Extrapolation from Progression Free Survival to Overall Survival in Oncology

Karla Hernandez-Villafuerte[a], Alastair Fischer[b], Nicholas Latimer[c] and Christopher Henshall[d]

[a]German Cancer Research Centre, [b]Office of Health Economics, [c]ScHARR-University of Sheffield, [d]Independent consultant

AES Spain, 2017

Background

- Differences in overall survival (OS) between experimental and control arms are often small and do not reach significance
  - Significance requires long follow-ups, sometimes very long ones
    - This increases costs of development and delays approval time
  - The size of treatment effects on OS are difficult to capture
    - Cross-over of patients from one therapy to another
- Need for surrogate endpoints
  - Progression free survival (PFS) will be available much earlier, so is cheaper and results will be known sooner

But PFS may not always proved to be highly correlated with OS or with treatment

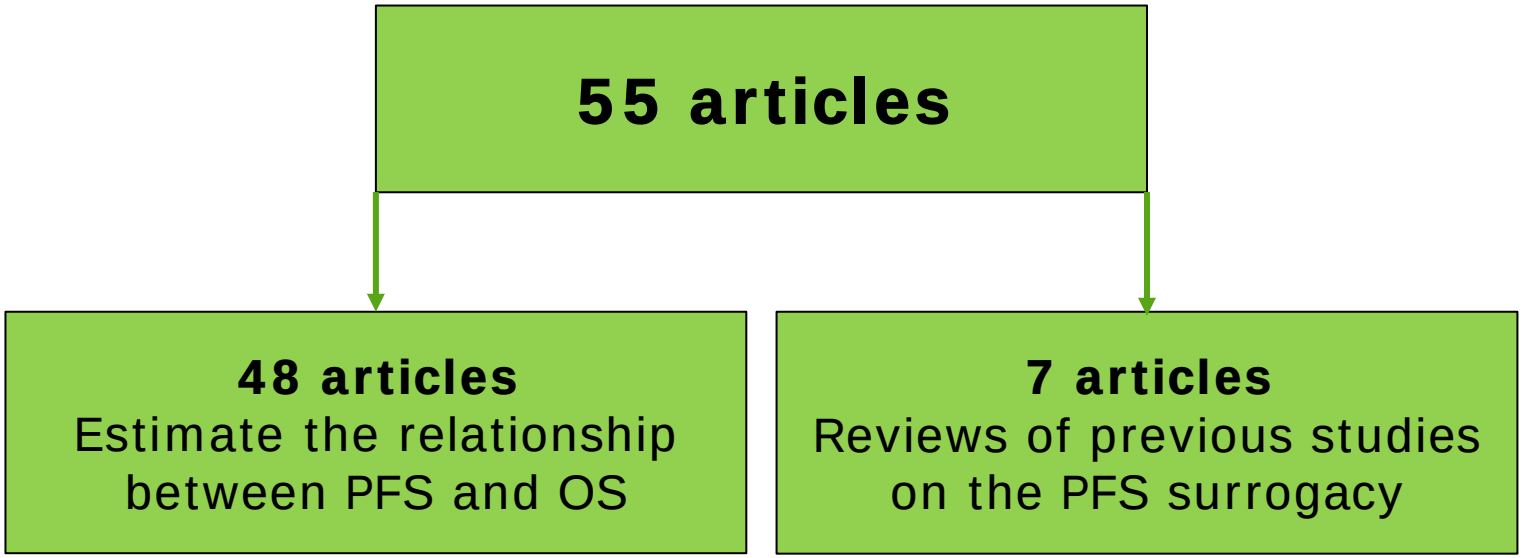
Objectives

- Identify and explain what the statistical and health economics issues are with current approaches to extrapolating from PFS to OS
- Identify the principal weaknesses and gaps in current methods and approaches where further research is required

Methodology

- Literature review - Citation searching
- Updated the evidence found by
  - Davis, S., Tappenden, P., Cantrell, A., 2012. *Review of studies examining the relationship between PFS and OS in advanced or metastatic cancer*. University of Sheffield
    - Relationship between PFS and OS in advanced or metastatic cancer (2001-2011): 19 articles
- Our citation search based on the 19 articles
  - Google Scholar: January 2012 to June 2016
  - Inclusion criteria similar to Davis et al. (2012)

RESULTS BASED ON



Comparison (1)

Table 1. Studies that estimate the relationship between PFS and OS

	Davis et al., 2012 (2001-2011)				Current Review (2012-2016)			
	All	ACTD*	IPD†	Both	All	ACTD*	IPD†	Both
#Articles	19	12 (63%)	4 (21%)	3 (16%)	48	32 (67%)	10 (21%)	6 (12%)
#Patients	193 – 44,125	4,323 - 44,125	193 - 1,296	870 – 3,953	35 - 43,459	2,148 - 43,459	35 – 2,331	689 - 16,762
#Clinical Trials	3 - 191	13 – 191	3 – 9	9 – 11	1- 153	6 – 153	1 – 7	8 – 29
R^2	0.26 - 0.98	0.26 - 0.65	NA	0.79 – 0.98	0.00 - 0.97	0.00 - 0.97	0.24 - 0.72	0.45 - 0.89
Correlation	0.30 - 0.89	0.47 - 0.89	0.30 - 0.66	0.48 – 0.82	0.13 - 0.87	0.26 - 0.87	0.13 - 0.86	0.45 - 0.85

* Aggregate clinical trial data (ACTD)
† Individual patient data (IPD)

Range has increased in every group for both R^2 and correlation value

Comparison (2)

Table 2. Cancer types*

	Davis et al., 2012 (2001-2011)	Current Review (2012-2016)
NSCLC	5	10
Colorectal Cancer	7	7
Others	3	7
Renal cell carcinoma	1	6
Gastric cancer	0	6
SCLC/Lung	1	4
Breast Cancer	6	3
Multiple myeloma	0	2
Urothelial	0	2
No particular cancer type	0	1

*For the 48 studies that estimate the relationship between PFS and OS

PFS as surrogate has grown in areas where surrogates were pioneered

Its used has spread to other forms of cancer

Methodologies

- Two factors are tested (in accordance with Prentice, 1989)
  - The PFS capacity of predicting OS (ACTD and IPD)
  - Treatment effect on PFS as predictor of the treatment effect on OS (ACTD)
- Similar to Davis et al. (2012), findings suggest that the most usual methods are
  - Correlation (34/48)
    - Spearman, Pearson and Kendall's τ
  - Weighted or unweighted linear regression (35/48)

Many different variations of these methodologies

Surrogate threshold effect (STE)

Minimum treatment effect on PFS that ensures with 95% confidence a non-zero effect on OS

	Cancer type	Type of Study	STE
Maugue et al. (2013)	Lung	Both*	From 0.93 to 1.00 depending on therapy
Sidhu et al. (2014)	Colorectal	ACTD	0.90
Chen et al. (2015)	Nasopharyngeal	ACTD	PFS vs OS: 0.88 / PFS 3 years vs 5 years OS: 0.84
Foster et al. (2015)	SCLC	Both*	0.67
Shi et al. (2015)	Colorectal	Both*	0.57
Laporte et al. (2013)	NSCLC	IPD	0.49-centers / 0.53-strata
Johnson et al. (2015)	Renal cell carcinoma	ACTD	All-trials and immunotherapy-only trials failed to demonstrate a STE. A targeted therapy trial needs a PFS difference of at least 3.7 months
Moriwaki et al. (2016)	Biliary tract	ACTD	0.83
Paoletti et al. (2013)	Gastric	Both*	0.56
Ciani et al. (2015)	Colorectal	ACTD	0.80
Michiels et al. (2016)	Breast	Both*	0.72

* “Both” means ACTD together with IPD

Appropriate surrogate | Depends on particular factors | PFS is not an appropriate surrogate

Lack of rigour in applying methodology

- It is unclear whether methodologies' main assumptions have been properly tested
  - e.g. Outliers

Fig 1. Advanced non-small cell lung cancer

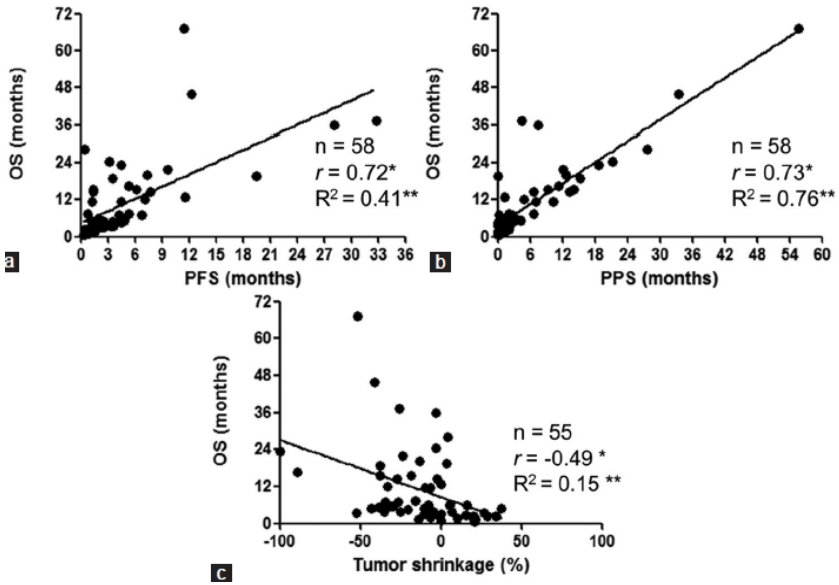
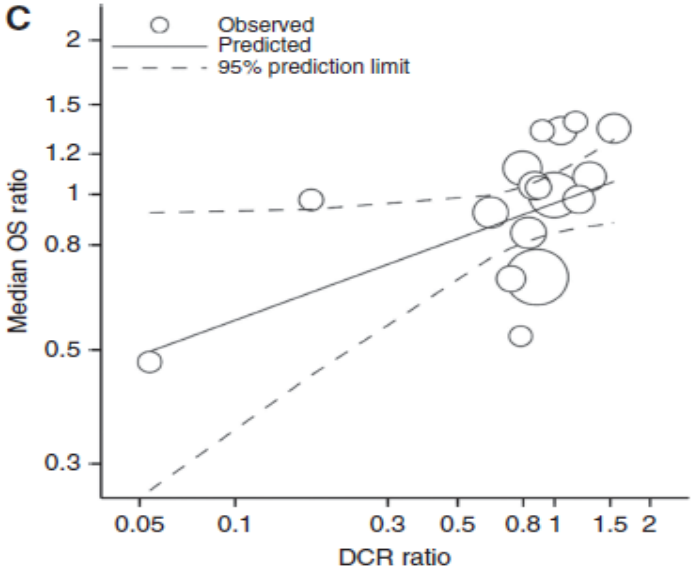


Fig 2. Advanced biliary tract cancer



Factors influencing PFS – OS relationship: Challenges

- Different types of treatment and/or therapy (24 articles)
  - Within the same cancer type often leads to PFS being a good surrogate in some cases and a poor one in others
- Treatment line 1st/2nd/3rd (13 articles)
- Year of the trial (13 articles)
  - The criteria applied to measure progression have changed (RECIST 2000 modified in 2010 to mRECIST)
- Sub-group of patients or tumour type (10 articles)

Factors influencing PFS – OS relationship: Challenges (2)

- Definition of PFS and other measures (9 articles)
  - Disease progression defined differently between clinical trials
    - e.g. time intervals between radiologic and clinical assessments
  - Studies combine PFS and TTP into a single surrogate measure (19/32 ACTD)
- Geographical context (6 articles)
  - Standard treatment varies between Europe and Asia
- Crossover (6 articles)
  - Results among crossover trials range from the strength of the association being higher, to no significant differences, to lower

Post-progression survival (PPS)

- PPS analysed together with PFS
- A group of Japanese researchers have studied factors that affect the relationship between PPS and OS
  - Number of regimens employed after progression
  - Response to the 2nd/3rd line treatment
  - Performance status at progression
  - PFS of first line chemotherapy
  - Tumour stage after initial treatment

Conclusions (1)

- In such a complicated area, rules of thumb to determine whether PFS can replace OS do not work in all situations
  - Surrogacy depends on multiple factors
- Lack of any substantial increase in the proportion of articles that include IPD
  - A case could be made for mandatory release of all IPD as a condition of publication
- Need to standardise clinical trial protocols to provide comparability between trials
  - Heterogeneity in the definition of progression
  - Lack of clear information in the clinical trial reports as to how disease progression was evaluated

Conclusions (2)

- Need for understanding factors that affect PPF
  - Protocols for following-up clinical trial patients
- High variation in the characteristics of the methodologies
  - Little apparent consistency in what should be considered appropriate statistical estimation methodology
  - Need for standardisation to facilitate the use of PFS and to increase speed and accuracy of the decision-making

The importance that validating PFS as a surrogate for OS has on allowing patients to access new health technologies more quickly should not be undermined by a poor knowledge of the methodology applied

THANKS FOR YOUR ATTENTION

This research is supported by funding from the Pharmaceutical Oncology Initiative group (POI)

To enquire about additional information and analyses, please contact
Dr. Karla Hernandez-Villafuerte at K.HernandezVillafuerte@dkfz.de