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The pitfalls of surrogate endpoints in cancer research

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The Pitfalls of Surrogate Endpoints in Cancer Research

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Declaration of interest

- Co-chief investigator on SPIRIT-SURROGATE and CONSORT-SUROGATE extensions has been funded by the UK Medical Research Council (grant number MR/V038400/1).

Presentation

- **Definition & rationale for surrogate endpoints in oncology trials**
- **Risks of surrogate endpoints**
- **Best practice for use of surrogate endpoints in oncology research**
  - Validation
  - Improved reporting

Surrogate Endpoints – Definition

- An endpoint that is used in clinical trials as a **substitute** for a direct measure of how a patient feels, functions, or survives.
- A surrogate endpoint does not measure the clinical benefit of primary interest in and of itself, but rather is expected to **predict** that clinical benefit or harm based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence.

Surrogate endpoints - rationale

- **Improve trial efficiency**
  - Reduce trial follow up, sample size, and thus, overall cost
- **Reduce final outcome bias**
  - Oncology: use of cross over (rescue) treatments in metastatic setting introduce OS bias
- **Accepted by regulators (FDA/EMA) in drug licensing**
  - “accelerated pathway” approval/orphan drug and biologic indications

FDA table of oncology surrogates


U.S. FOOD & DRUG ADMINISTRATION

← Home / Drugs / Development & Approval Process | Drugs / Development Resources / Table of Surrogate Endpoints That Were the Basis of Drug Approval or Licensure

Table of Surrogate Endpoints That Were the Basis of Drug Approval or Licensure

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Development Resources

Antibacterial Drug Development Task Force

BEST Resource Taxonomy

Clinical Outcome Assessment

What is the purpose of the Surrogate Endpoint Table?

FDA's surrogate endpoint table provides valuable information for drug developers on endpoints that may be considered and discussed with FDA for individual development programs. This table also fulfills a 21st Century Cures Act requirement to publish a list of "surrogate endpoints which were the basis of approval or licensure (as applicable) of a drug or a biological product" under both accelerated and traditional approval pathways.

https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure

Surrogate endpoint	Treatment setting
Durable objective response rates (ORR)	solid/heam
Progression-free survival (PFS)	solid/heam
Disease-free survival (DFS)	solid [adj]
Event-free survival (EFS)	solid/heam
Pathological complete response	breast
Metastasis-free survival	nonmetastatic castrate-resistant prostate
Plasma testosterone levels	adv prostate
Major hematologic & cytogenic response	heam
Major molecular response	haem

Use of surrogate endpoints

Disease-centered characteristics ⟷ *Patient-centered characteristics*

Biomarker

defined characteristic (molecular, histologic, radiographic, or physiologic that is measured as an indicator of responses to an exposure or intervention, including therapeutic interventions*

e.g., SBP/LDL-chol

e.g., PFS/ORR

Final patient relevant outcome

measurement that reflects how an individual feels, functions, or survives.
Most credible measurement when assessing the risks and benefits of interventions**

Cardiovascular events

Overall Survival

**FDA-NIH Biomarker Working Group, 2021*
***https://jamanetwork.com/journals/jama/fullarticle/2762451*

Use of surrogate endpoints

Disease-centered characteristics ⟷ *Patient-centered characteristics*

Intermediate outcome

an endpoint measuring a clinical outcome that can be measured earlier than an effect on [final outcome] and that is considered reasonably likely to predict the medical product's effect on [final outcome]" *

Final patient relevant outcome

e.g., exercise capacity → **HF Mortality/HRQoL**

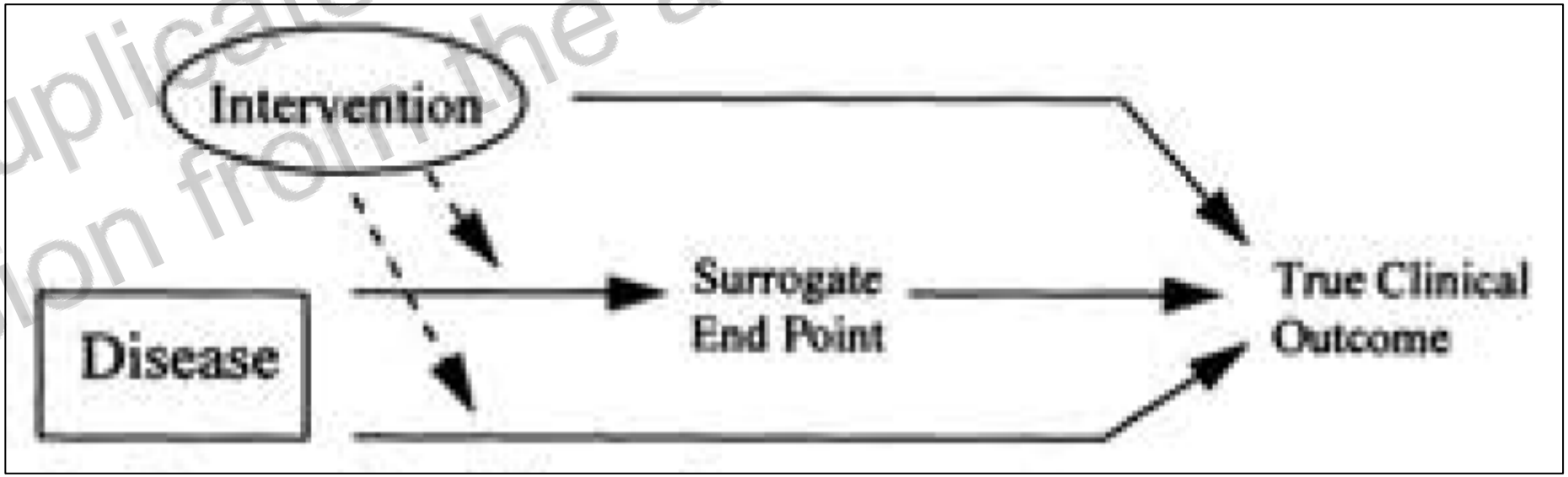
e.g., fruit & veg consumption → **CV events**

**FDA-NIH Biomarker Working Group, 2021*

Risk of surrogates

- Overestimation of treatment effects (& cost-effectiveness)

- Surrogate failure: no true (final outcomes) benefit or more harm than benefit

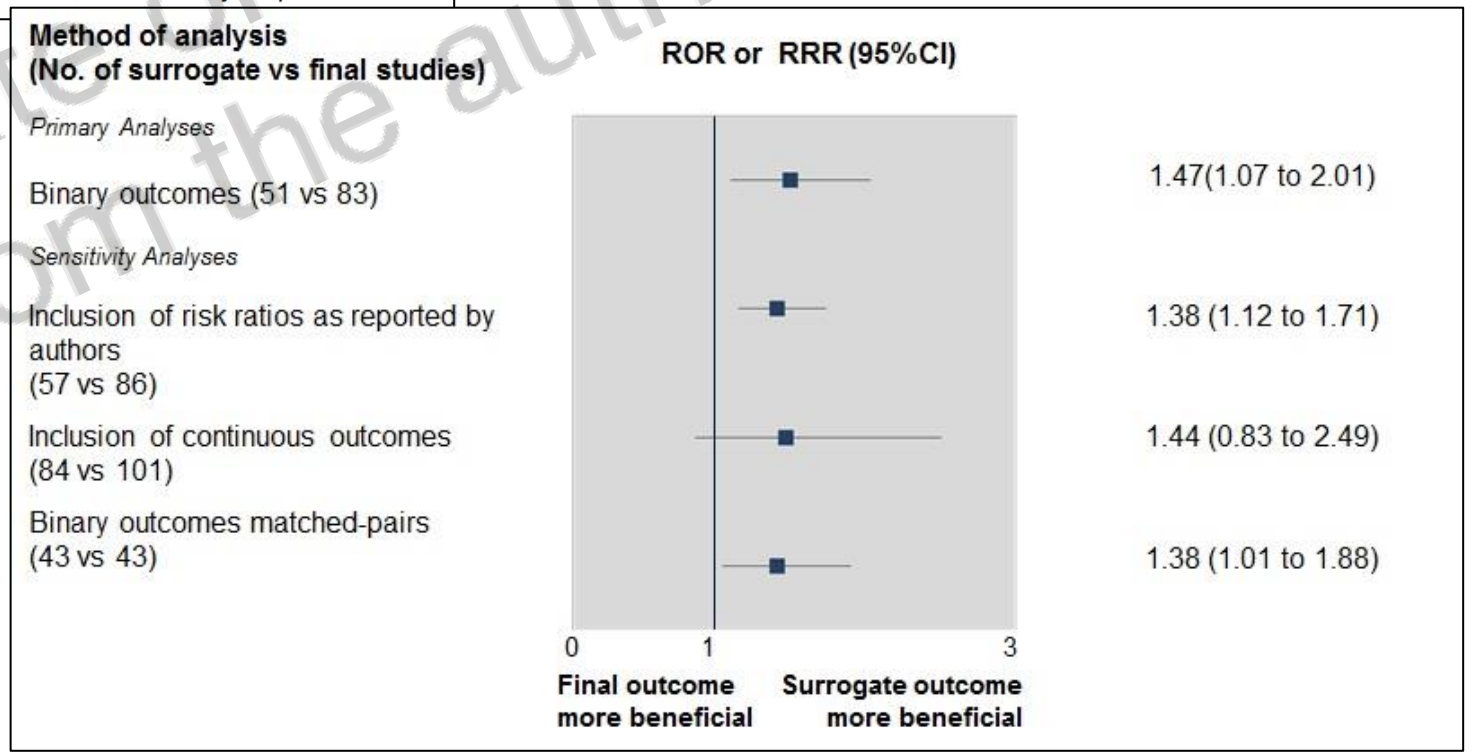


Overestimation of treatment effects

Comparison of treatment effect sizes associated with surrogate and final patient relevant outcomes in randomised controlled trials: meta-epidemiological study

BMJ 2013;346:f457 BMJ

Oriana Ciani *PhD candidate*[1], Marc Buyse *chairman*[2], Ruth Garside *senior lecturer*[1], Toby Pavey *research fellow*[3], Ken Stein *professor*[1], Jonathan A C Sterne *professor*[4], Rod S Taylor *professor*[1]



Bevacizumab (Avastin) & Breast Cancer

The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 2007;357:2666-76.

ORIGINAL ARTICLE

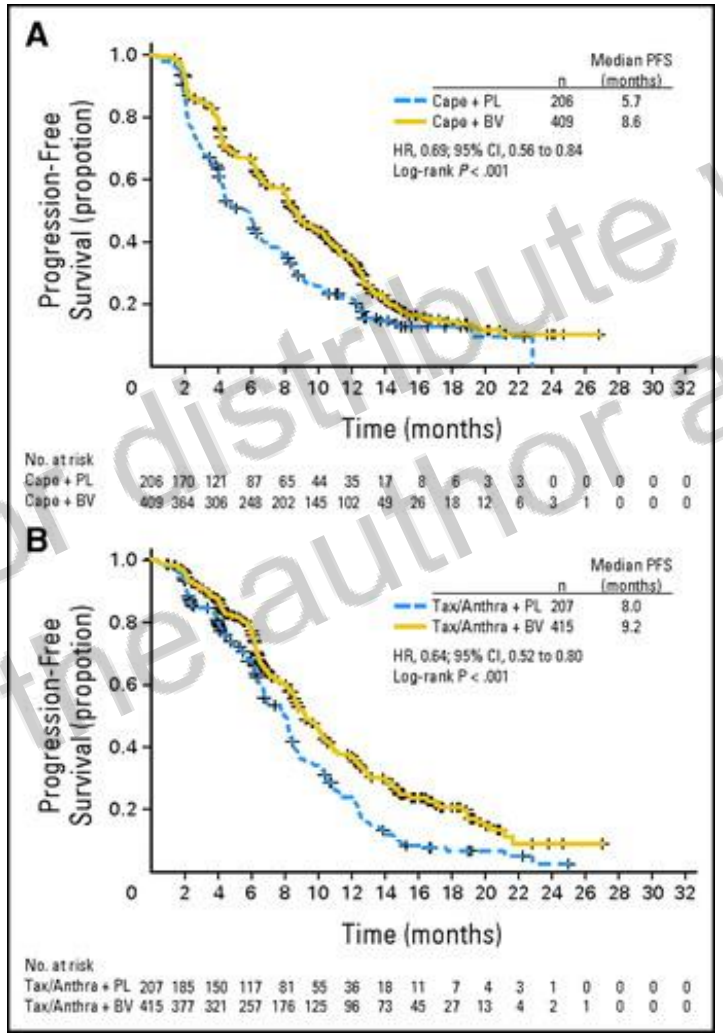
Paclitaxel plus Bevacizumab versus Paclitaxel Alone for Metastatic Breast Cancer

Kathy Miller, M.D., Molin Wang, Ph.D., Julie Gralow, M.D., Maura Dickler, M.D., Melody Cobleigh, M.D., Edith A. Perez, M.D., Tamara Shenkier, M.D., David Cella, Ph.D., and Nancy E. Davidson, M.D.

J Clin Oncol 29:1252-1260. © 2011

RIBBON-1: Randomized, Double-Blind, Placebo-Controlled, Phase III Trial of Chemotherapy With or Without Bevacizumab for First-Line Treatment of Human Epidermal Growth Factor Receptor 2–Negative, Locally Recurrent or Metastatic Breast Cancer

Nicholas J. Robert, Véronique Diéras, John Glaspy, Adam M. Brufsky, Igor Bondarenko, Oleg N. Lipatov, Edith A. Perez, Denise A. Yardley, Stephen Y.T. Chan, Xian Zhou, See-Chun Phan, and Joyc



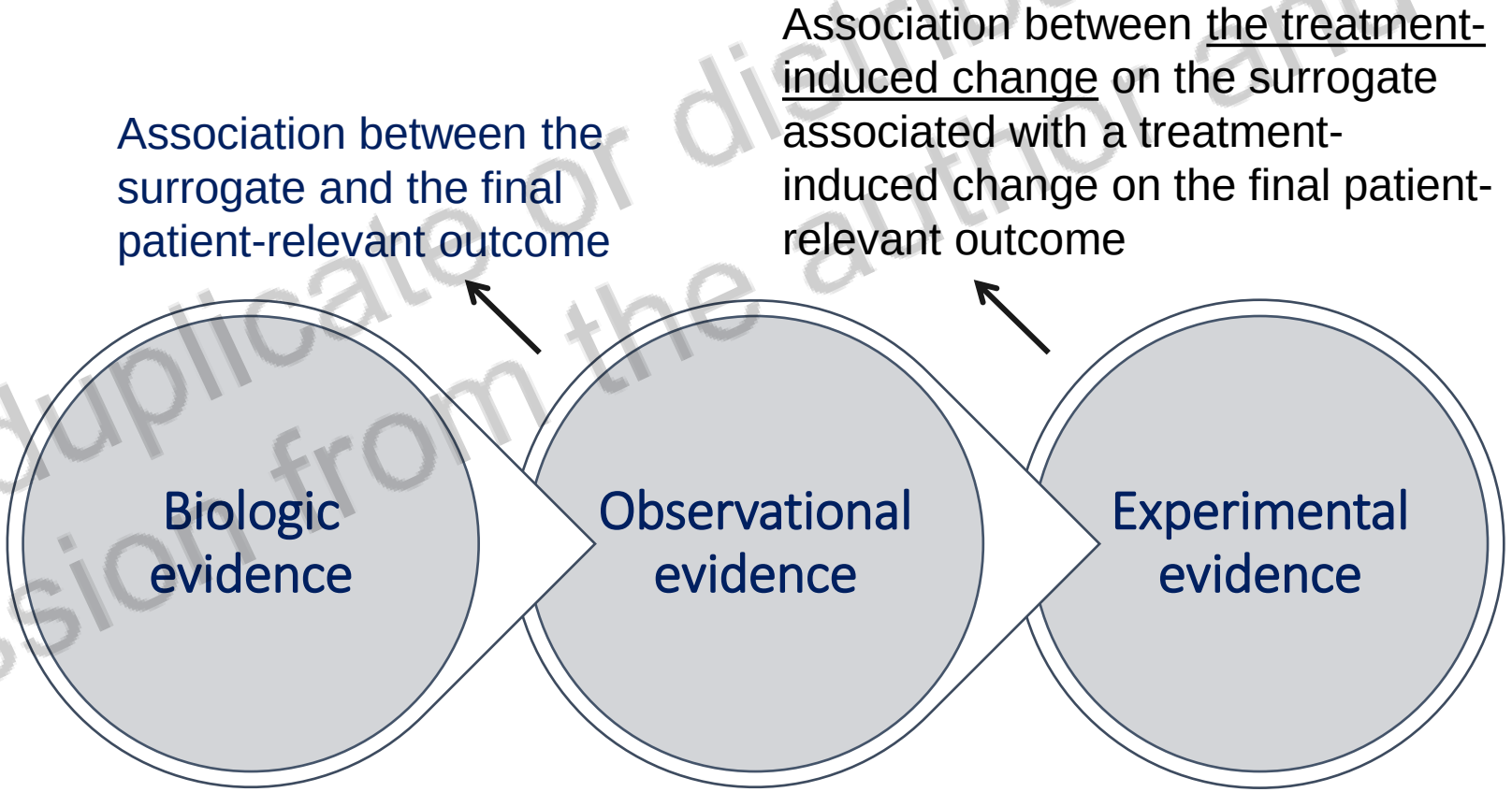
Jul 2010 FDA withdrew approval

EMA approval remains

	OS HR (95% CI)
Cape +placebo vs Cape +BV	0.85 (0.623 to 1.14)
Tax/Anthra + placebo vs Tax/Anthra + BV	1.03 (0.77 to 1.38)

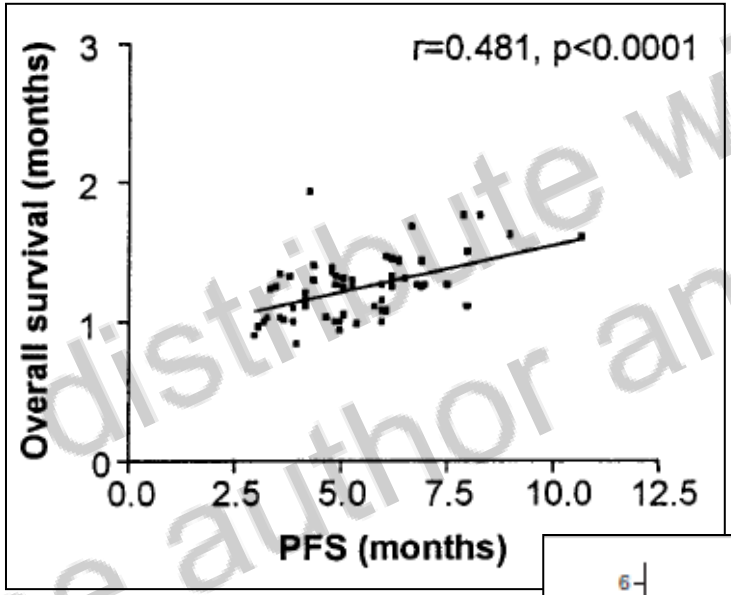
Validation of surrogate endpoints

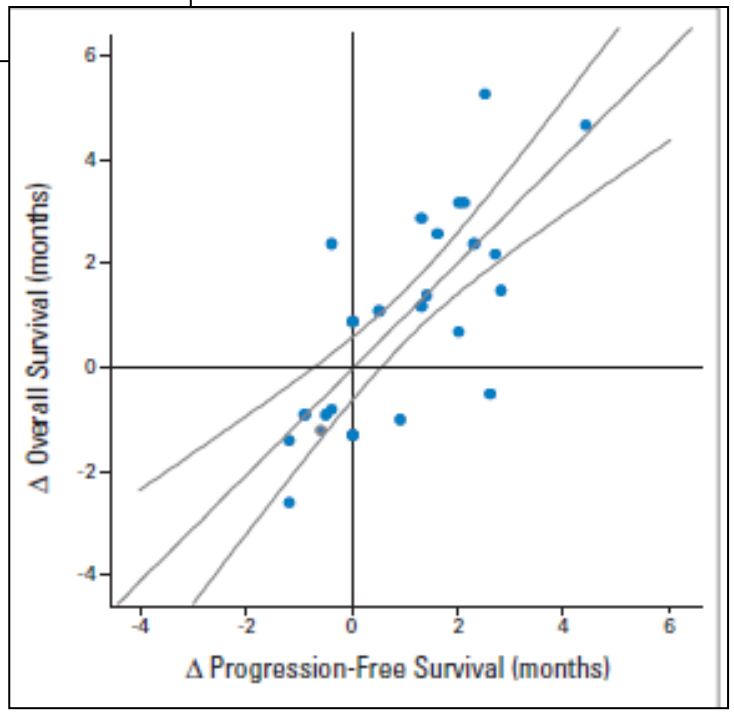
- It is fundamental then to establish the **"validity" of a putative surrogate**
- **i.e., the effect of the intervention on the propsed surrogate endpoint reliably predicts its effect on the final patient relevant outcome**



Validation of Surrogate Endpoints

- Variety of proposed statistical techniques and metrics for validation
- Correlation-based' and 'meta-analytic' approaches currently dominate the field
- Individual-level association (Observational or 1 RCT suffice) & **Trial-level association** (several RCTs needed)





Performance of Proposed Oncology Surrogate Endpoints

Critical Reviews in Oncology / Hematology 123 (2018) 21–41

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Meta-analyses evaluating surrogate endpoints for overall survival in cancer randomized trials: A critical review

Marion Savina[a,b,c,d,*], Sophie Gourgou[e], Antoine Italiano[f,g], Derek Dinart[a], Virginie Rondeau[c], Nicolas Penel[h], Simone Mathoulin-Pelissier[a,b,c,d], Carine Bellera[a,b,c,d]

- 164 meta-analyses across all cancer types/settings
- Categorised associations as 'high' if r>0.7 or R^2>0.50
- Only 12 meta-analyses [illegible] eria

Endpoint	Cancer localization	Disease specifications	Treatment specifications
DFS	Colon cancer	Stage II or III patients	Adjuvant setting, fluoropyrimidines alone or in combination
	Lung cancer	Operable and locally advanced NSCLC	Adjuvant treatment by chemotherapy and/or radiotherapy
	Gastric cancer	Curatively resected gastric cancer	Adjuvant chemotherapy
	Head & neck cancer	Locally advanced disease	Adjuvant chemotherapy
PFS	Colorectal cancer	Advanced/Metastatic disease	Fluorouracil- and leucovorin-based chemotherapy
	Lung cancer	Locally advanced NSCLC	Radiotherapy alone or in combination with chemotherapy
	Lung cancer	Locally advanced SCLC or NSCLC	Radiotherapy
	Head & neck cancer	Locally advanced disease	Radiotherapy

Conclusions

- Surrogate endpoints (for OS) widely used in interventional trials in oncology and will continue to be…
  - involve a trade off before trial efficiency/speed of access vs decision uncertainly
- Focus licensing/coverage/clinical practice on surrogate endpoints with strong statistical evidence of validation
  - OS can be confounded due to treatment-over/use rescue therapy
  - Setting specific (treatment regimen, treatment line, cancer type, cancer stage) association
- Future application
  - Increased focus on HRQoL? New surrogates
    More transparent trial reporting

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Reporting Guidelines for Surrogate Endpoints

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The next e-ESO Session

will take place on 3rd May 2022, at the same time

Cancer cachexia

Expert: **Prof Jann Arends**, University of Freiburg, Freiburg, Germany

Discussant: **Dr Tora Skeidsvoll Solheim**, St.Olavs University Hospital, Trondheim, Norway

Thank you!

for participating in this
e-session
For additional information, please visit
www.e-eso.net