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Event-Free Survival as a Surrogate Endpoint for Overall Survival in Neoadjuvant Treatment of Resectable NSCLC: A Systematic Review and Meta-Analysis

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Cheng, XM; Ma, YY; Wang, Q; Zhao, X; Yang, FQ; Pan, BH; Wang, GX; Ni, J; Han, HD.

Corresponding author:
Hedong Han

he_dong1102@126.com

Author Affiliation:
Department of Respiratory and Critical Care Medicine, Jinling Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing, Jiangsu, China.

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INTRODUCTION

Review question / Objective To evaluate event-free survival (EFS) as a surrogate endpoint for overall survival (OS) in neoadjuvant therapy for resectable non-small cell lung cancer (NSCLC), and to examining how this association is modulated by the introduction of immunotherapy.

Condition being studied Non-small cell lung cancer accounts for the majority of primary lung malignancies and is associated with substantial mortality worldwide. For patients with resectable disease, neoadjuvant therapy, including conventional chemotherapy and modern immunochemotherapy regimens, has become a standard therapeutic strategy to downstage tumors, eliminate micrometastases, and improve long-term survival outcomes.

METHODS

Participant or population Patients with histologically confirmed resectable non-small cell lung cancer (NSCLC) who received neoadjuvant therapy.

Intervention Neoadjuvant treatment regimens administered prior to surgery.

Comparator This review does not compare two different treatment groups directly. Instead, the analysis evaluates the association between event-free survival (EFS) and overall survival (OS) as endpoints reported in the included trials. For trials with a control arm, the comparator will be the control regimen reported in the study (e.g., chemotherapy alone vs immunochemotherapy).

Study designs to be included Randomized controlled trials.

Eligibility criteria Studies were eligible for inclusion if they met the following predefined criteria: (1) enrolled patients with histologically confirmed resectable NSCLC (stages I-III); (2) were RCTs investigating neoadjuvant therapeutic regimens; (3) reported hazard ratio (HR) and 95% confidence intervals (CI) for both EFS and OS, or provided sufficient raw data (e.g., Kaplan-Meier curves) to reliably estimate these metrics. Studies specifically focusing on driver gene-mutated NSCLC (e.g., EGFR-mutated) were excluded. For the same study population, when updated data became available (e.g., from new publications or conference abstracts), only the most recent or comprehensively updated data was included.

Information sources A comprehensive literature search was performed across PubMed, Scopus, the Cochrane library, and Web of Science up to July 1, 2025. To capture recent and potentially unpublished evidence, abstracts from major oncology conferences (including ASCO, ESMO, and WCLC) were manually searched.

Main outcome(s) Outcome data included HR and 95% CI for EFS and OS. We assess whether treatment effects on EFS could serve as a valid surrogate for those on OS.

Quality assessment / Risk of bias analysis Methodological quality and risk of bias for each included RCT were independently evaluated using the Cochrane Risk of Bias tool.

Strategy of data synthesis All analyses were based on log-transformed HR from experimental versus control group comparisons. We performed weighted correlation and weighted linear regression analyses to evaluate whether treatment effects on EFS could serve as a valid surrogate for those on OS.

Subgroup analysis For subgroup analyses, stratified assessments were performed based on pre-defined factors to explore the heterogeneity of the EFS-OS association: 1) treatment era (pre-immunotherapy era vs. immunotherapy era); 2) median follow-up duration (<3 years vs. ≥3 years); 3) trial sample size (<400 patients vs. ≥400 patients); 4) intervention regimen (continuous neoadjuvant therapy + surgery + adjuvant therapy vs. neoadjuvant therapy + surgery without adjuvant therapy); and 5) control group regimen (surgery alone vs. other therapies).

Sensitivity analysis Initially, an alternative weighting strategy was applied to assess result consistency. Instead of trial sample size, the inverse variance of the log-transformed OS HR served as the weighting factor in both weighted correlation and weighted linear regression models, examining the stability of the observed EFS-OS association. Subsequently, a multivariable weighted regression analysis was conducted to adjust for key variables. The primary model was adjusted for median follow-up duration, trial sample size, and treatment era (pre-immunotherapy vs. immunotherapy era), thereby quantifying their potential influence on the relationship between EFS and OS treatment effects.

Country(ies) involved China.

Keywords Non-small cell lung cancer; Neoadjuvant therapy; Event-free survival; Surrogate endpoint; Immunotherapy.

Contributions of each author
Author 1 - Xiaomei Cheng.
Author 2 - Yangyang Ma.
Author 3 - Qin Wang.
Author 4 - Xin Zhao.
Author 5 - Fangqing Yang.
Author 6 - Binhai Pan.
Author 7 - Guoxin Wang.
Author 8 - Juan Ni.
Author 9 - Hedong Han.