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Clinical Utility and Surrogacy of ctDNA Clearance for Early Treatment Response in Solid Tumors

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Data analysis.

Conflicts of interest - No conflicts of interest were declared. The authors have no financial or personal relationships that could inappropriately influence the conduct or reporting of this systematic review and meta-analysis.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 6 December 2025 and was last updated on 6 December 2025.

INTRODUCTION

Review question / Objective The review aims to determine how well changes in circulating tumor DNA (ctDNA) levels, particularly clearance during early treatment, reflect treatment effects on major clinical outcomes in randomized trials of solid tumors. Specifically, the objective is to quantify the strength and consistency of the relationship between ctDNA clearance and endpoints such as overall survival, progression-free survival, and recurrence-related outcomes.

Condition being studied The review focuses on solid tumors treated with adjuvant or perioperative systemic therapy. These malignancies often carry a risk of microscopic residual disease after primary treatment, which may lead to recurrence or early progression. Circulating tumor DNA is increasingly used to reflect the presence of residual disease and early molecular response, making these conditions suitable for evaluating ctDNA-based biomarkers.

METHODS

Search strategy A comprehensive search was conducted in PubMed, Embase, Web of Science, and ClinicalTrials.gov from database inception to December 2025. The search combined controlled vocabulary and free-text terms related to circulating tumor DNA, minimal or molecular residual disease, early treatment response, and randomized clinical trials. No limits were applied to cancer type or treatment modality. Reference lists of eligible reports and relevant reviews were additionally screened to identify studies not captured through electronic searches.

Participant or population The review includes adults with solid tumors enrolled in randomized controlled trials of adjuvant or perioperative systemic therapy. Eligible participants were required to have ctDNA measurements at baseline or during early treatment to assess molecular response or clearance.

Intervention The interventions of interest are systemic treatments administered in the adjuvant or perioperative setting for solid tumors, as evaluated in randomized controlled trials. These may include chemotherapy, targeted agents, immunotherapy, or combinations thereof, provided that ctDNA clearance or early molecular response was measured.

Comparator The comparator consists of the control arms of eligible randomized trials, which may include standard-of-care therapy, placebo, observation, or alternative systemic treatment regimens. Comparators were accepted as long as ctDNA measurements were available for evaluating differences in molecular response.

Study designs to be included Only randomized controlled trials will be included, as these study designs allow for unbiased comparisons of treatment-related changes in ctDNA clearance and clinical outcomes.

Eligibility criteria Additional eligibility criteria included the requirement that studies report quantifiable ctDNA measurements—such as baseline detection, clearance, or early molecular response—in both trial arms. Trials needed to provide sufficient numerical data to derive treatment effects, including hazard ratios or clearance proportions. Studies were excluded if ctDNA results were incomplete, not measurable, or presented only in narrative form without extractable values. Non-randomized designs, conference abstracts without usable data, reviews, single-arm studies, and trials lacking ctDNA endpoints were also excluded.

Information sources Information will be obtained from multiple electronic databases, including PubMed, Embase, Web of Science, and ClinicalTrials.gov. Trial registries and reference lists of eligible publications will also be reviewed to identify additional studies. No restrictions on publication year or tumor type will be applied.

Main outcome(s) The primary outcomes of interest are treatment effects on overall survival, progression-free survival, and recurrence-related endpoints. These outcomes will be extracted as hazard ratios with corresponding confidence intervals from the earliest available post-treatment analyses reported in eligible randomized trials. Trial-level differences in ctDNA clearance between intervention and control groups will be summarized as relative risk or log-transformed measures to assess their relationship with clinical outcomes.

Additional outcome(s) Secondary outcomes will include measures related to the clinical or methodological interpretation of ctDNA dynamics, such as absolute risk reductions, numbers-needed-to-treat, surrogate threshold effects, and Bayesian model estimates. Additional prognostic analyses comparing ctDNA-positive and ctDNA-negative patients will also be considered when available.

Data management All records identified through database searches will be imported into reference management software for deduplication and organization. Screening decisions, eligibility assessments, and extracted variables will be managed using standardized spreadsheets with predefined fields. Data entry will be performed independently by two reviewers, and discrepancies will be resolved through consensus. Final datasets used for quantitative analysis will be stored in secure, access-controlled files.

Quality assessment / Risk of bias analysis Risk of bias in the included randomized trials will be evaluated using the Cochrane RoB 2.0 tool. Each study will be assessed across the standard domains, including randomization processes, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting. Two reviewers will independently perform all assessments, and disagreements will be resolved through discussion. The overall judgement for each study will be determined according to the domain-level ratings.

Strategy of data synthesis Data from eligible randomized trials will be synthesized using quantitative trial-level analyses. Treatment effects on ctDNA clearance will be transformed into log-relative measures and examined in relation to hazard ratios for overall survival, progression-free survival, and recurrence-related outcomes. Weighted regression models will be used to evaluate associations between molecular and clinical effects, supplemented by correlation and dependence metrics. Sensitivity analyses, including leave-one-out procedures and predefined subgroups, will be conducted to assess robustness. Prognostic comparisons based on ctDNA status will be pooled using random-effects or fixed-effect models depending on heterogeneity. All analyses will be performed using appropriate statistical software.

Subgroup analysis Subgroup analyses will be performed to explore whether the association between ctDNA clearance and clinical outcomes varies across specific study characteristics. Planned subgroups include tumor type, duration of follow-up, timing of ctDNA assessment, and treatment modality. Additional analyses will evaluate the influence of individual trials through leave-one-out procedures. Results from these subgroups will be compared to the main findings to assess consistency.

Sensitivity analysis Sensitivity analyses will be conducted to examine the robustness of the findings. These will include leave-one-out procedures to determine the influence of individual trials, as well as stratified analyses based on tumor type, follow-up duration, ctDNA sampling intervals, and treatment modality. Estimates from these analyses will be compared with the primary results to assess the stability of the observed associations.

Language restriction No language restrictions will be applied during the search. Studies published in any language will be considered, and translations will be sought when necessary.

Country(ies) involved China.

Keywords circulating tumor DNA (ctDNA), surrogate endpoints, clearance, trial-level surrogacy, early treatment response.

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