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Associations of Recurrence-Free Survival and Quality of Life, and Their Relation to Overall Survival in Adjuvant Immunotherapy Trials

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 19 November 2025 and was last updated on 19 November 2025.

INTRODUCTION

Review question / Objective To evaluate how recurrence-free survival (RFS), progression-free survival (PFS), and quality of life (QoL) relate to overall survival (OS) in randomized clinical trials of perioperative and adjuvant immunotherapy for resectable solid tumors. The review aims to determine the extent to which early disease-control endpoints and patient-reported outcomes serve as meaningful indicators of long-term survival benefit.

Rationale With the expanded use of adjuvant immunotherapeutic strategies across multiple early-stage cancers, the suitability of OS as the principal endpoint has become increasingly limited. Contemporary trials often require prolonged follow-up, and survival after recurrence is substantially influenced by effective salvage treatments. As a result, early endpoints such as RFS, DFS, PFS, and QoL are frequently reported, yet their value as surrogates for OS in the immunotherapy setting remains uncertain. A structured, quantitative assessment is needed to clarify their performance and inform endpoint selection in future perioperative and adjuvant immunotherapy trials.

Condition being studied The review focuses on patients with resectable solid tumors who have undergone standard curative-intent treatment (e.g.,

surgery) followed by adjuvant or perioperative immunotherapy. Tumor types represented in eligible trials are expected to include melanoma, non–small cell lung cancer, esophageal cancer, and malignancies of the digestive and urinary systems. These early-stage populations are typically disease-free after surgery but remain at risk of recurrence, making early endpoints clinically relevant.

METHODS

Search strategy Electronic databases including PubMed, Embase, Web of Science, and the Cochrane Library will be searched from 2016 onward. Search terms will combine concepts related to cancer, adjuvant/perioperative immunotherapy, randomized trials, and survival/QoL endpoints.
A general framework of the search structure is:
Cancer-related terms (e.g., cancer, tumor, neoplasm)
Immunotherapy-related terms (e.g., immunotherapy, immune-based therapies, immune checkpoint inhibitors, named agents)
Treatment setting terms (adjuvant, perioperative, postoperative, resection)
Study design terms (randomized, RCT)
Endpoint terms (RFS, PFS, DFS, EFS, OS, QoL, QLQ-C30).

Participant or population Adults diagnosed with solid tumors who completed curative-intent therapy (typically surgery) and were subsequently enrolled in randomized trials evaluating adjuvant or perioperative immunotherapy. Only Phase II and Phase III RCTs will be eligible.

Intervention Any form of adjuvant or perioperative immunotherapy, including but not limited to:
Immune checkpoint–targeted agents (PD-1, PD-L1, CTLA-4)
Cancer vaccines
Cytokine-based therapies (e.g., IL-2, interferon)
Cell-based or other immune-modulating strategies.
Comparator arms may include placebo, observation, or standard post-operative management without immunotherapy

Comparator Control groups receiving placebo, observation, or standard-of-care without adjuvant immunotherapy.

Study designs to be included Randomized controlled trials (Phase II or Phase III) assessing adjuvant or perioperative immunotherapy following standard curative-intent treatment for solid tumors.

Eligibility criteria Inclusion Criteria
Study design:
Randomized controlled trials (Phase II or Phase III), including parallel-group designs evaluating adjuvant or perioperative immunotherapy.
Population: Adult patients with resectable solid tumors who completed standard curative-intent treatment (typically surgery) before receiving immunotherapy.
Interventions: Any adjuvant or perioperative immunotherapeutic strategy, including checkpoint-targeted agents (PD-1, PD-L1, CTLA-4 inhibitors), cancer vaccines, cytokine-based therapies, or other immune-modulating treatments.
Comparators: Placebo, observation, or standard-of-care management without adjuvant immunotherapy.
Outcomes: Trials must report at least one surrogate or survival-relevant endpoint such as RFS, DFS, PFS, EFS, OS, or Quality of Life (QLQ-C30). Studies with extractable survival curves were also eligible.
Publication characteristics: Peer-reviewed articles published from 2016 onward in English.

Exclusion Criteria
Non-randomized designs, including observational studies, single-arm trials, retrospective analyses, or quasi-experimental studies.
Interventions not classified as immunotherapy, such as targeted therapies lacking immune-modulating mechanisms, chemotherapy-only regimens, or radiotherapy-alone strategies.
Studies involving unresectable, metastatic, or recurrent disease where therapy was not delivered in a perioperative or adjuvant context.
Reports lacking relevant endpoints, including trials without survival data (RFS/DFS/PFS/EFS/OS) or QoL outcomes, and studies where such data could not be reliably extracted.
Non–peer-reviewed sources, including conference abstracts, letters, editorials, reviews, protocols, or preclinical studies.

Information sources We will identify eligible studies through a comprehensive search of major electronic databases and supplementary sources. The primary information sources will include:
1. Electronic Databases:PubMed, Embase, Web of Science Core Collection, Cochrane Central Register of Controlled Trials (CENTRAL)
These databases will be searched from 2016 to the present using predefined search strategies tailored to each platform.

2.Trial Registries: ClinicalTrials.gov, WHO International Clinical Trials Registry Platform (ICTRP)

These sources will be screened to identify ongoing or recently completed randomized trials evaluating adjuvant or perioperative immunotherapy.

3. Supplementary Searches: Reference lists of included studies and relevant systematic reviews will be manually examined to capture additional eligible trials not retrieved through database searches.
When necessary, study authors may be contacted for clarification or access to unpublished outcome data.

4. Grey Literature: Conference abstracts, dissertations, regulatory documents, and other grey literature will not be included due to insufficient methodological detail and limited availability of extractable survival data.
All searches will be conducted independently by two reviewers, with discrepancies resolved through consensus.

Main outcome(s)
Primary outcomes
Recurrence-free survival (RFS)
Overall survival (OS)
Quality of life (QoL; EORTC QLQ-C30)
Secondary outcomes
Progression-free survival (PFS)
Disease-free survival (DFS)
Event-free survival (EFS)
Other available survival metrics.

Quality assessment / Risk of bias analysis The methodological quality of included trials will be evaluated using the Cochrane Risk of Bias 2.0 tool.

Strategy of data synthesis Data from eligible randomized controlled trials will be synthesized using a structured, multi-level analytical framework. Extracted outcomes will include hazard ratios (HRs), survival probabilities at prespecified time points, and mean differences in quality-of-life scores. Whenever required, survival estimates will be reconstructed from published Kaplan–Meier curves using validated digitization procedures.
1. Effect Measures
Time-to-event endpoints (RFS, DFS, PFS, EFS, OS): Hazard ratios and corresponding 95% confidence intervals will be used as the primary effect measure.
Quality of life outcomes: Mean differences (MD) between treatment and control groups will be analyzed.
2. Analytical Levels
Two complementary approaches will be performed:
a. Trial-level analysis: Associations between endpoints (e.g., RFS–OS, PFS–OS, RFS–QoL) will be evaluated using weighted linear regression of log-transformed HRs. Inverse-variance weighting will be applied to account for differences in precision across studies.
b. Arm-level analysis: Regression analyses will be conducted using survival rates from individual treatment arms. Multi-arm studies will be adjusted by proportionally redistributing the effective sample size to prevent overweighting.
3. Surrogacy Evaluation
For each endpoint pairing, the following metrics will be estimated: Regression slope, Coefficient of determination (R^2) as a measure of surrogacy strength,9 5% confidence intervals derived from non-parametric bootstrap resampling (1,000 iterations)
Associations will be interpreted according to prespecified thresholds: $R^2 < 0.50$ (weak), 0.50–0.70 (moderate), ≥0.70 (strong).
4. Subgroup Analyses
Prespecified subgroup analyses will evaluate surrogacy relationships across: Tumor types, Study phase (Phase II vs. Phase III), Treatment strategies (monotherapy vs. combination therapy), Median follow-up duration, Immune therapeutic target class,
5. Sensitivity Analyses
A leave-one-out procedure will be performed for each regression model to assess the robustness of the findings. Cross-validated R^2 values and prediction intervals will be evaluated to determine the consistency and generalizability of endpoint associations.
6. Software
Analyses will be conducted using R 4.5.2 (metafor, survival, and related packages). All statistical tests will be two-sided with a significance threshold of $p < 0.05$.

Subgroup analysis Predefined subgroup analyses will be performed to explore potential sources of heterogeneity in the associations between surrogate endpoints and overall survival. Subgroups will be selected based on clinical relevance and the characteristics reported in eligible randomized trials. The analyses will be conducted at both the trial and treatment-arm levels. The following subgroups will be evaluated:
1. Study phase: Phase II trials, Phase III trials
2. Tumor type: Skin cancers, Digestive system cancers, Urinary system cancers, Non–small cell lung cancer (NSCLC)
3. Treatment strategy: Monotherapy, Combination immunotherapy
4. Follow-up duration:<3 years, 3–5 years, 5 years

5. Immunotherapy target class: PD-1 inhibitors, PD-L1 inhibitors, CTLA-4 inhibitors

Associations within each subgroup will be analyzed using the same regression framework applied in the primary analyses. Differences in slopes, coefficients of determination (R^2), and confidence intervals will be used to determine whether surrogate performance is consistent across clinical settings.

Sensitivity analysis Sensitivity analyses will be conducted to evaluate the robustness and consistency of the findings across multiple analytical dimensions. The following procedures will be applied:
1. Leave-one-out validation
Each trial will be iteratively excluded from the dataset, and the regression model assessing the association between surrogate endpoints (RFS–OS and QoL–RFS) will be refitted using the remaining studies. For each iteration, the coefficient of determination (cross-validated R^2) will be recorded. The distribution of these values will be examined to determine whether the observed associations are driven by any single influential study.
2. Prediction interval assessment
For each endpoint pairing, observed and model-predicted values will be compared, and 95% prediction intervals will be estimated. This will help evaluate the stability and generalizability of the relationship between early endpoints and overall survival, as well as between QoL and early disease-control metrics.
3. Heterogeneity evaluation
Changes in heterogeneity statistics (e.g., I^2) will be monitored across leave-one-out iterations to identify whether specific trials contribute disproportionately to between-study variability.
4. Robustness of QoL analyses
Sensitivity analyses will also be applied to the QoL models to assess whether the relationship between QoL improvement and recurrence reduction persists after sequential removal of individual trials. Stability of regression slopes, R^2 values, and prediction intervals will be evaluated.

Language restriction Only studies published in English will be included. This restriction is applied to ensure consistency in data extraction, reduce the risk of misinterpretation of survival and QoL measures, and maintain.

Country(ies) involved This study is being conducted by a research team based in China, with all investigators affiliated with academic and clinical institutions within the country.

Keywords Adjuvant immunotherapy, Recurrence-free survival, Overall survival, Quality of life, Surrogate endpoints.

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