functions, or survives.*

Surrogate endpoint: *a biomarker or endpoint that is intended to substitute for a clinical endpoint. A good « correlate » may not make a good « surrogate ».*

*A surrogate endpoint is **expected to predict** clinical benefit (or harm) or lack thereof.*

# VALIDATION OF SURROGATE ENDPOINTS

Trt

Randomized  
treatment

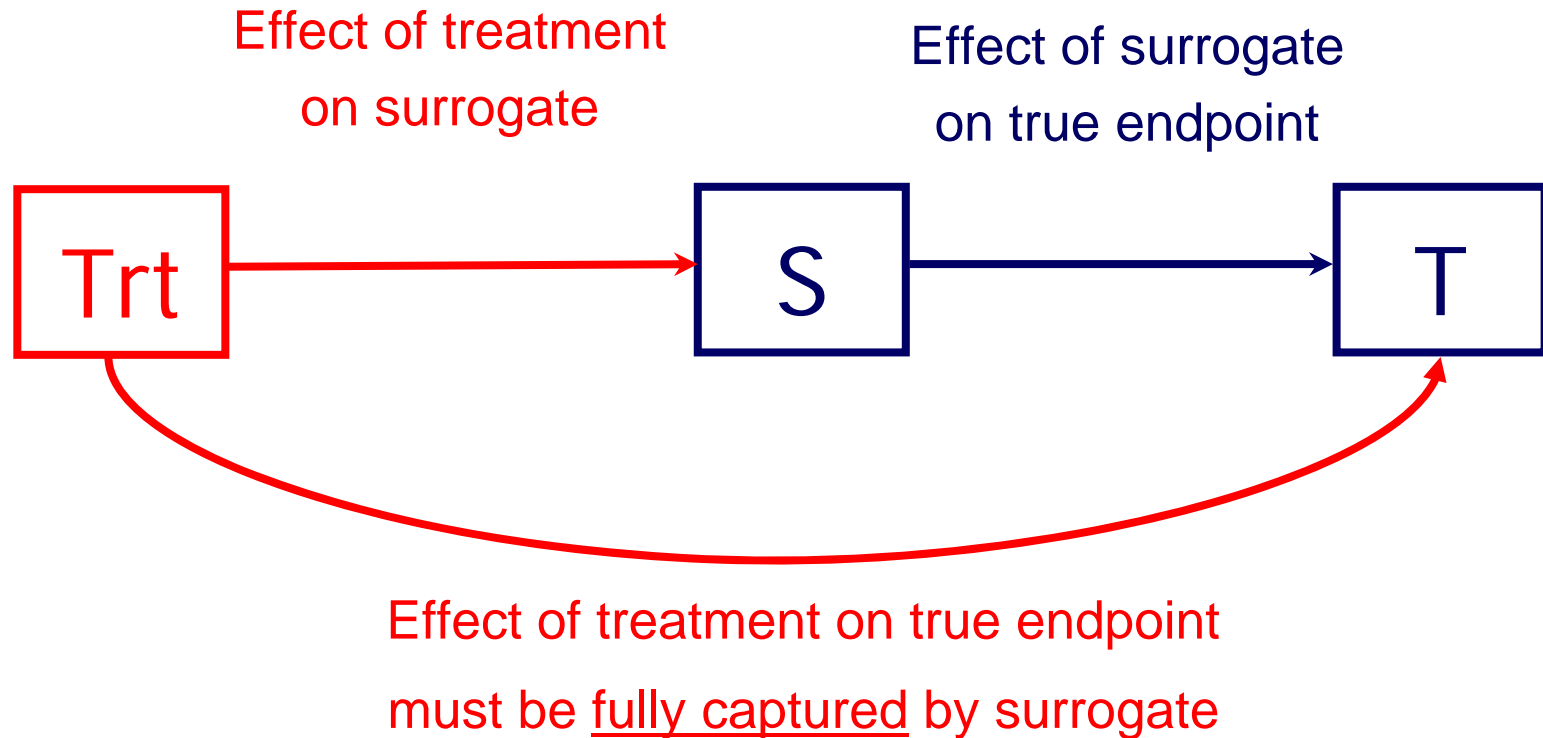
S

Potential  
surrogate  
(intermediate)  
endpoint or  
marker

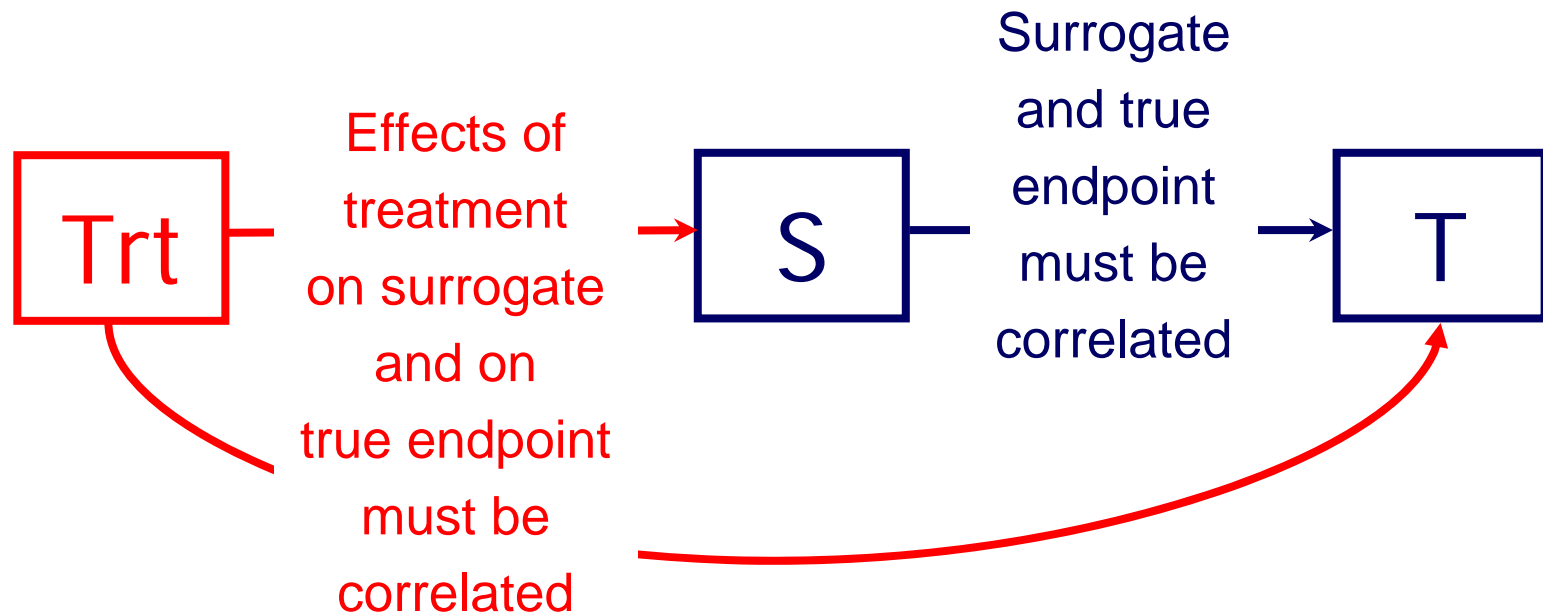
T

True  
clinical  
endpoint

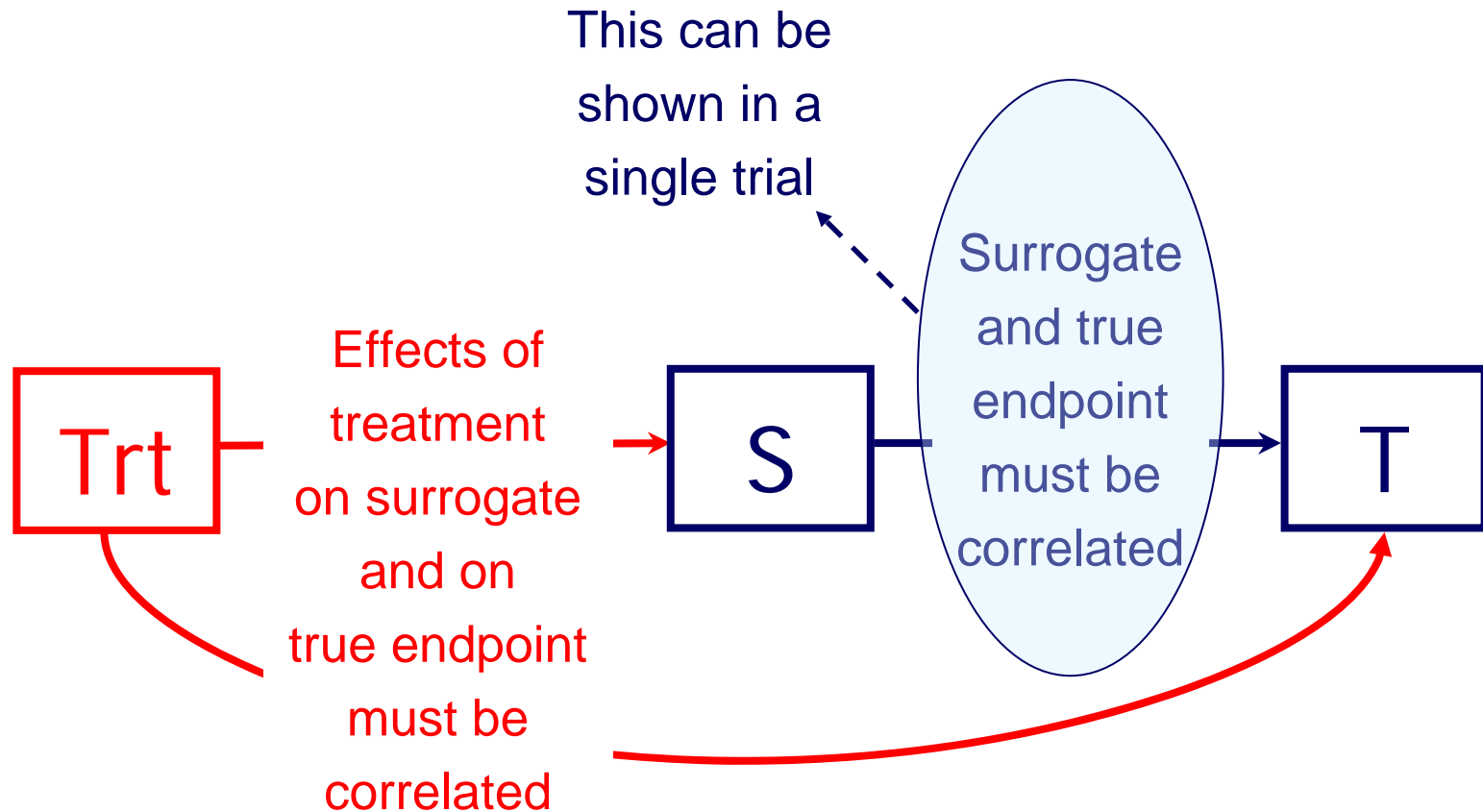
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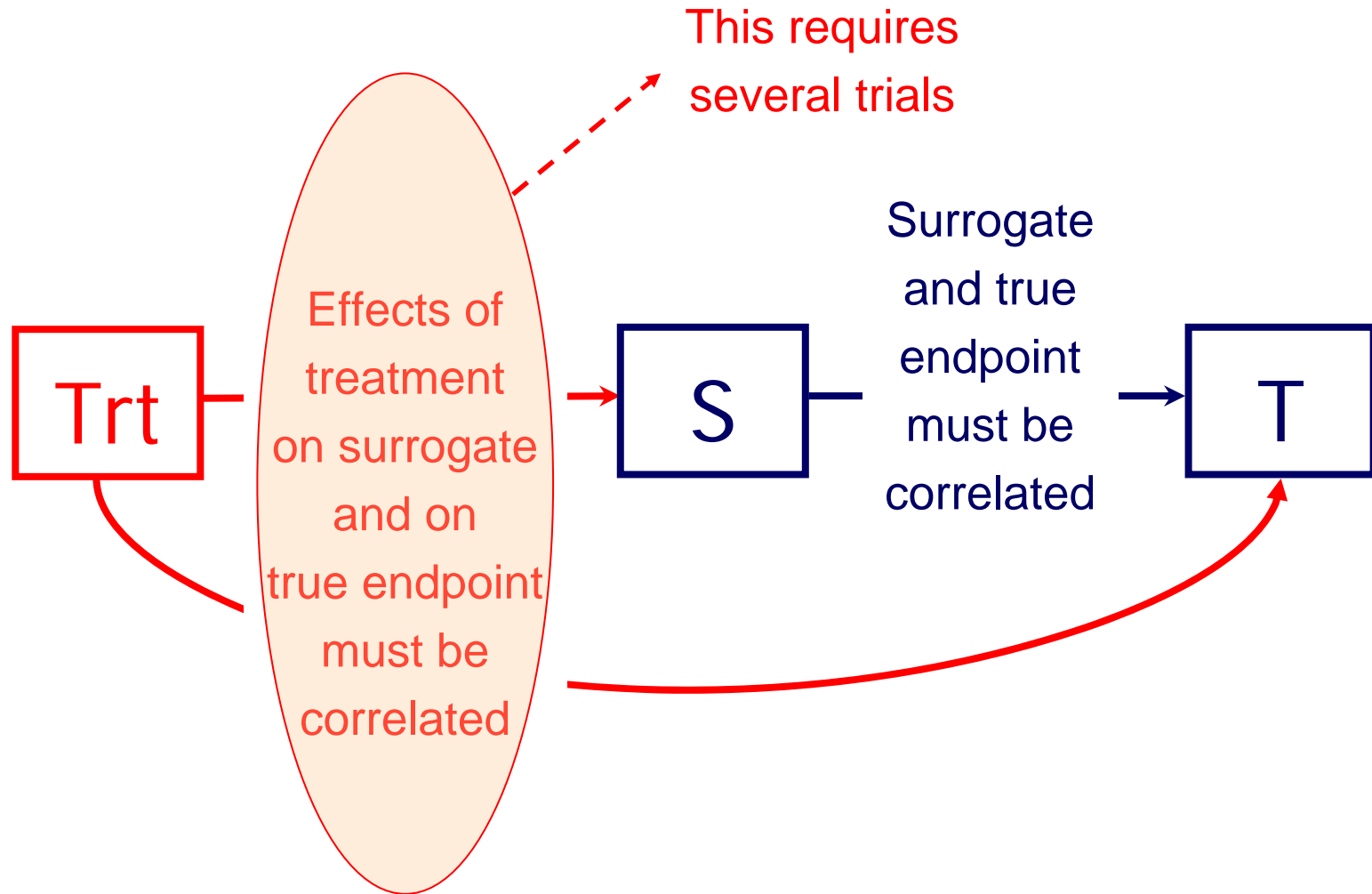
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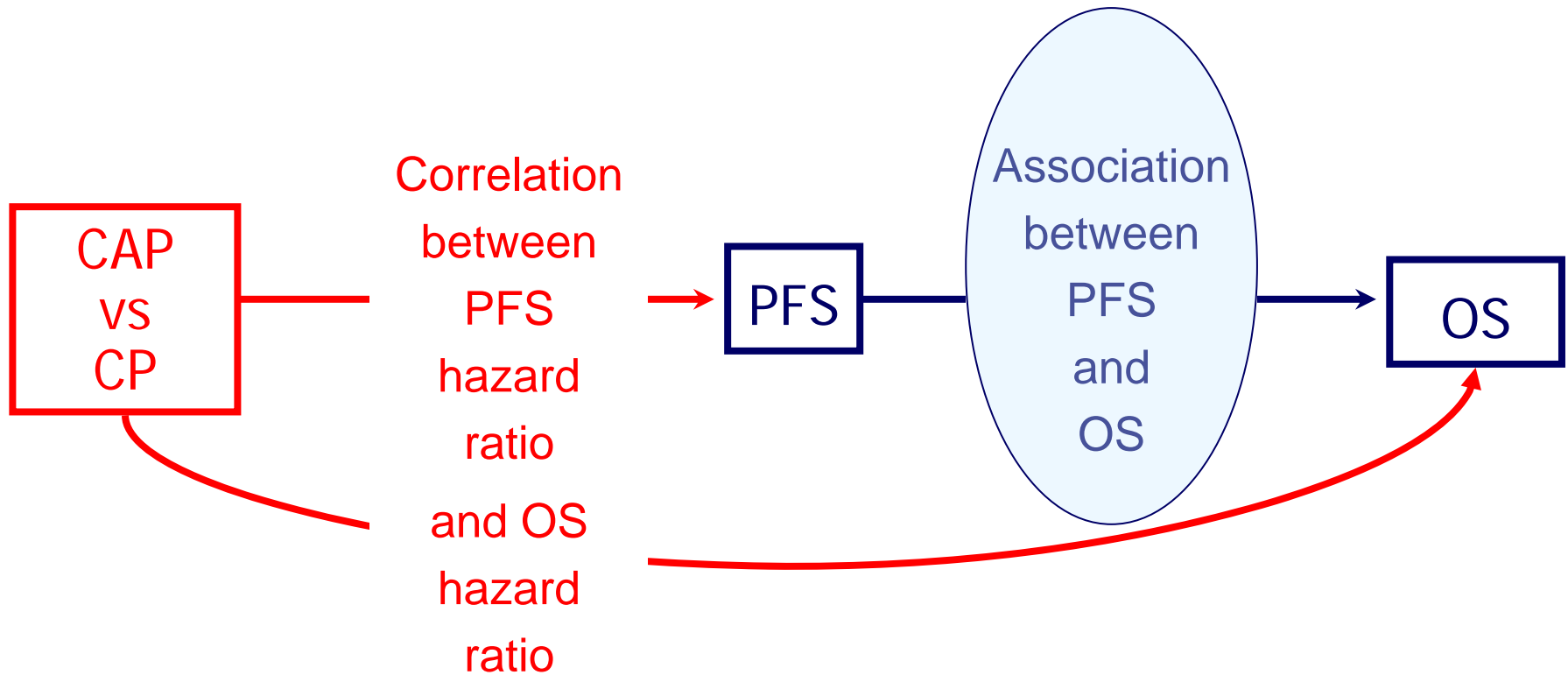
# ADVANCED OVARIAN CANCER

- 4 trials comparing CP with CAP:
  - Gynecologic Oncology Group (GOG, US)
  - Gruppo Interegionale Cooperativo Oncologico Ginecologia (GICOOG, Italy)
  - Danish Ovarian Cancer Group (DACOVA, Denmark)
  - Gruppo Oncologico Nord-Ovest (GONO, Italy)
- Accrual 1980-1986, median follow-up > 10 years
- 1,194 patients (952 deaths)
- 39 centers with > 3 patients per treatment arm
- Endpoints: clinical response, PFS and survival

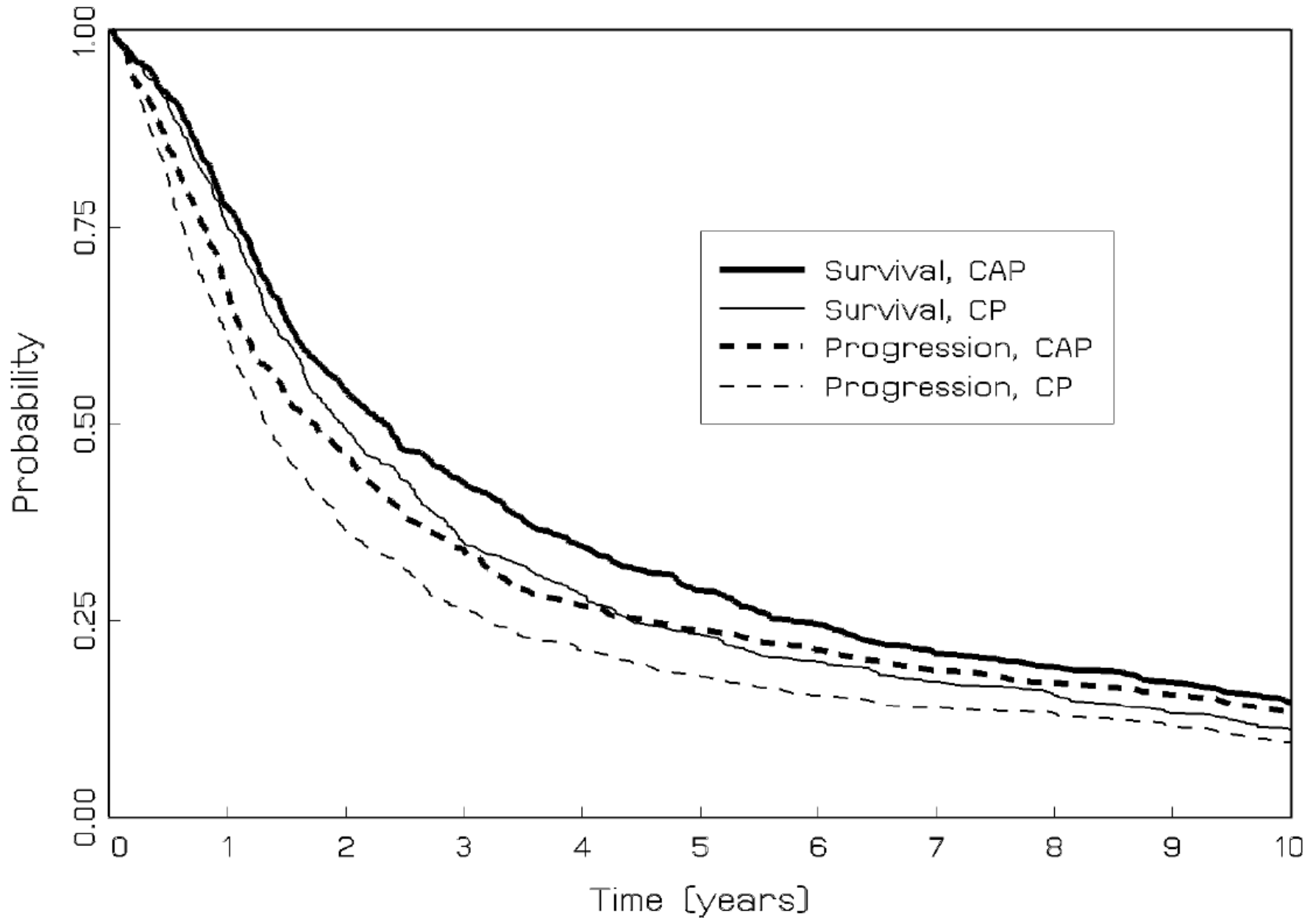
*Refs: Ovarian Cancer Meta-Analysis Project, JCO 1991;9:1668  
Class Papers Curr Comments 1998;3:237.*



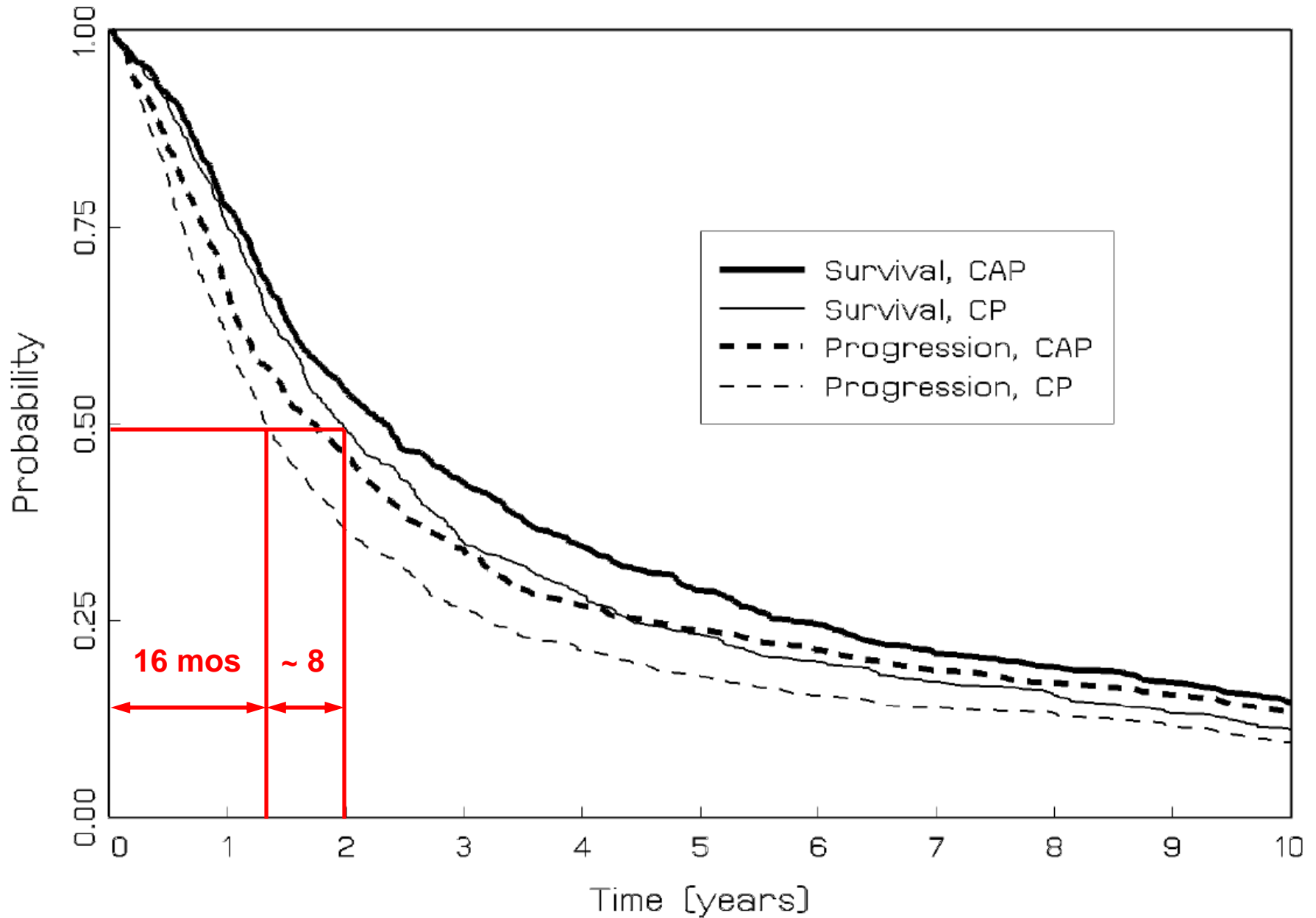
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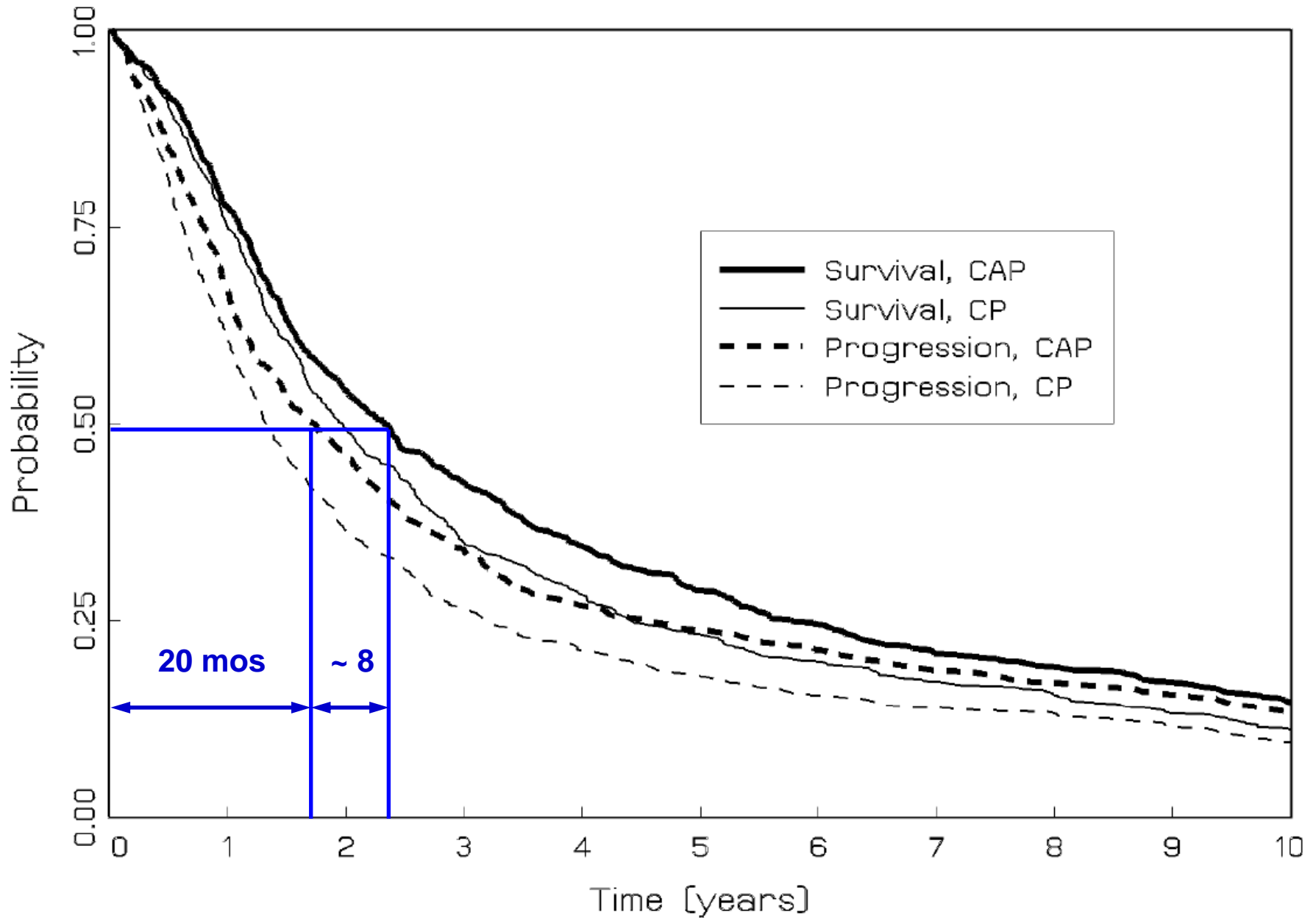
# PFS AND OS CURVES



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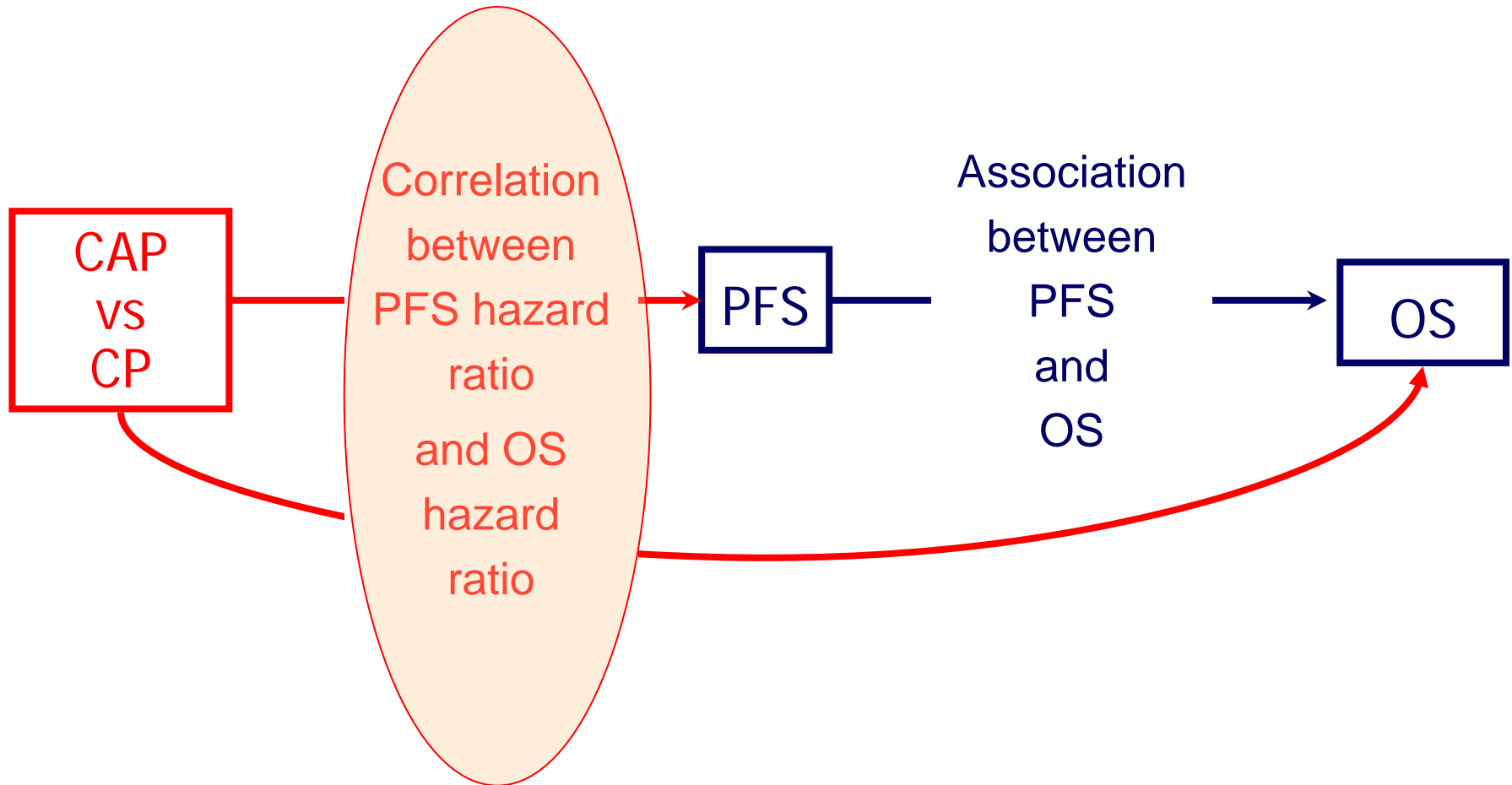
# PFS AND OS CURVES



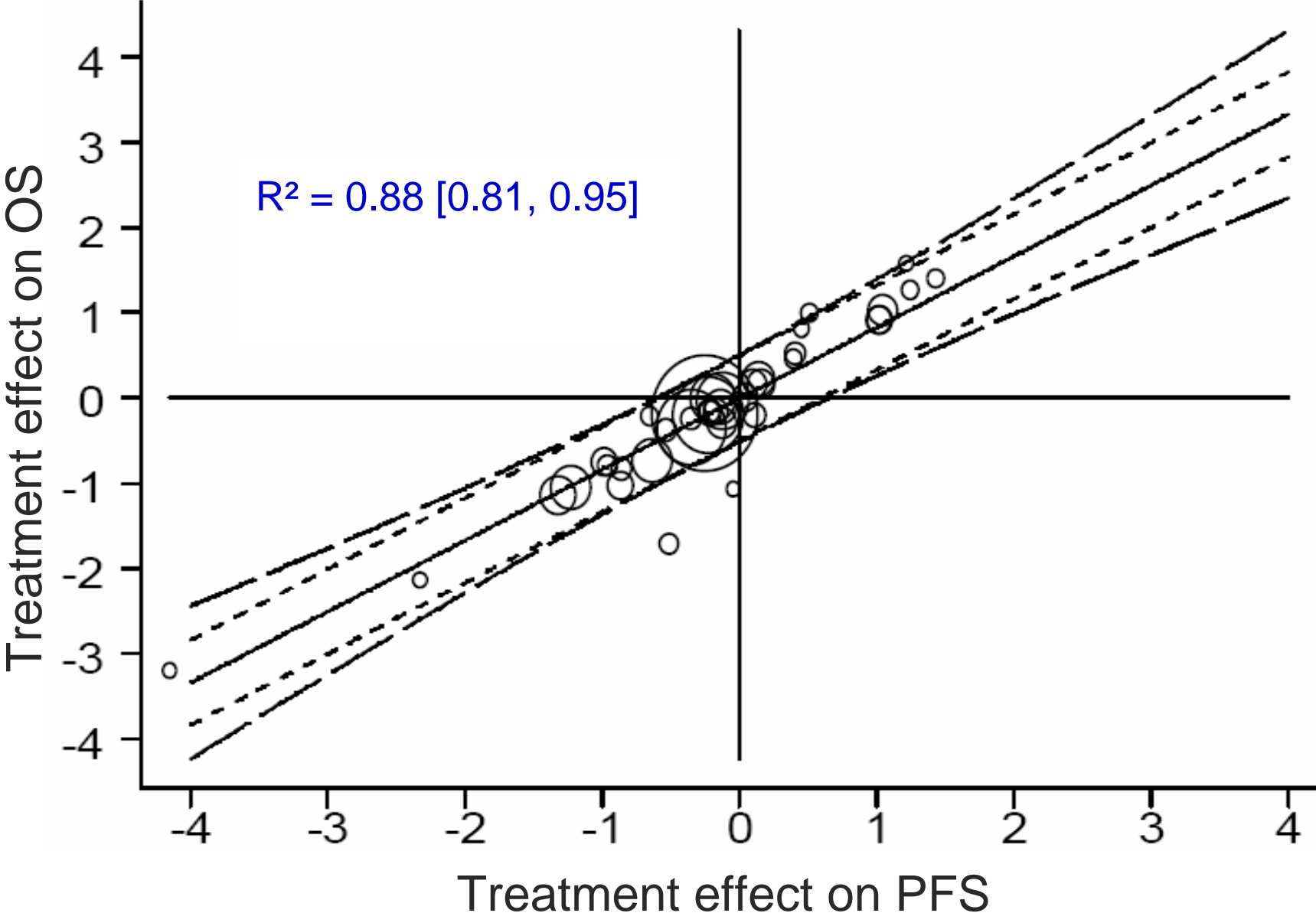
# INDIVIDUAL-LEVEL ASSOCIATION (BETWEEN ENDPOINTS)

- Bivariate distribution of PFS and OS modelled through a copula function
- Measure of association: Kendall's  $\tau$   
(range [-1, +1], with 0 indicating no association)
- $\tau = 0.853$  [0.842, 0.863]

# ADVANCED OVARIAN CANCER



# CORRELATION BETWEEN EFFECTS

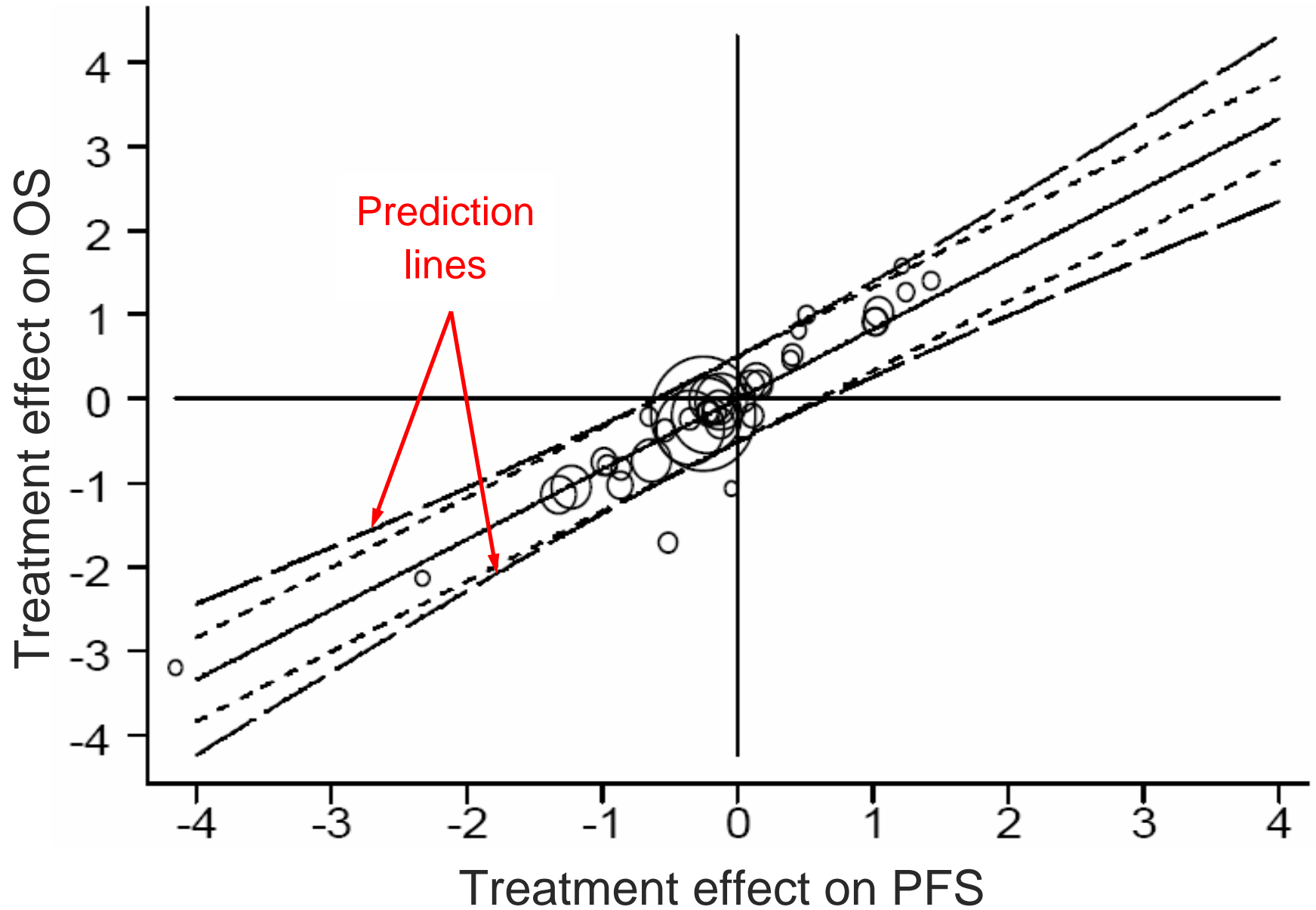


# GROUP-LEVEL ASSOCIATION (BETWEEN TREATMENT EFFECTS)

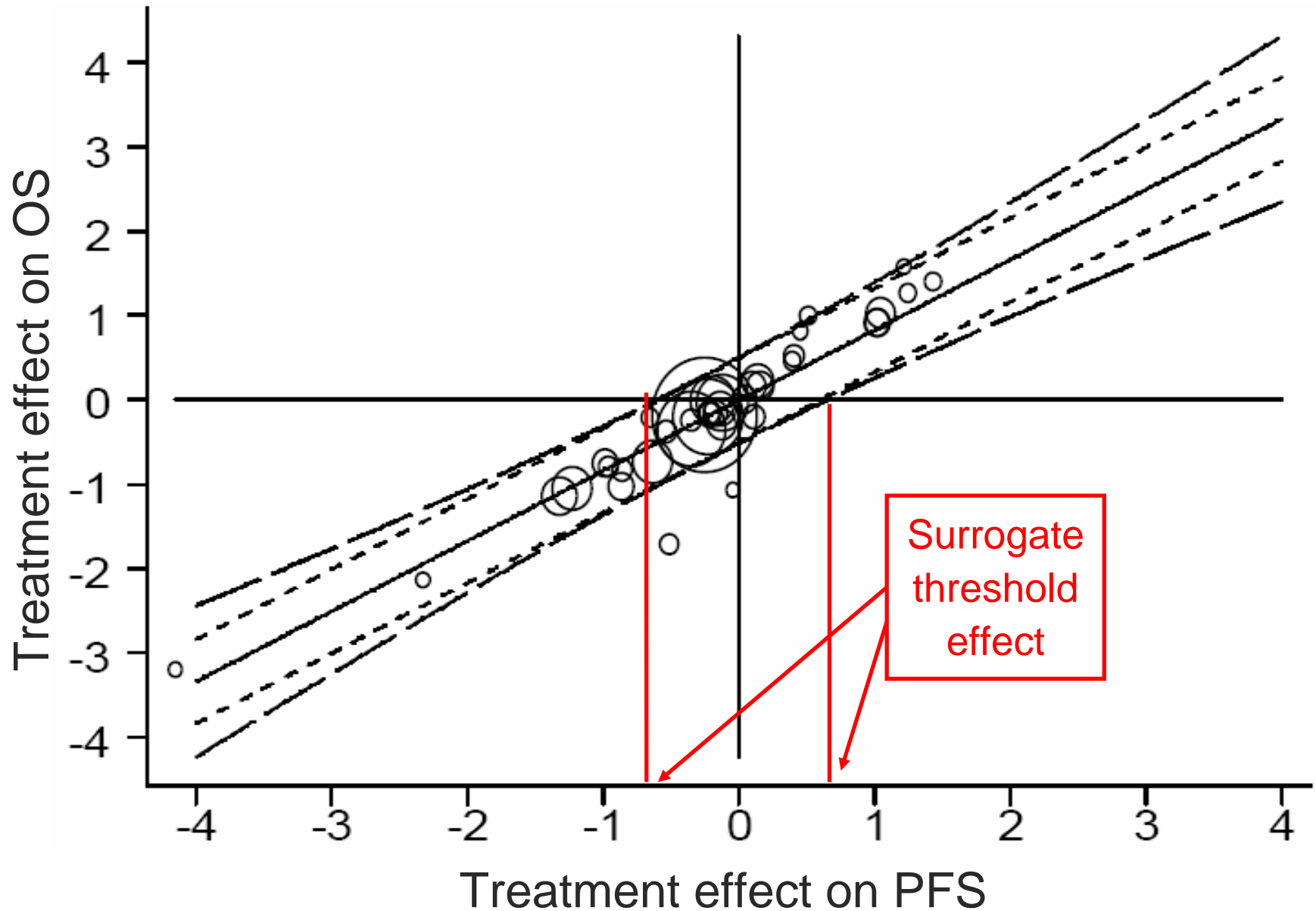
- Effects of treatment (CAP compared with CP) in centers modelled through linear regression between  $\log HR_{PFS}$  and  $\log HR_{OS}$
- Measure of association: Pearson's correlation coefficient  $\rho$
- $\rho = 0.94$  [0.90, 0.97]



# PREDICTION LINES



# SURROGATE THRESHOLD EFFECT



# SURROGATE THRESHOLD EFFECT

- Effects of treatment (CAP compared with CP) modelled through linear regression between  $\log HR_{PFS}$  and  $\log HR_{OS}$
- Surrogate threshold effect is treatment effect on PFS that predicts significant treatment effect on OS
- $STE = HR_{PFS} = 0.55$  (i.e. treatment must cut risk of progression or death by at least 45% for a survival benefit to be expected)

# INDIVIDUAL- vs. GROUP-LEVEL SURROGACY

- Individual-level surrogacy establishes a strong association between PFS and OS

▶ *useful for patient management*

- Trial-level surrogacy establishes a strong association between the effects of treatment (CAP vs CP) on PFS and OS

▶ *useful to assess new treatments*

# IDEAL REQUIREMENTS FOR VALIDATION

- Individual patient data from multiple comparative (preferably randomized) trials or other analysis units (eg centers or countries)
- Observations of S and at least some T
- Range of treatment effects on S and T (heterogeneity an asset)
- Range of treatment questions ( $Z_1, Z_2, \dots$ ) to assess treatment dependency of surrogacy
- Large numbers of observations and of analysis units

*Refs: Temple, JAMA 1999;282:790*

*Burzykowski, Molenberghs and Buyse, Springer Verlag 2005*