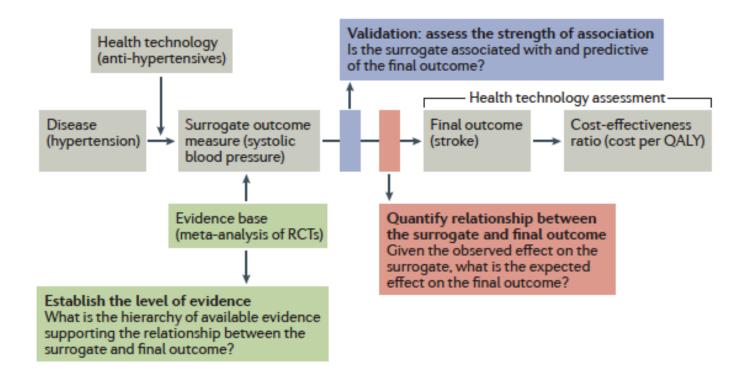


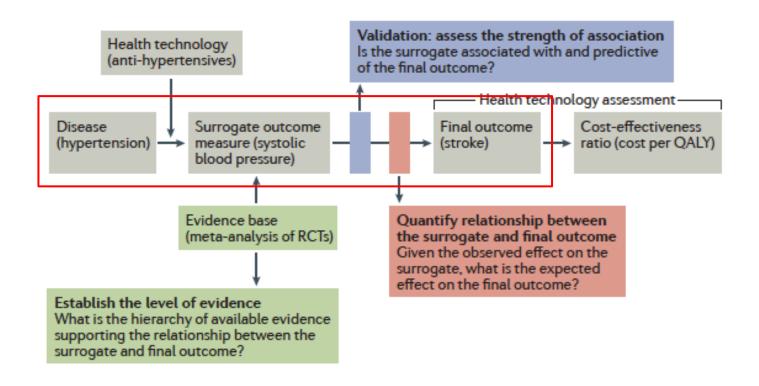


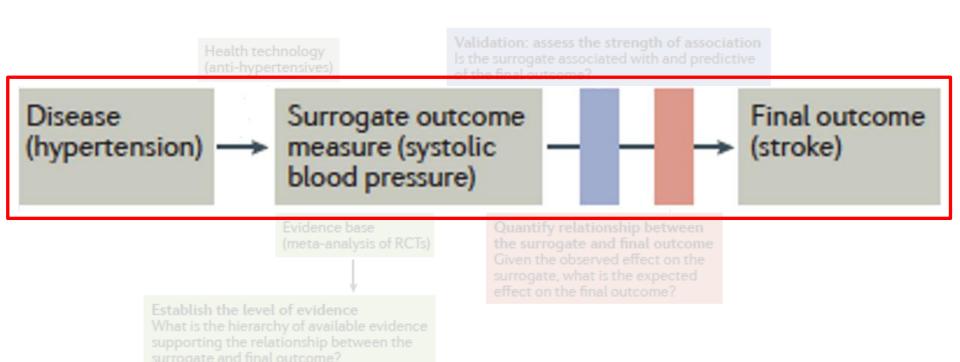
# Are surrogate endpoints ready for HTA? A statistical view

Marc Buyse, ScD October 2022



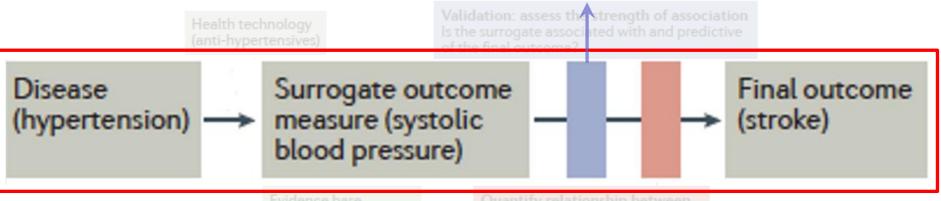






"Individual-level surrogacy"

Correlation between **endpoints** 



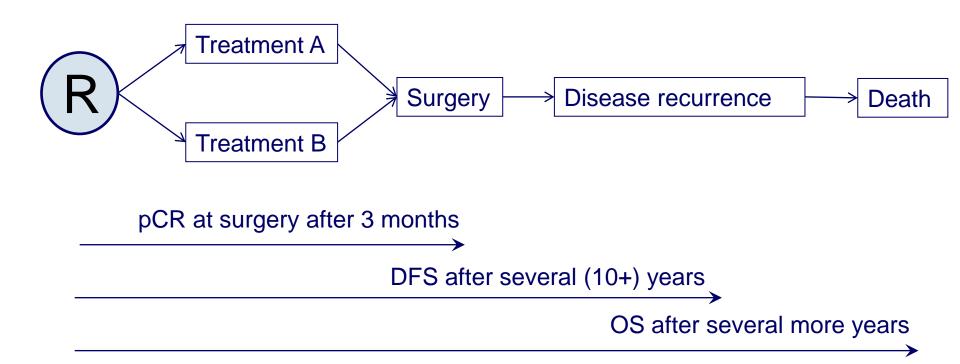
ablish the level of evidence at is the hierarchy of available evidence porting the relationship between the Quantify relationship between the surrogate and final outcome Given the observed effect on the surrogate, what is the expected effect on the final outcome?

"Individual-level surrogacy" Correlation between **endpoints** Validation: assess the strength of association Is the surrogate associated with and predictive Final outcome Disease Surrogate outcome measure (systolic (stroke) (hypertension) blood pressure) Quantify relationship between the surrogate and final outcome Given the observed effect on the surrogate, what is the expected "Trial-level surrogacy" Correlation between treatment effects on these endpoints

Ref: Buyse et al., Biostastistics 2000; 1:49.

### pCR as surrogate for OS in early breast cancer

Is pathological complete response (pCR) an acceptable surrogate for overall survival (OS) for patients receiving treatment before surgery of early breast cancer?

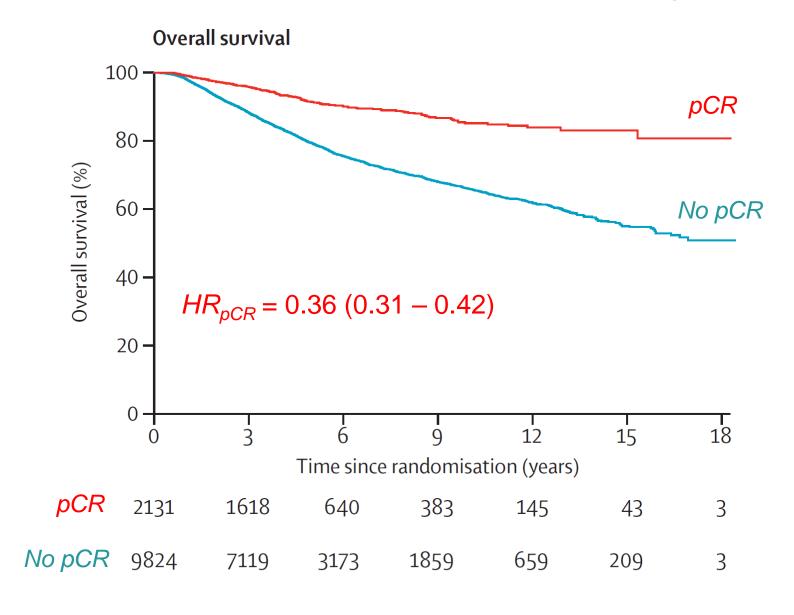


### pCR as surrogate for OS in early breast cancer

FDA performed a meta-analysis of 12 randomized trials (11,955 patients) submitted for approval All trials compared an experimental therapy given before surgery to immediate surgery

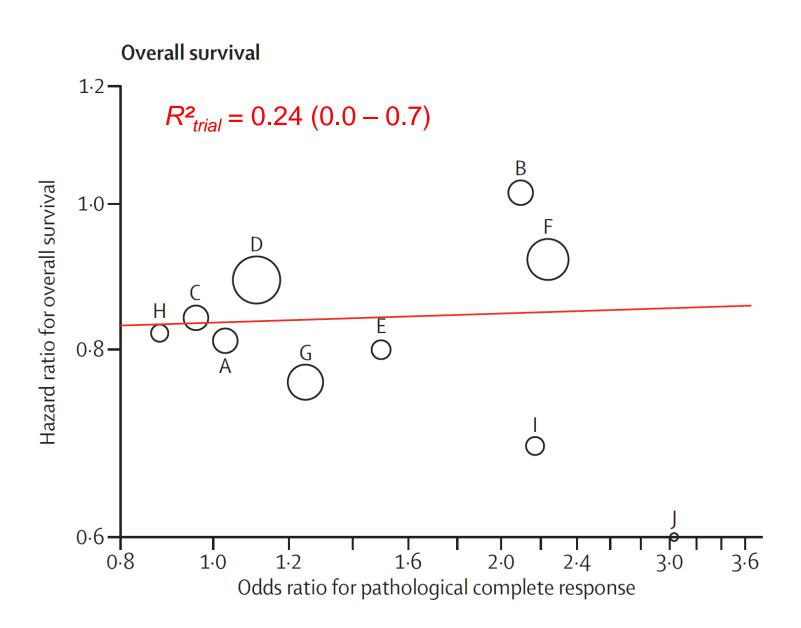
Ref: Cortazar et al., Lancet Oncol 2014; 356:373.

#### pCR is an individual-level surrogate

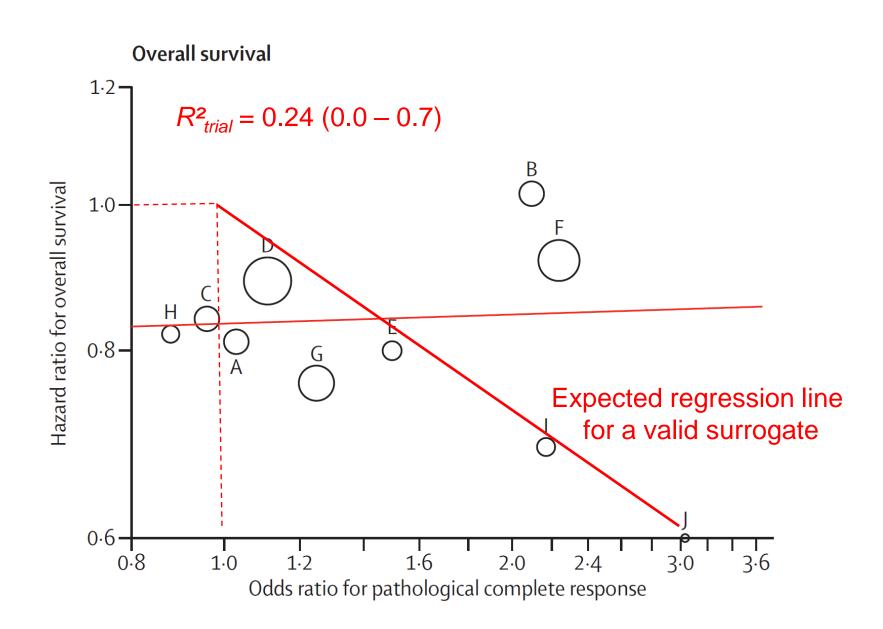


Ref: Cortazar et al., Lancet Oncol 2014; 384:164.

### pCR is NOT a trial-level surrogate!



#### This would be expected of a trial-level surrogate



### What does this example show?

The fact that pCR has a huge impact on OS (« individual-level surrogacy ») does not imply that a treatment-induced change in pCR will induce a treatment-induced change in OS (« trial-level surrogacy »).

Ref: Buyse et al., The Oncologist 2022; 27:266.

#### What does this example imply for HTA?

Intermediate outcomes or biomarkers that have a big impact on the final outcome may or may not be valid surrogates.

Real-world or epidemiological evidence, regardless of size and quality, only address individual-level surrogacy.

We need large-scale, randomized evidence to assess the validity of a surrogate in terms of trial-level surrogacy.



Pathological Complete
Response in Neoadjuvant
Treatment of High-Risk
Early-Stage Breast Cancer:
Use as an Endpoint to
Support Accelerated
Approval
Guidance for Industry

July 2020 Clinical/Medical Revision 1