IRCCS Sacro Cuore Don Calabria
Cancer Care Center Negrar - Verona

ESMO Designated Centers of Integrated Oncology and Palliative Care

Con il Patrocinio di

AIOM · RAO · SICO · Società Italiana di Psico-Oncologia

STUDI CLINICI: METODOLOGIA

Coordinatore
Dr.ssa Stefania Gori

Evento ECM MODULO 2

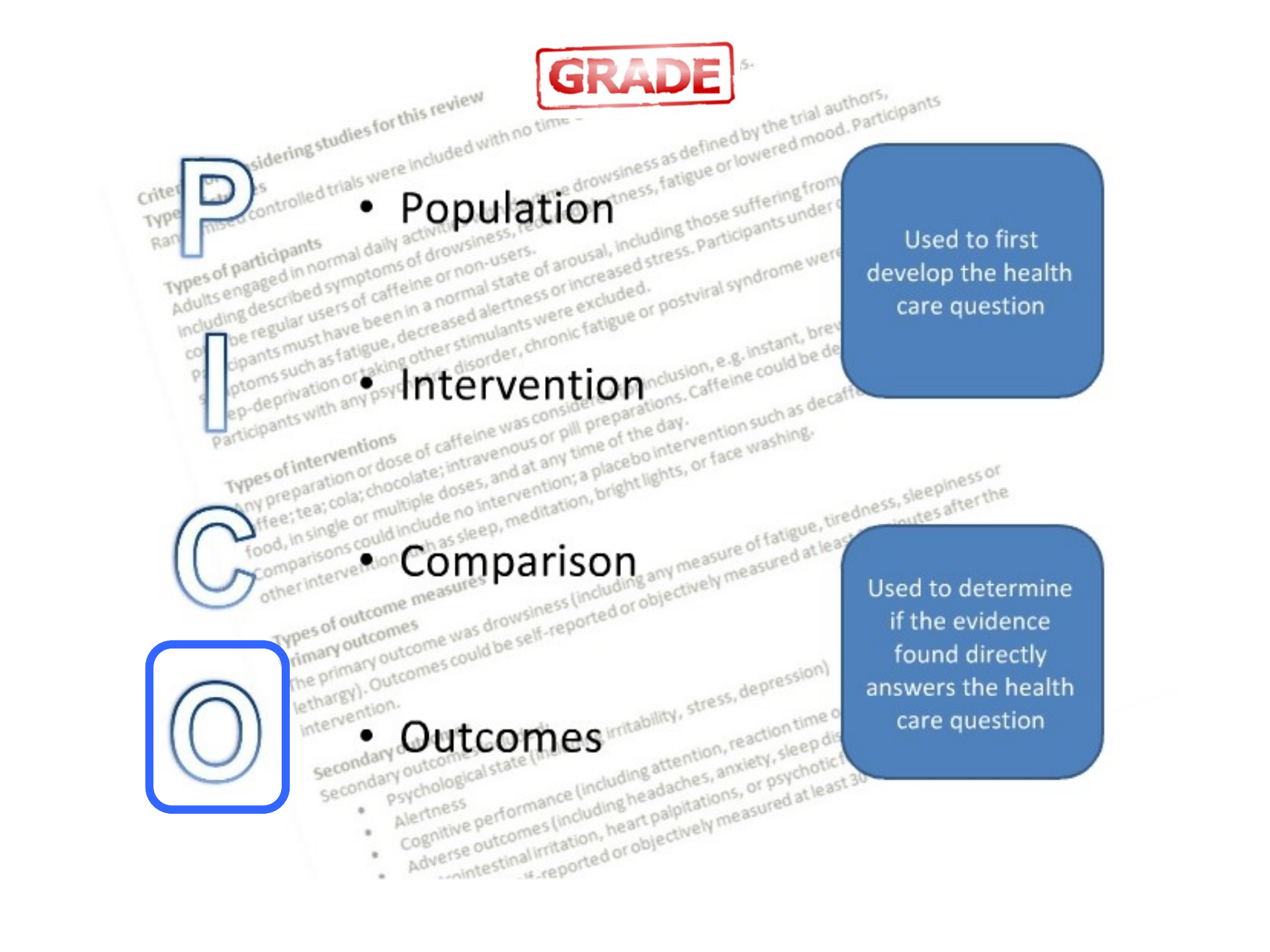
FORMAZIONE AVANZATA

NEGRAR
8/9 Marzo
2019

Centro Formazione
IRCCS Ospedale Sacro Cuore
Don Calabria

Directness

P.I.C.O.


GRADE
P
I
C
O
• Population
• Intervention
• Comparison
• Outcomes
Used to first develop the health care question
Used to determine if the evidence found directly answers the health care question

Strutturazione del Quesito Clinico sec. modello P.I.C.O.

P	Nei **P**azienti con…	Specifiche caratteristiche di malattia (stadio, classe di rischio, ecc.)
I	l'**I**ntervento	Intervento terapeutico oggetto linico
		altrimenti consi- lternativa all'inter- me
O	riguardo agli **O**utcome di beneficio/danno…	Parametri clinico-laboratoristici ritenuti essenziali per la decisio-ne terapeutica

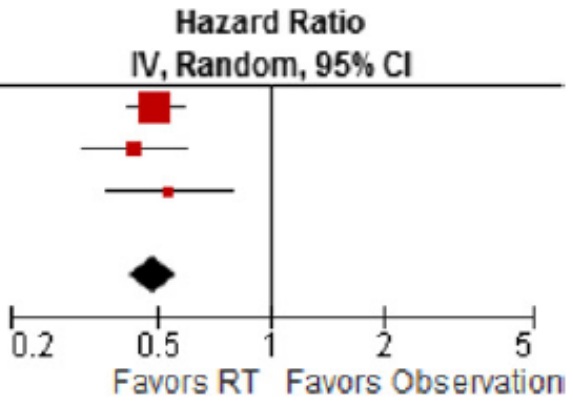
Non necessariamente coincidenti con gli outcome di efficacia delle evidenze disponibili – considerare anche gli outcome di tollerabilità!

Adjuvant Radiotherapy in Localized PCa

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Bolla 2012	-0.713	0.093	65.0%	0.49 [0.41, 0.59]
Thompson 2009	-0.844	0.164	20.9%	0.43 [0.31, 0.59]
Wiegel 2009	-0.635	0.2	14.1%	0.53 [0.36, 0.78]
Total (95% CI)			**100.0%**	**0.48 [0.42, 0.56]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.74$, $df = 2$ ($P = 0.69$); $I^2 = 0\%$

Test for overall effect: $Z = 9.73$ ($P < 0.00001$)



Meta-analysis of [redacted] data from SWOG 8794,[26] EORTC 22911[25] and ARO 96–02[15]

AUA/ASTRO guidelines, J Urol; 190:441-9, 2013

- Endpoint di convenienza?
- Surrogato della sopravvivenza globale?
- Endpoint di valenza clinica per sé?

Validation of Surrogate Endpoints

Property of a Valid Surrogate

Effect of the Intervention
on the Clinical Endpoint

is reliably predicted by the

Effect of the Intervention
on the Surrogate Endpoint

D. Sargent, ASCO 2011

Prentice's Criteria

- To be a direct substitute for a clinical benefit endpoint on inferences of superiority and inferiority
  - The surrogate endpoint must fully capture the net effect of treatment on the clinical outcome

EUROPEAN UROLOGY 68 (2015) 775–776

Postprostatectomy Radiotherapy for Patients with High-risk Features on Definitive Pathology: A Plea for Evidence-based Medicine

Alberto Bossi[a,*], *Thomas Wiegel*[b], *Mack Roach*[c]

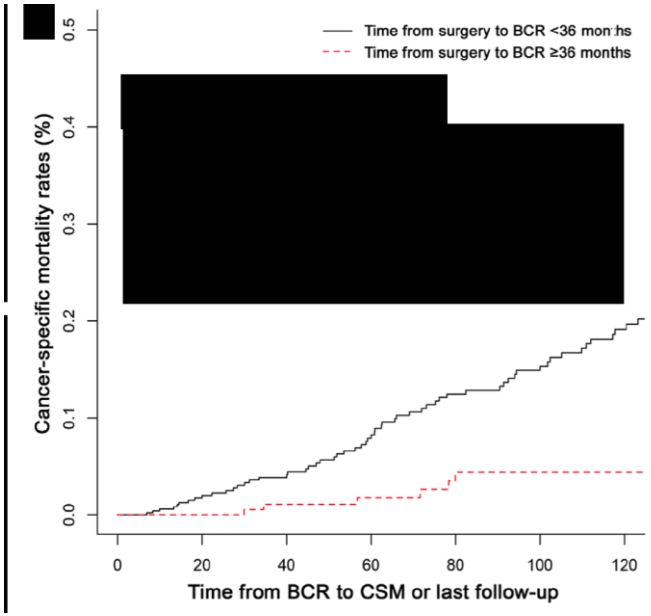
It is noteworthy that multivariate analysis clearly demonstrated a [redacted] between (early) biochemical recurrence and the risk of dying fromPCa

Urologic Oncology: Seminars and Original Investigations 33 (2015) 163.e7–163.e13

Natural history of surgically treated high-risk prostate cancer

Alberto Briganti, M.D.[a,*,1], Robert Jeffrey Karnes, M.D.[b,1], Giorgio Gandaglia, M.D.[a], Martin Spahn, M.D.[c], Paolo Gontero, M.D.[d], Lorenzo Tosco, M.D.[e], Burkhard Kneitz, M.D.[f], Felix K.H. Chun, M.D.[g], Emanuele Zaffuto, M.D.[a], Maxine Sun, M.D.[h], Markus Graefen, M.D.[i], Giansilvio Marchioro, M.D.[j], Detlef Frohneberg, M.D.[k], Simone Giona, M.D.[d], Pierre I. Karakiewicz, M.D.[h], Hein Van Poppel, M.D.[e], Francesco Montorsi, M.D.[a], Steven Joniau, M.D.[e], on behalf of the European Multicenter Prostate Cancer Clinical and Translational Research Group (EMPaCT)

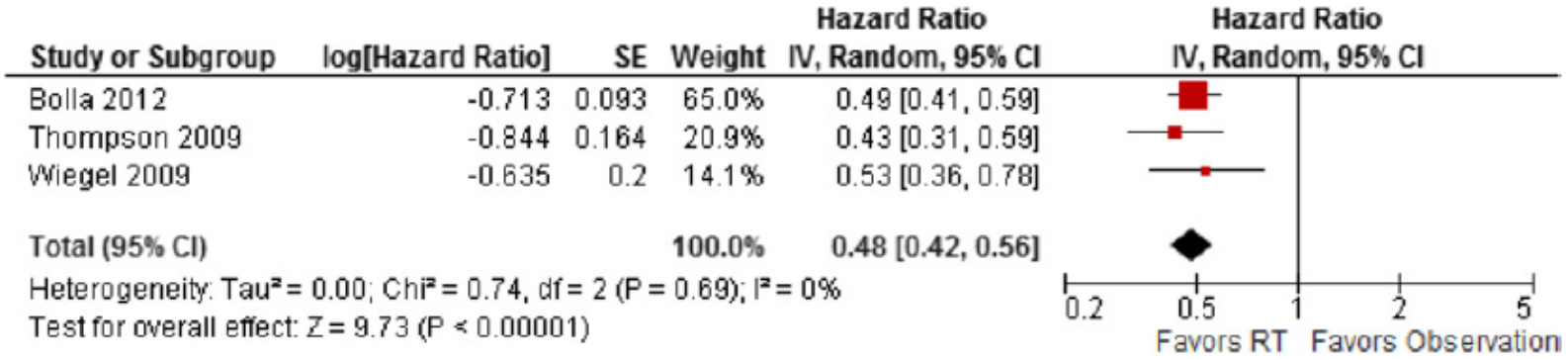
Individuals who experienced BCR within 3 years from surgery had significantly higher CSM rates compared with those who developed late BCR. At competing-risks regression analyses, [redacted] after accounting for the risk of OCM.



Prentice's Criteria

- To be a direct substitute for a clinical benefit endpoint on inferences of superiority and inferiority
  - The surrogate endpoint must be correlated with the clinical outcome

Adjuvant RT PCa



Meta-analysis of [redacted] data from SWOG 8794,[26] EORTC 22911[25] and ARO 96–02[15]

EUROPEAN JOURNAL OF CANCER 42 (2006) 1344–1350

Prostate-specific antigen (PSA) alone is not an appropriate surrogate marker of long-term therapeutic benefit in prostate cancer trials

Laurence Collette[a,], Tomasz Burzykowski[b], Fritz H. Schröder[c]*

We review the published literature pertaining to the validation of PSA endpoints as surrogate in all disease stages.

We discuss the limitations of these studies and conclude that so far, PSA is not a validated surrogate endpoint in any of the disease settings and treatment conditions considered.

Neo-adjuvant chemotherapy for muscle-invasive bladder cancer: a look ahead

R. Sawhney[1], D. Bourgeois[2] & U. B. Chaudhary[1]*

Annals of Oncology 17: 1360–1369, 2006

In order to suggest a pT0 at cystectomy as a surrogate clinical end point for neo-adjuvant chemotherapy (NC) for bladder cancer, we would have to demonstrate the following:

(1) NC must have a significant effect on OS; ✓

(2) NC must have a significant effect on the incidence of pT0; ✓

(3) there must be a significant association between achievement of pT0 and OS; ✓

(4) the full effect of NC on OS must be explained by achievement of pT0 status ✓

For all patients who had a pT0 at cystectomy, the OS appeared to be independent of the initial treatment intervention (5-year OS for CT and surgery arms 85% and 82%, respectively

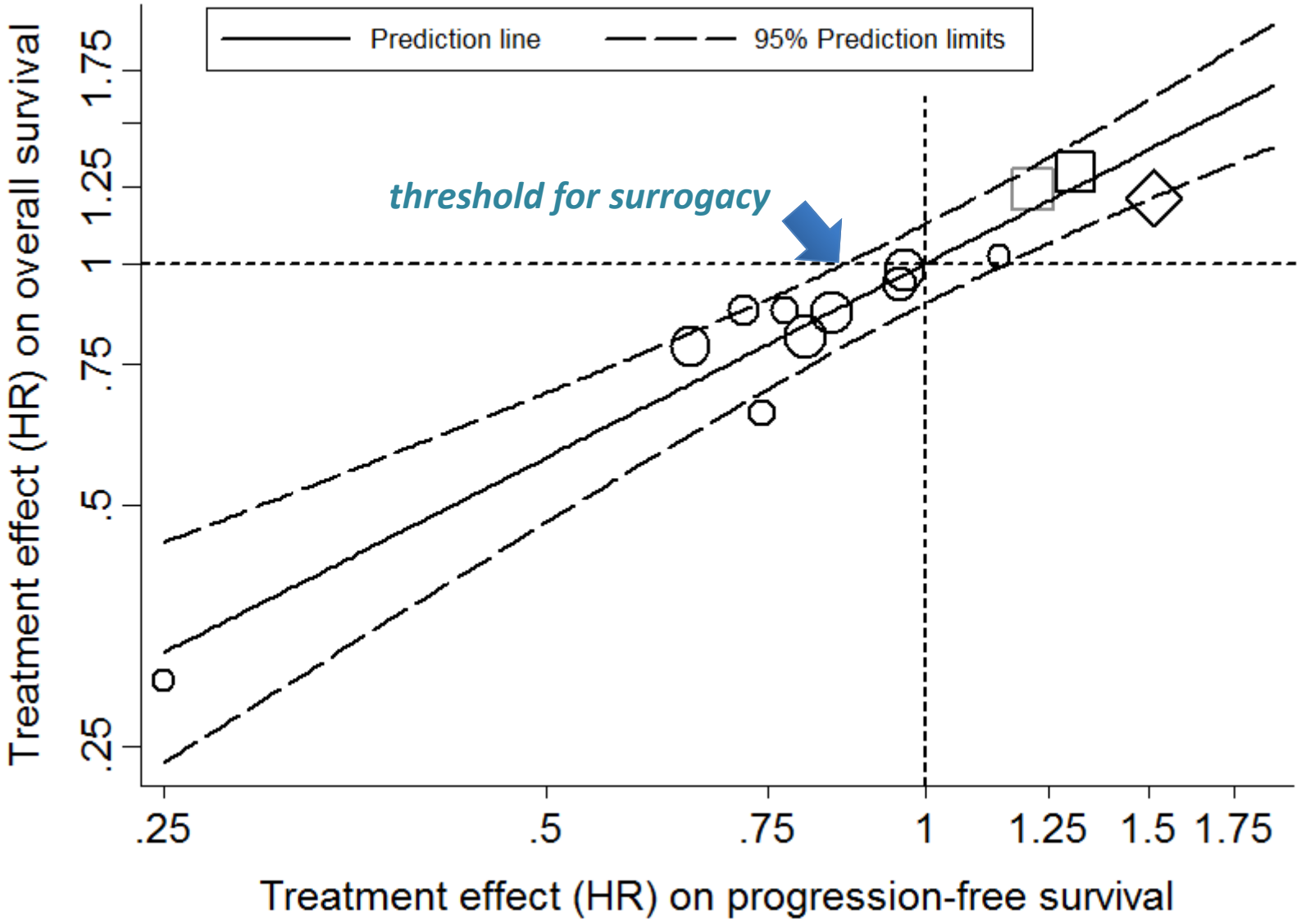
Quando si hanno dati di molti RCT…

… si deriva un modello di regressione:

- **che possa predire la magnitudine**
- **dell'effetto del trattamento sull'endpoint "vero"**
- **in base all'effetto del trattamento sull'end-point (candidato) surrogato**

Il surrogato è tale se la predizione è sufficientemente precisa

TRIAL LEVEL CORRELATION BETWEEN EFFECTS

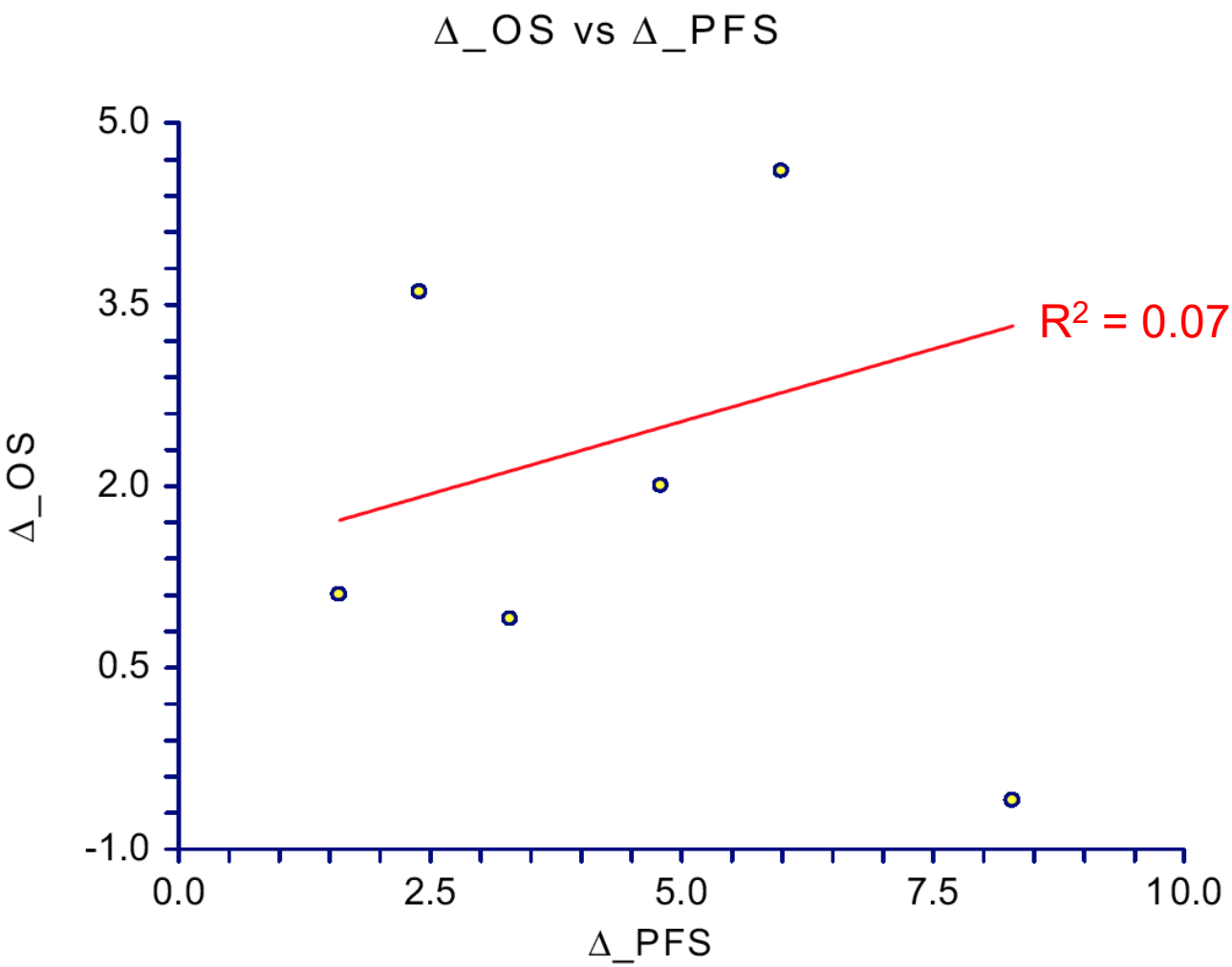


Burzykowski and Buyse, Pharmaceutical Statist 2006;5:173

Surrogate End Points in Renal Cell Carcinoma: An Analysis of First-Line Trials With Targeted Therapies

Fausto Petrelli, Sandro Barni

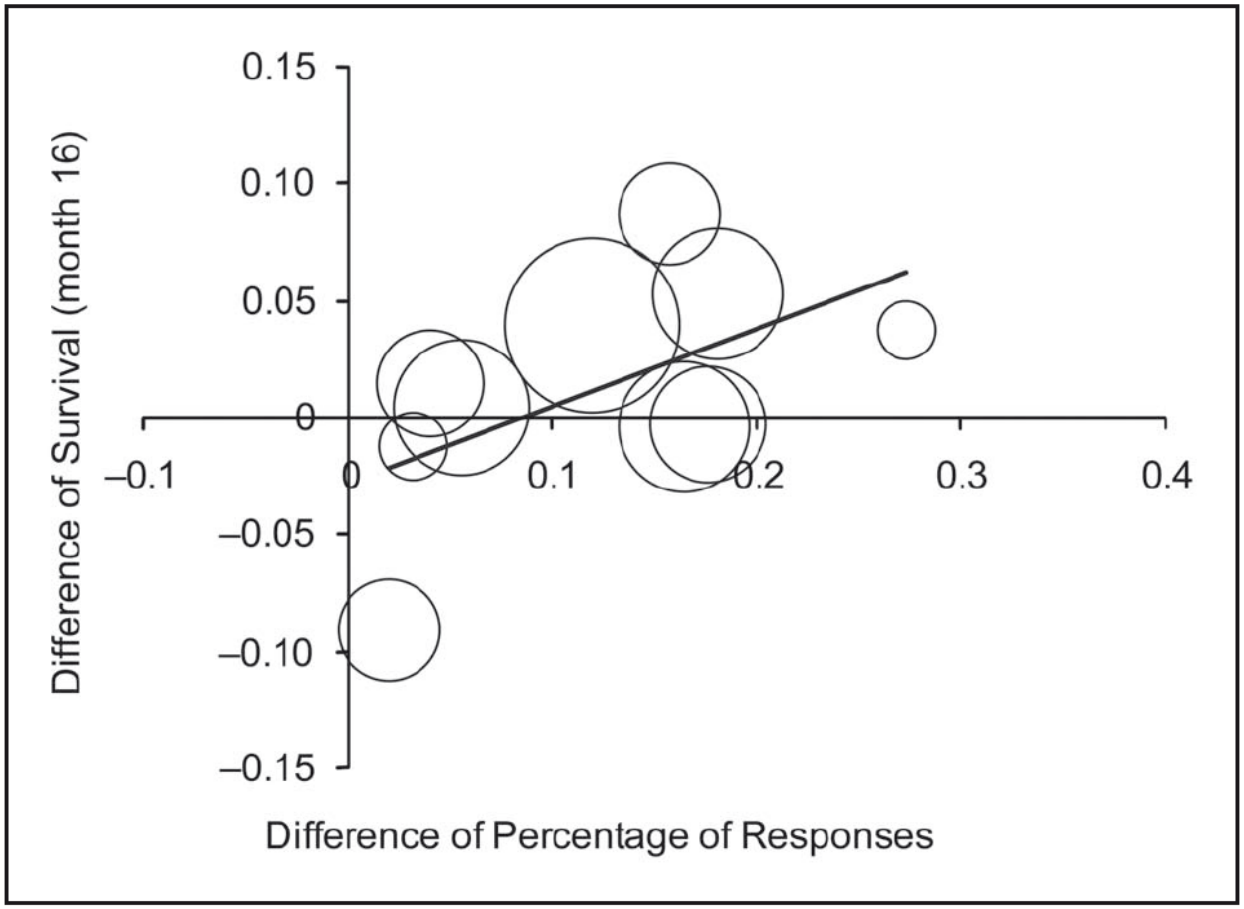
Clinical Genitourinary Cancer, Vol. 11, No. 4, 385-9 © 2013 Elsevier Inc.



Objective Response to Chemotherapy As a Potential Surrogate End Point of Survival in Metastatic Breast Cancer Patients

Paolo Bruzzi, Lucia Del Mastro, Maria P. Sormani, Lars Bastholt, Marco Danova, Christian Focan, George Fountzilas, James Paul, Riccardo Rosso, and Marco Venturini

J Clin Oncol 23:5117-5125. © 2005 by American Society of Clinical Oncology

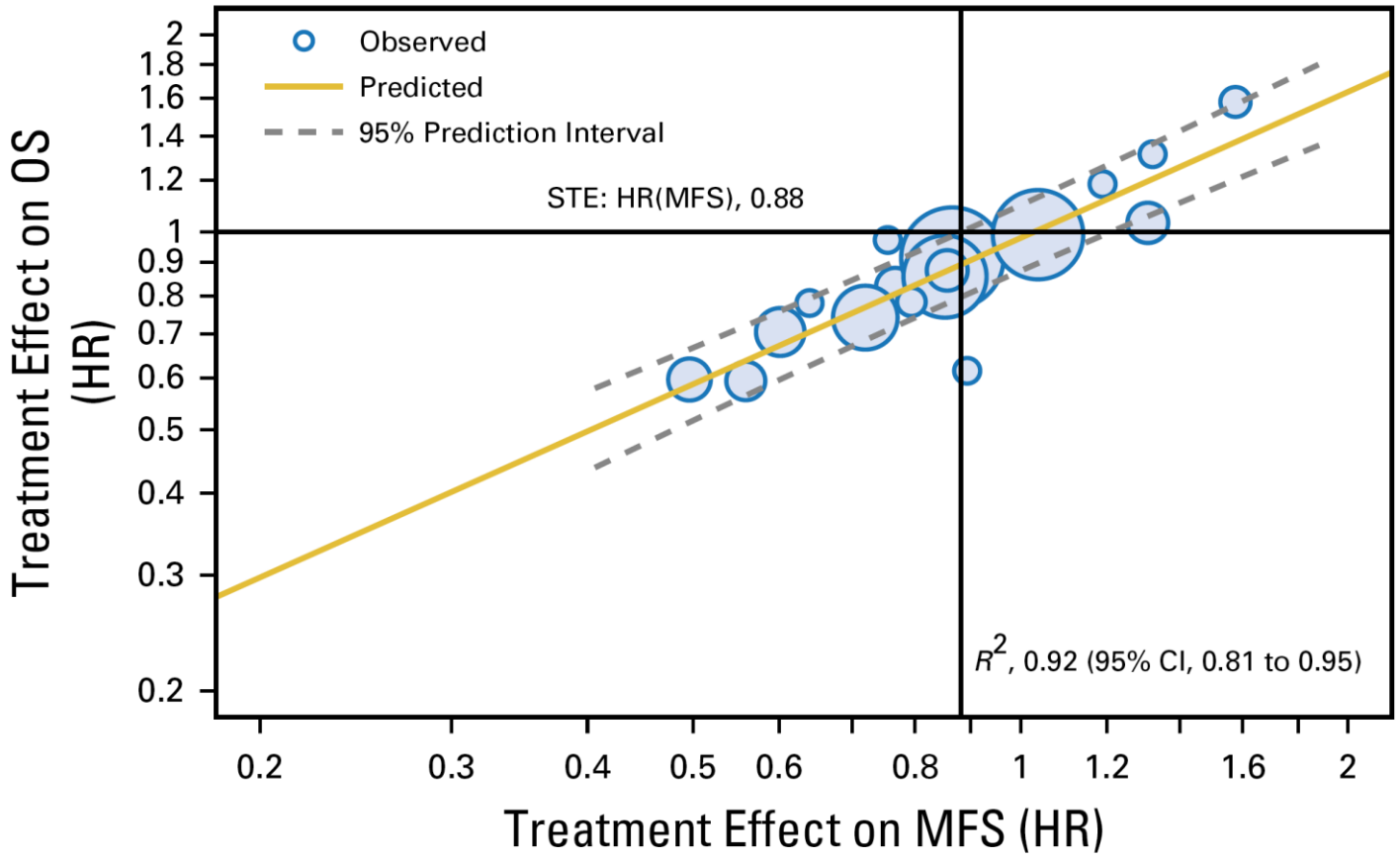


($R^2 = 0.20$; 95% CI, 0 to 0.65)

Metastasis-Free Survival Is a Strong Surrogate of Overall Survival in Localized Prostate Cancer

Wanling Xie, Meredith M. Regan, Marc Buyse, Susan Halabi, Philip W. Kantoff, Oliver Sartor, Howard Soule, Noel W. Clarke, Laurence Collette, James J. Dignam, Karim Fizazi, Wendy R. Paruleker, Howard M. Sandler, Matthew R. Sydes, Bertrand Tombal, Scott G. Williams, and Christopher J. Sweeney, on behalf of the ICECaP Working Group

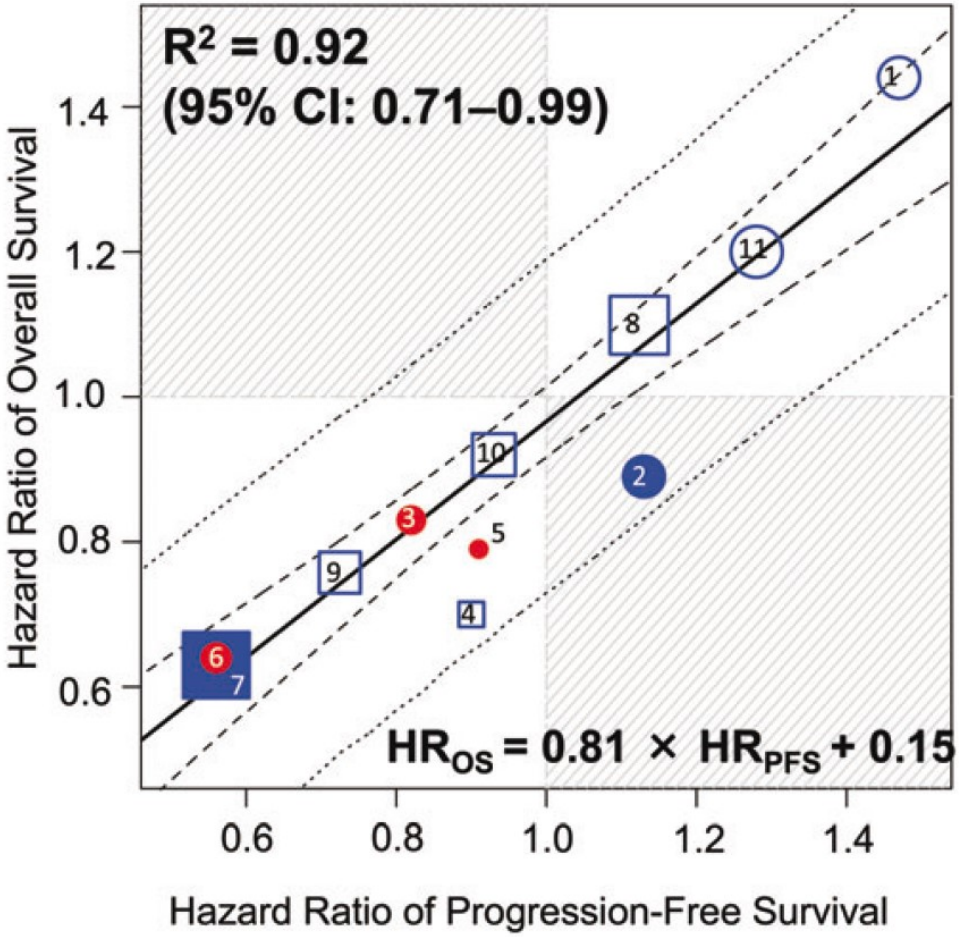
J Clin Oncol 35:3097-3104. © 2017 by American Society of Clinical Oncology



Progression-free survival as a surrogate endpoint for overall survival in glioblastoma: a literature-based meta-analysis from 91 trials

Kelong Han, Melanie Ren, Wolfgang Wick, Lauren Abrey, Asha Das, Jin Jin, and David A. Reardon

Neuro-Oncology 16(5), 696–706, 2014



Round symbols:	Glioblastoma
Square symbols:	Mixed high-grade glioma
Solid symbols:	Newly diagnosed
Hollow symbols:	Recurrent
———	Weighted linear fit
- - - - -	95% confidence interval
----------	95% prediction interval
Blue symbols:	Head-to-head comparison
Red symbols:	Single-arm trials using historical data as control

Linear regression determined that a 10% PFS risk reduction would yield an 8.1% ± 0.8% OS risk reduction.

Prostate-Specific Antigen (PSA) as a Surrogate End Point for Survival in Prostate Cancer Clinical Trials

Laurence Collette

EUROPEAN UROLOGY 53 (2008) 6–9

Prognostic versus surrogate

A [redacted] is a set of physical signs or laboratory measurements that occur in association with a [redacted] and are significantly ass[redacted]lution and survival of [redacted]emical relapse after radical prostatectomy is prognostic for clinical relapse.

…in the individual patient

A [redacted] a "(set of) biochemical measurements [redacted] clinical signs used as [redacted]t in the assess-me[redacted]

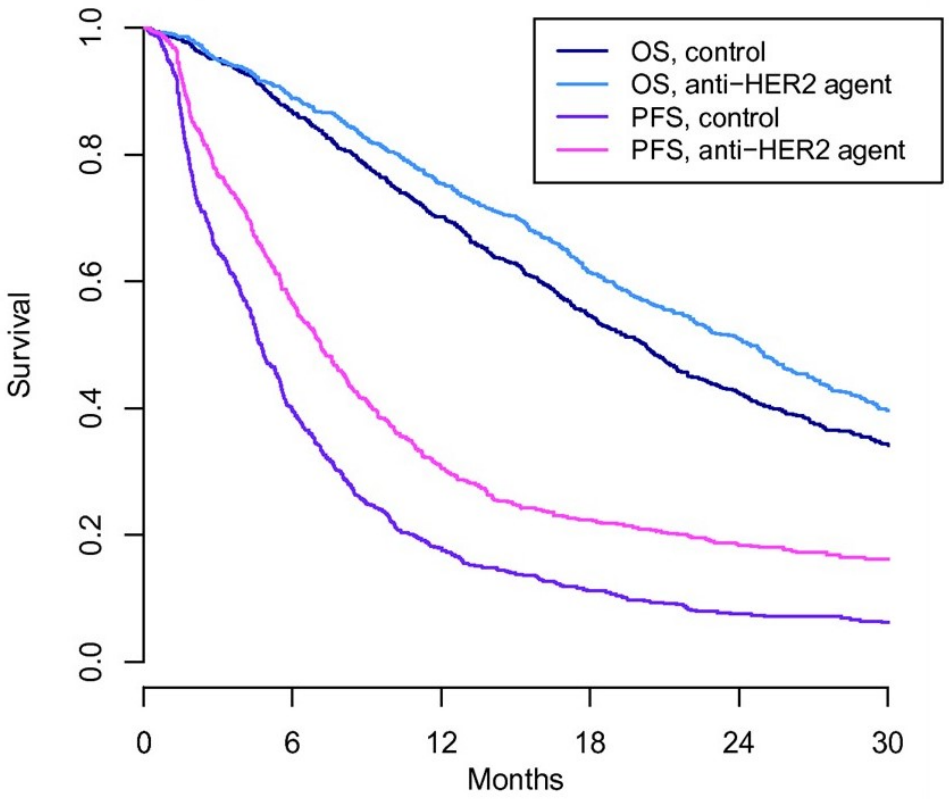
…across groups of patients

Progression-free survival (PFS) as surrogate endpoint for overall survival (OS) in clinical trials of HER2-targeted agents in HER2-positive metastatic breast cancer (MBC): An individual patient data (IPD) analysis.

S. Michiels[1,2], L. Pugliano[1,3], D. Grun[1], S. Marguet[2], J. Barinoff[4], D. Cameron[5], M. Cobleigh[6], A. Di Leo[7], S. Johnston[8], G. Gasparini[9], B.Kaufman[10], M. Marty[11], V. Nekjudova[12], S. Paluch-Shimon[13], F.Penault-Llorca[14], D. Slamon[15], C. Vogel[16], G. von Minckwitz[12], M. Buyse[17], M. Piccart[1,3]

ASCO 2013
CHICAGO
30 MAY - 04 JUN

Individual level ρ=0.66 (95% CI 0.65-0.66)



- For HER2-targeted therapies in HER2+ MBC, PFS is moderately correlated with OS at the individual level (ρ=0.66)

Progression-free survival (PFS) as surrogate endpoint for overall survival (OS) in clinical trials of HER2-targeted agents in HER2-positive metastatic breast cancer (MBC): An individual patient data (IPD) analysis.

S. Michiels[1,2], L. Pugliano[1,3], D. Grun[1], S. Marguet[2], J. Barinoff[4], D. Cameron[5], M. Cobleigh[6], A. Di Leo[7], S. Johnston[8], G. Gasparini[9], B.Kaufman[10], M. Marty[11], V. Nekjudova[12], S. Paluch-Shimon[13], F.Penault-Llorca[14], D. Slamon[15], C. Vogel[16], G. von Minckwitz[12], M. Buyse[17], M. Piccart[1,3]

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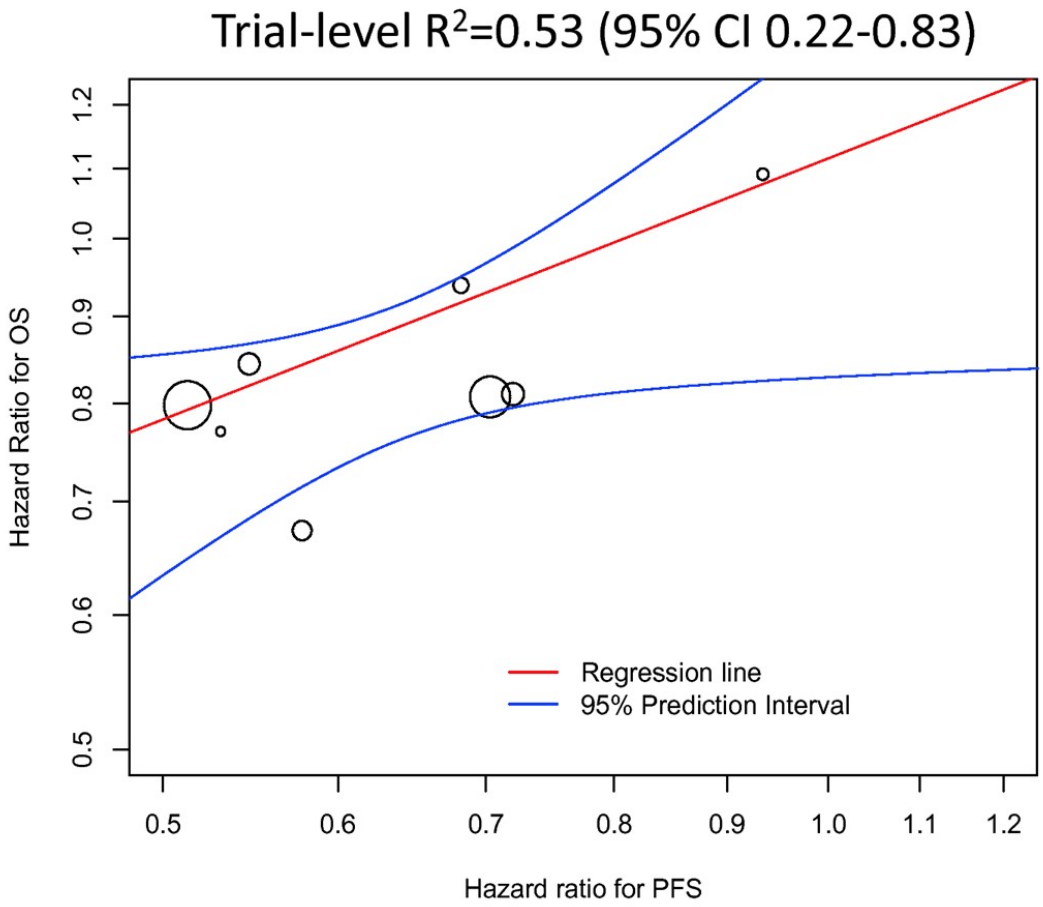

- At the trial level, only 53% of the variation in treatment effects on OS can be explained by effects on PFS (trial-level R^2=0.53).

Surrogate outcome markers in research and clinical practice

Scott Twaddell

(Aust Prescr 2009;32:47–50)

Table 1

Surrogate markers often used in clinical practice

Generally accepted as valid		Doubt still exists about validity	
Surrogate marker	**Predicts**	**Surrogate marker**	**Predicts**
HbA1c	Diabetic microvascular complications	HbA1c	Diabetic macrovascular complications
FEV_1	Mortality in chronic obstructive pulmonary disease	Bone mineral density	Fracture risk
Blood pressure	Primary and secondary cardiovascular events	Prostate specific antigen	Prognosis of prostate cancer
Viral load	Survival in HIV infection	Suppression of arrhythmia	Long-term survival
Cholesterol concentration	Primary and secondary cardiovascular events	Carotid intima-media thickness	Coronary artery disease
Intraocular pressure	Visual loss in glaucoma	Albuminuria	Cardiovascular events

HbA1c glycated haemoglobin

FEV_1 forced expiratory volume in one second