INPLASY

Beyond resectability: from surgical feasibility to survival benefit in choosing primary surgery or neoadjuvant chemotherapy for advanced ovarian cancer — protocol for a systematic review and meta-analysis

INPLASY202680058
doi: 10.37766/inplasy2026.8.0058
Received: 13 August 2026
Published: 13 August 2026

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ADMINISTRATIVE INFORMATION

Support - No support.

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

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202680058

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 13 August 2026 and was last updated on 13 August 2026.

INTRODUCTION

Review question / Objective To evaluate pretreatment selection for survival benefit from primary cytoreductive surgery (PDS) versus neoadjuvant chemotherapy (NACT), apart from resectability and operative suitability.

Rationale Selection for primary cytoreductive surgery in advanced ovarian cancer has become increasingly structured through assessment of patient fitness, disease burden, technical resectability, and surgical expertise. However, the ability to identify patients in whom surgery is feasible is conceptually distinct from identifying those who derive greater survival benefit from PDS than from NACT. Randomized trials provide the appropriate framework for evaluating treatment-effect modification, but subgroup evidence has not been systematically assessed for interaction credibility and independent replication. This review therefore evaluates the evolution of pretreatment selection, evidence for differential survival benefit, and the evidence requirements for prospective treatment-selection markers.

Condition being studied Advanced epithelial ovarian, fallopian tube, and primary peritoneal cancer in patients considered for first-line treatment with primary cytoreductive surgery or neoadjuvant platinum-based chemotherapy followed by interval cytoreductive surgery.

METHODS

Search strategy PubMed/MEDLINE, Embase, CENTRAL, and Web of Science were searched from inception through August 13, 2026. Search concepts combined controlled vocabulary and free-text terms for ovarian, fallopian tube, and primary peritoneal cancer; primary cytoreductive/debulking surgery; neoadjuvant chemotherapy; interval cytoreductive/debulking surgery; randomized trials; treatment selection; resectability; and treatment-effect modification. Reports belonging to the same randomized trial

were linked into trial families to avoid double counting. Reference lists of eligible studies, systematic reviews, guidelines, and relevant trial reports were hand-searched. ClinicalTrials.gov and WHO ICTRP were searched for ongoing or unpublished randomized studies relevant to treatment-sequence selection.

Participant or population Women with newly diagnosed advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer eligible for randomized comparison of primary cytoreductive surgery and neoadjuvant chemotherapy followed by interval cytoreductive surgery.

Intervention Primary cytoreductive surgery followed by platinum-based chemotherapy.

Comparator Neoadjuvant platinum-based chemotherapy followed by interval cytoreductive surgery.

Study designs to be included Randomized controlled trials comparing PDS with NACT followed by interval cytoreductive surgery. Companion publications from eligible randomized trial families were included when they provided selection criteria, subgroup analyses, survival outcomes, treatment-policy information, or methodological data.

Eligibility criteria Eligible reports originated from randomized PDS-versus-NACT trial families and provided information relevant to pretreatment selection, baseline treatment-effect modification, overall survival, or treatment-policy interpretation. Nonrandomized comparative cohorts were excluded from quantitative treatment-effect analyses. Duplicate reports were linked within trial families rather than treated as independent studies.

Information sources PubMed/MEDLINE, Embase, CENTRAL, Web of Science, ClinicalTrials.gov, WHO ICTRP, reference lists of eligible trial reports, systematic reviews and guidelines, and companion publications belonging to eligible randomized trial families.

Main outcome(s) The primary outcome was evidence that a pretreatment characteristic modifies the comparative overall-survival effect of PDS versus NACT. Evidence was evaluated using randomized treatment-by-characteristic interactions, credibility of subgroup findings, and independent replication across trial families. Overall-survival effects were expressed as hazard ratios oriented consistently as PDS versus NACT.

Additional outcome(s) Secondary outcomes included the evolution of pretreatment selection across fitness/operability, disease burden, technical resectability, and center/surgical quality; pooled overall survival; the association between trial-level technical-resectability enrichment and treatment effect; treatment-policy and estimand comparability across trials; and the number of events required to validate candidate treatment-selection markers.

Data management Reports were organized by randomized trial family. Data were extracted into structured evidence tables covering trial characteristics, eligibility and selection criteria, treatment policies, survival estimates, subgroup analyses, interaction tests, and replication status. Effect estimates were harmonized to a common PDS-versus-NACT orientation before quantitative synthesis.

Quality assessment / Risk of bias analysis Randomized trials were assessed using RoB 2 principles. Treatment-effect modification claims were additionally evaluated for formal interaction testing, prespecification, biological plausibility, multiplicity, consistency, and independent replication, informed by established credibility criteria for subgroup analyses.

Strategy of data synthesis Trial-level overall-survival hazard ratios were harmonized as PDS versus NACT and synthesized using random-effects meta-analysis. Pretreatment selection was characterized across four prespecified domains: fitness/operability, disease burden, technical resectability, and center/surgical quality. Baseline characteristics were evaluated for randomized treatment interaction, credibility, and independent replication. Trial-level meta-regression explored the relationship between technical-resectability enrichment and comparative survival effect. Event-driven Monte Carlo Cox simulations estimated the number of events required to validate treatment-selection markers, with analytic interaction-information calculations used as a cross-check.

Subgroup analysis Candidate treatment-effect modifiers included FIGO stage, metastatic disease burden and distribution, age, performance status, histologic subtype, tumor burden, and other pretreatment characteristics reported in randomized trial families. Subgroup findings were interpreted primarily through formal treatment-by-characteristic interaction tests rather than within-subgroup significance.

Sensitivity analysis Sensitivity analyses included alternative pooling assumptions where appropriate, leave-one-trial-out analyses for trial-level meta-regression, assessment of influential contemporary trials, and attenuation scenarios for treatment-by-marker interaction effects. Analytic interaction-information calculations were compared with Monte Carlo simulation results as a methodological cross-check.

Language restriction No language restrictions were imposed.

Country(ies) involved Turkey.

Other relevant information This registration is retrospective. The review had reached the completed-but-not-published stage at registration. Registration timing and any protocol-to-review deviations will be reported transparently in the manuscript. Trial-family linkage was prespecified to distinguish independent randomized evidence from multiple publications arising from the same trial.

Keywords ovarian cancer; primary cytoreductive surgery; neoadjuvant chemotherapy; resectability; treatment selection.

Dissemination plans Results will be submitted for publication in a peer-reviewed gynecologic oncology journal. Supporting extraction tables, analytic documentation, and reproducibility materials will be deposited in a public research repository where permitted.

Contributions of each author

Author 1 - Serhat Şen - Conceived and designed the study, executed the searches, performed independent screening and coding, wrote the statistical analysis plan, curated the data, and drafted the manuscript.
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Author 2 - Feyza Gulgel Sen - Performed independent blinded screening and full-text assessment, independent outcome-naive selection-architecture coding, participated in consensus adjudication, and critically revised the manuscript.
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