



Disease-Free Survival as a Potential Surrogate Endpoint for Overall Survival in Patients with Early-stage Non-small Cell Lung Cancer: A Systematic Literature Review and Meta-Analyses

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Cancer Immunotherapies in ES-NSCLC

- There is ongoing research on the efficacy and safety of adjuvant **cancer immunotherapies** (CIT) for the treatment of **resectable early-stage non-small cell lung cancer** (ES-NSCLC).
- Available results show that CIT may improve disease-free survival (DFS).

Current Evidence on Surrogate Endpoints

There is **sparse evidence** on the use of DFS as a surrogate for overall survival (OS) in ES-NSCLC. Mauguen et al (2013) previously supported the validity of DFS as a surrogate for OS, using patient- and study-level data from trials of adjuvant chemotherapy.²

Objective & Background

Role of Surrogate Endpoints

Surrogate endpoints can be very useful to provide an **earlier measurement of the treatment effect**, especially when a long follow-up time is required for the measurement of the final clinical outcome.¹

Aim

To investigate **DFS as a potential surrogate endpoint** for overall survival (OS) among patients with **resectable ES-NSCLC**.

1. Bujkiewicz, et al. NICE DSU TSD 20. 2019.

2. Mauguen, et al, Lancet Oncol. 2013.

CIT, cancer immunotherapies; DFS, disease-free survival; ES-NSCLC, early-stage non-small cell lung cancer; OS, overall survival.

Introduction - DFS/OS Surrogacy in Context



Limited research has been done on the **surrogacy** of **DFS** for **OS**



2013

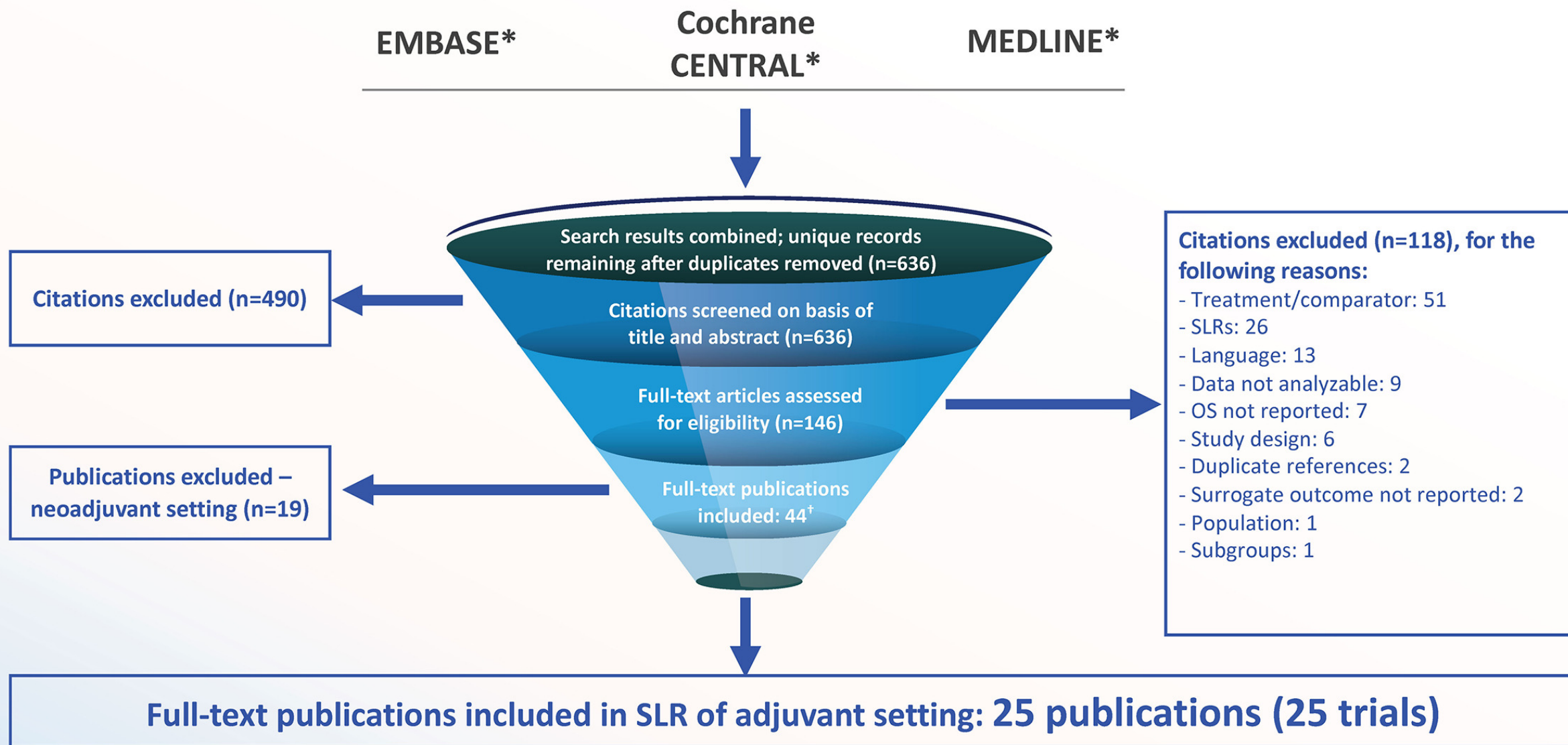
- **Mauguen 2013** evaluated the individual-level and trial-level correlation of 3-year DFS and 5-year OS, as well as HRs for DFS and OS among trials of adjuvant chemotherapy in NSCLC
- Strong correlations were found, with a stronger association among trials assessing post-operative radiotherapy
- Study found high-level evidence that DFS is a **valid surrogate** for **OS** in studies with adjuvant chemotherapy for NSCLC

2022

- **Current study** focuses only on relative treatment effects (HRs)
- Current study includes **14 newer studies** (2013-2022)
- **Greater range of therapies** are included, including newer targeted therapies (gefitinib, pazopanib, erlotinib, osimertinib, bevacizumab, Icotinib)



Methods – Systematic Literature Review



OS, overall survival; SLR systematic literature review.

*Electronic databases were searched via Ovid to identify relevant studies.

†Sixteen citations were included from other sources.

Results – Systematic Literature Review



25 trials were identified, 4 of which were conducted on a global scale, while the other 21 had a regional focus

The median follow-up duration was **1.6 to 7.5** years

5 trials investigated RFS, 1 investigated FFS, while 19 investigated DFS*

6 trials allowed Stage IA patients to enroll (1-10%); 3 trials enrolled Stage IIIB patients (1-7%)

Characteristic	Median (Range)
Age (years)	61 (56.5, 64.5)
% Males	64 (30, 87)
% Squamous	36 (1, 65)
% ECOG 1	42.5 (20, 73.3)

Trials were reasonably similar in terms of age, but there was substantial variation in histology, ECOG, and disease stage

5 trials were excluded from bivariate meta-analysis

- **1** study evaluated **post-operative radiotherapy (PORT)**
- **2** studies used definitions of **DFS** that **differed substantially** from the **remainder**
- **2** studies did not report an **HR** for either **DFS** or **OS**, or both

Remaining 20 trials were deemed sufficiently similar for inclusion for bivariate meta-analysis

- Treatments included gefitinib, pazopanib, erlotinib, osimertinib, bevacizumab, icotinib, as well as standard chemotherapy regimens

*Despite different terminology, DFS, RFS, and FFS were reported consistently as disease recurrence/progression or death due to any cause. Two studies did not include death as a component of DFS.

DFS, disease-free survival; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; FFS, failure-free survival; OS, overall survival; PFS, progression-free survival; RCT, randomized controlled trial; RFS, recurrence-free survival

- **There is no consensus on an acceptable measure of surrogate validity¹**
- Following the National Institute for Health and Care Excellence (NICE) guidance, 3 bivariate meta-analysis (BMA) models were fit to the data
 - **Bivariate random-effects model** (BRMA) in the standard form, which assumes random effects (exchangeability) for the surrogate variable
 - **Product normal formulation** (BMA-PNF) model, which assumes random effects with a different parameterization
 - **Daniels and Hughes** (BMA-DH) model, which treats the surrogate variable as a study-specific fixed effect
- For each model, the **surrogate threshold effect** (STE) was calculated
 - Minimum treatment effect on the surrogate necessary to predict a non-zero effect on the true endpoint²
- Take-one-out **cross-validation** was performed to determine whether observed OS fell within the predicted 95% CI for OS in each study

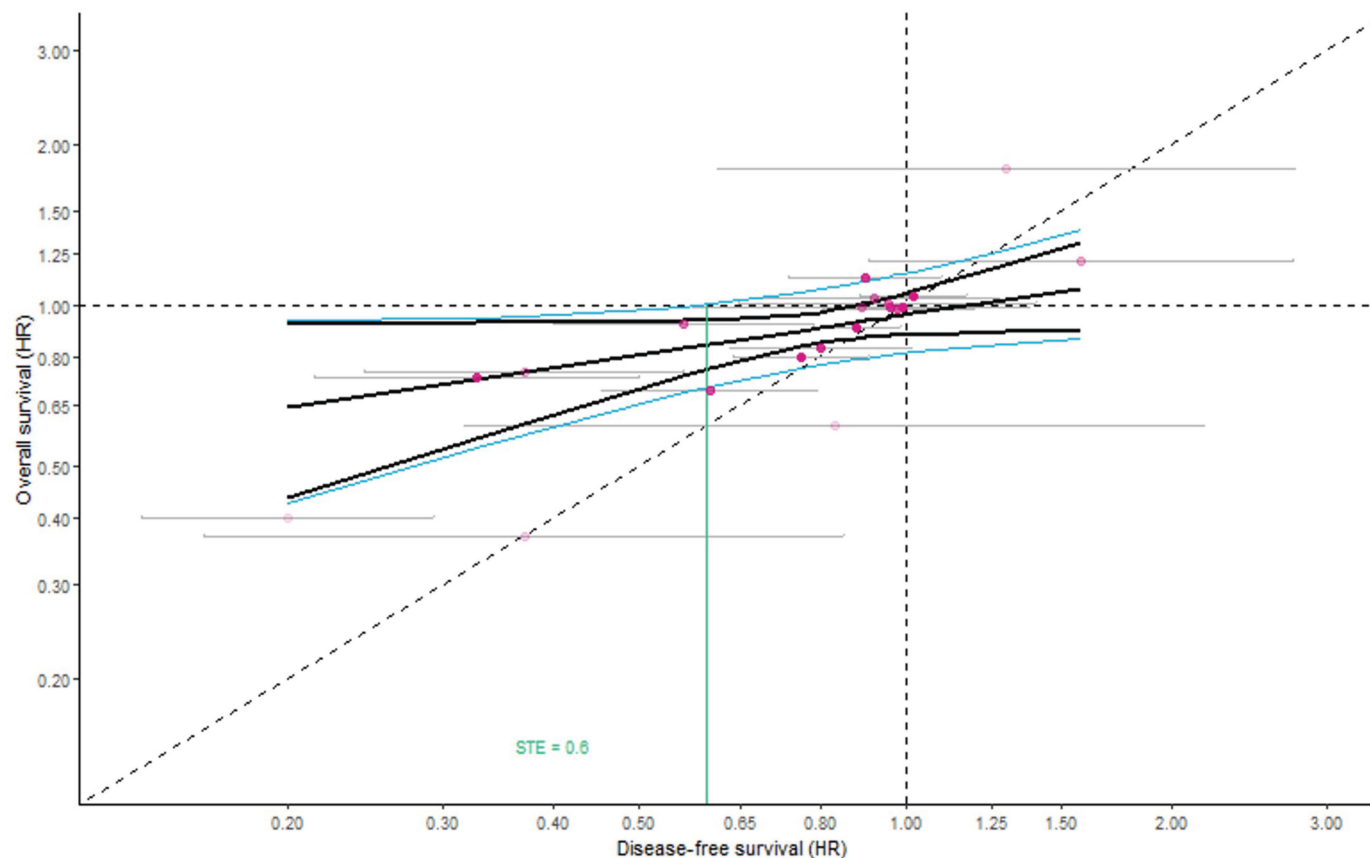
1. IQWiG. General Methods: Version 5.0 of 10. Institute for Quality and Efficiency in Health Care (IQWiG). July 2017.

2. Buzykowsi T, et al. *Pharm Stat*. 2006 Jul-Sep; 5(3): 173-186.

OS, overall survival

Results – Surrogacy Analysis STE

Evaluating the usefulness of **DFS** as a surrogate for **OS** with the **BRMA-standard model**



- **5 of 20** studies reported **DFS** that falls **below the STE** (0.60); **3** with 95% CIs below STE
- **BMA-PNF** and **BMA-DH** models provided **similar results**, with STE 0.59 and 0.68, respectively

Results – BMA Model Parameters

	BRMA	BMA-PNF	BMA-DH
Parameter estimates (median, 95% CrI)			
Slope	0.239 (-0.006, 0.519)	0.241 (-0.005, 0.504)	0.375 (0.177, 0.614)
Intercept	-0.043 (-0.129, 0.049)	-0.045 (-0.134, 0.047)	-0.012 (-0.092, 0.072)
Conditional variance	0.003 (0.000, 0.021)	0.003 (0.0000, 0.021)	0.0021 (0.000, 0.021)
Rho_{between}*	0.871 (-0.123, 0.994)	0.871 (-0.117, 0.994)	-
R²	0.760 (0.025, 0.988)	0.759 (0.023, 0.988)	
DIC	-36.32	-37.35	-25.54
Absolute difference between predicted and observed log HR OS, median (range)	0.099 (0.027 to 0.797)	0.098 (0.0265 to 0.796)	0.105 (0.001 to 0.616)

BMA-DH, bivariate meta-analysis – Daniels and Hughes; BMA-PNF, bivariate meta-analysis - product normal formulation; BRMA, bivariate random-effects meta-analysis; DIC, deviance Information criterion; HR, hazard ratio; OS, overall survival

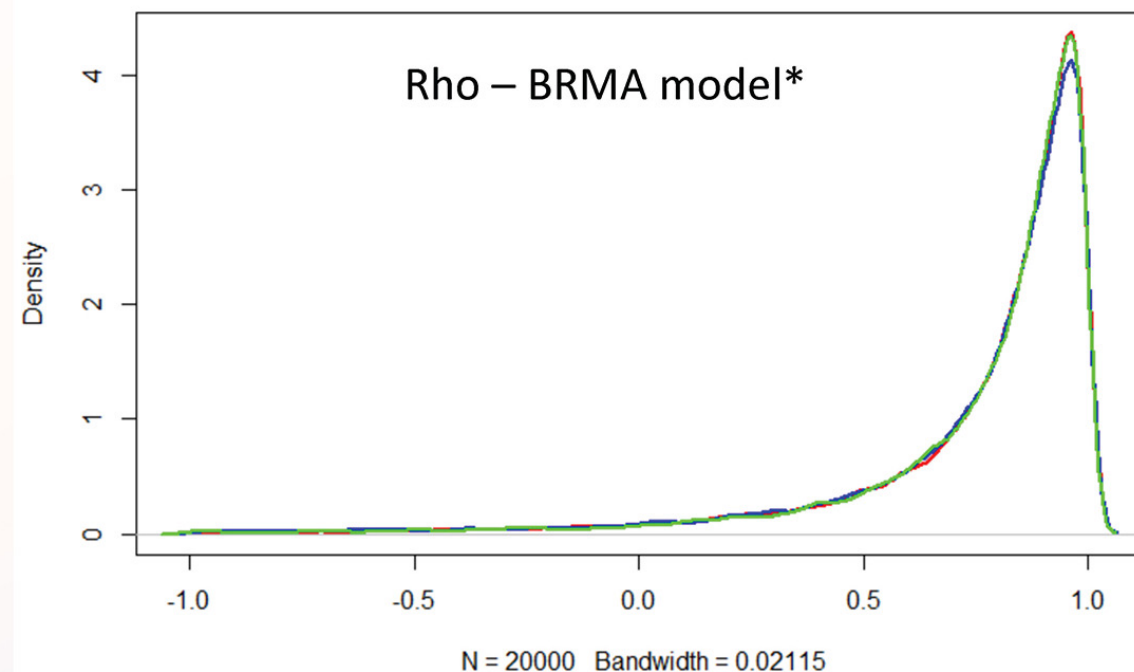
*Rho_{between} represents the between-studies correlation.

Note: Presented results use the following priors: rho_{within} ~ U(-0.999, 0.999); rho_{between} ~ U(-0.999, 0.999); tau ~ U(0,2); D ~ N(0, 1000).

Results – Model Performance and Validity

- Posterior distributions for **rho** from **BMA-PNF** and **BRMA** models were **highly skewed**

Threshold	PNF	BRMA
P(rho > 0.6)	0.833	0.841
P(rho > 0.7)	0.763	0.771
P(rho > 0.8)	0.642	0.653
P(rho > 0.9)	0.412	0.430



- Strength of **R²** was “very good” for BMA-PNF and BRMA models[†]
- Sensitivity analyses** using a variety of prior distributions were performed
 - Measures of central tendency (mean, median) were **consistent** between analyses
- Cross-validation** produced good prediction in all 20 studies with all 3 models (observed OS fell within study-specific 95% prediction interval)

BMA-DH, bivariate meta-analysis – Daniels and Hughes; BMA-PNF, bivariate meta-analysis - product normal formulation; BRMA, bivariate random-effects meta-analysis; DIC, deviance Information criterion; HR, hazard ratio; OS, overall survival

*Posterior distribution for the BMA-PNF model is similar (not shown).

[†] Using the same classification as Mauguen 2013.

DFS does have the potential to be a **useful surrogate** for OS in patients with **ES-NSCLC**

1

Strong correlation between DFS and OS (BRMA model: 0.87; PNF model: 0.87)*

2

5 of 20 studies reported a DFS point estimate below the STE of 0.60 (3 with the upper bound of the DFS 95% CI below the STE)

3

Indicates that this **STE** is somewhat **achievable** in this disease area with these treatments

4

Cross-validation supports the **surrogacy relationship**

5

Results are in line with **Mauguen 2013**, but add data on newer targeted therapies

*Estimates are highly skewed, but for both models, $P(\rho > 0.7)$ is greater than 0.75.

BRMA, bivariate random-effects meta-analysis; CI, confidence interval; DFS, disease-free survival; ES-NSCLC, early-stage non-small cell lung cancer; PNF, product normal formulation; STE, surrogate threshold effect; OS, overall survival