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Cytoreductive surgery plus chemotherapy versus chemotherapy alone for recurrent epithelial ovarian cancer (Protocol)

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[Intervention Protocol]

Cytoreductive surgery plus chemotherapy versus chemotherapy alone for recurrent epithelial ovarian cancer

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To evaluate the benefits and harms of secondary CRS and chemotherapy in comparison to chemotherapy alone for women with platinum-sensitive recurrent epithelial ovarian cancer.

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BACKGROUND

Ovarian cancer is the eighth most common cause of cancer-related deaths amongst females and the leading cause of gynaecological-related deaths worldwide (Hilpert 2007; Sung 2021). The National Cancer Institute reports an ovarian cancer incidence rate of 10.9 per 100,000 cases, and a death rate of 6.7 per 100,000 cases per year (National Cancer Institute 2024). Incidence rates for ovarian cancer increase parallel to age and peak around the seventh and eighth decades of life (Salman 2020; US Cancer Statistics Working Group 2020). The median age is about a decade earlier in low-income countries. Five-year survival in women with early-stage disease is 80% to 90% compared to 25% for women with advanced-stage disease (Colombo 2006). The poor survival associated with ovarian cancer is a reflexion of the disease's advanced presentation and further highlights the challenges faced in achievement of effective management strategies (Lheureux 2019; Siegel 2023).

The standard management of primary ovarian cancer is a combination of surgery with the aim of removing all visible disease deposits (cytoreductive surgery (CRS)) and platinum-based chemotherapy (Coleridge 2021; Vergote 2020). A recent Cochrane review demonstrated that chemotherapy before surgery (neoadjuvant chemotherapy) versus surgery followed by chemotherapy (adjuvant chemotherapy) for the initial treatment of advanced ovarian epithelial cancer had similar oncological survival outcomes; however, neoadjuvant chemotherapy was associated with fewer postoperative adverse effects (Coleridge 2021).

Description of the condition

Up to 80% of women with advanced ovarian cancer will relapse despite optimal management with maximal CRS and platinum-based chemotherapy (Bickell 2018; Buechel 2019). Recurrence can present as single-site localised disease or as a widespread recurrence. Women with recurrent disease comprise a heterogeneous group with variable prognosis, with 10-year rates of disease-free survival reported to be less than 15% (Berek 2021; Dood 2018). Presenting symptoms might include abdominal pain or discomfort, fatigue, gastrointestinal or urinary symptoms or systemic symptoms depending on the site of recurrence (Zachou 2023). The time elapsed since last front-line platinum chemotherapy appears to represent the most important prognosticator regarding response to chemotherapy reinduction (Colombo 2023).

Depending on the timing of recurrence following the last platinum-based chemotherapy treatment, women are classified as having either platinum-sensitive (≥ 6 months) or platinum-resistant disease stages (≤ 6 months) (Buechel 2019). It should be noted that the terms 'platinum-resistant' and 'platinum-sensitive' ovarian cancer have been replaced with 'early' and 'late' recurrent ovarian cancer, respectively (Claussen 2020). Women with 'early' recurrent ovarian cancer have a median overall survival (OS) of approximately 12 to 18 months with poor response rates (< 15%) to alternative single-agent chemotherapy and progression-free survival (PFS) of 9 to 12 months. Conversely, women with 'late' recurrent ovarian cancer have a PFS of up to 24 months (Atallah 2023; Baert 2021; Lheureux 2019). Currently, the main treatment offered in women with relapsed platinum-sensitive epithelial ovarian cancer is further chemotherapy, with or without poly-adenosine diphosphate-ribose polymerase inhibitors (PARPi) or vascular endothelial growth factor A (VEGF-A) inhibitors, or both, as maintenance therapy (Cortez 2018).

Description of the intervention

Options for treatment at the time of relapse include systemic anticancer treatment (SACT), including chemotherapy or SACT plus further surgery aiming to remove all visible disease, known as secondary CRS. Secondary CRS can entail complex multivisceral resection including organs from the lower or upper abdomen, or both. However, CRS, and especially secondary surgery, can cause severe complications, such as severe bleeding, infection, pulmonary and thromboembolic events, ranging from 5.5% to 19% (Middel 2023). Approximately 30% of cases will require bowel resection with a subsequent stoma formation in 20% of cases (Grimm 2017). Whilst the evidence for benefits to OS is inconclusive, secondary CRS can help to extend PFS (Al Rawahi 2013), as treatment given at the time of relapse aims to prolong life rather than having curative intent.

The introduction of new SACT agents, such as anti-angiogenic agents (e.g. bevacizumab), has added to the debate about how to treat women with relapsed disease. Bevacizumab has shown efficacy in prolonging PFS for women with newly diagnosed and recurrent platinum-sensitive ovarian cancer (Coleman 2019b; Pfisterer 2020; Pignata 2021). It is currently approved for use in combination with common chemotherapeutic agents such as carboplatin and paclitaxel. Furthermore, the use of bevacizumab in second-line chemotherapy for women with platinum-sensitive relapsed ovarian cancer has shown improved PFS when compared with chemotherapy (Coleman 2017; Gaitskell 2023; Pignata 2021).

Following the AGO-OVAR 2.21 trial, PARPi, such as olaparib or rucaparib (Pfisterer 2020), became standard therapy for recurrent ovarian cancer that was responsive to further platinum-based chemotherapy (Coleman 2019a; Pfisterer 2020). PARPi have been shown to prolong PFS in women with relapsed high-grade serous or endometrioid ovarian cancer who had platinum-sensitive disease and a BRCA1 DNA repair associated (*BRCA1*) or BRCA2 DNA repair associated (*BRCA2*) (BRCA1/2) gene mutation (Tattersall 2022). PARPi have shown the greatest efficacy in *BRCA1*-mutated ovarian tumours (Ray-Coquard 2019). However, according to the European Society for Medical Oncology (ESMO) and European Society of Gynaecologial Oncology (ESGO) (ESMO-ESGO) recommendations for women with recurrent ovarian cancer who respond to platinum-based therapy, the gold standard is PARPi maintenance therapy (olaparib, niraparib, and rucaparib), irrespective of BRCA or homologous recombination deficiency (HRD) status (Colombo 2019). These developments led to bevacizumab and PARPi usage earlier in these therapy algorithms.

How the intervention might work

The ultimate surgical goal of both primary and secondary CRS is to achieve no macroscopic residual disease (NMRD). The theory is that this will minimise the number of chemoresistant tumour cells and enhance the benefit of further chemotherapy alone, increasing the time taken for the disease to regrow.

Secondary CRS is commonly used in platinum-sensitive cases, as women with platinum-resistant ovarian cancer have a poorer prognosis and are less likely to benefit (Galaal 2010). Therefore, most evidence on the use of secondary CRS is for the platinum-

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sensitive subgroup. Data derived from randomised controlled trials have shown higher OS in women who had NMRD after an attempt at surgical cytoreduction, indicating the necessity of the implementation of objective algorithms or tools in the patient selection process. A balance should be found between the prospect of progression-free and overall survival benefits against the potential morbidities that can negate the anticipated benefits. Hence, careful evaluation of the potential harms of surgery and chemotherapy is crucial to ensure quality of life, which should be the primary aim in a non-curative setting. Meticulous patient selection combined with adequate surgical expertise could offer further optimisation and better outcomes in the management of relapsed ovarian cancer (Du Bois 2017).

Why it is important to do this review

Management of recurrent epithelial ovarian cancer remains challenging and a subject of considerable debate amongst professionals and societies. Given the high incidence of recurrence, irrespective of the primary treatment, the ideal scenario would be to consider advanced ovarian cancer as a chronic disease, that is present but controlled. A previous Cochrane review suggested that secondary CRS may be effective in improving OS in women with recurrent ovarian cancer (Al Rawahi 2013). In addition, Galaal 2010 investigated the effectiveness of CRS in combination with platinum-based chemotherapy compared to chemotherapy alone in women with recurrent ovarian cancer. Both reviews were unable to reach confident conclusions regarding the role of secondary CRS, due to the scarcity of level I evidence. However, with the completion of the DESKTOP III study and other randomised phase III clinical trials (Coleman 2019b; Du Bois 2017), an update to these systematic reviews is required.

Given the continued debate, the emergence of new treatment modalities, and the recent publication of important studies, we aim with this review to evaluate the effectiveness and safety of secondary CRS and chemotherapy in comparison to chemotherapy alone for women with platinum-sensitive recurrent epithelial ovarian cancer.

OBJECTIVES

To evaluate the benefits and harms of secondary CRS and chemotherapy in comparison to chemotherapy alone for women with platinum-sensitive recurrent epithelial ovarian cancer.

METHODS

Criteria for considering studies for this review

Types of studies

We will search for randomised controlled trials (RCTs) that compare secondary CRS followed by chemotherapy versus chemotherapy alone in women with platinum-sensitive recurrent epithelial ovarian cancer. We will include studies that used chemotherapy with or without PARPi or VEGF-A, or both, during and/or as maintenance therapy after chemotherapy, if the regimens were the same in both arms.

We will exclude quasi-randomised trials, non-randomised trials, prospective and retrospective cohort studies, and case series.

Types of participants

We will include women diagnosed with recurrent platinum-sensitive high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who received a combination of CRS and platinum-based chemotherapy when they were newly diagnosed, prior to their relapse.

We will exclude women with a diagnosis of low-grade serous ovarian cancer, germ cell tumours, or granulosa cell tumours, and women with other concurrent malignancies.

Studies that include only a subset of relevant participants will be eligible for inclusion if the relevant subset is analysed separately in a subgroup analysis. We aim to add this study to the main meta-analysis if the relevant subset represents more than 50% (arbitrary decision) of the total study population or the subgroup analysis that includes this subset.

Types of interventions

Intervention: secondary CRS followed by platinum-based chemotherapy

Comparison: platinum-based chemotherapy without secondary CRS

We aim to include all reported data regarding the intensity, frequency, and duration of interventions.

Types of outcome measures

We will collect data for direct outcome measures, including benefits, harms, and quality of life data, as specified below. Reporting the outcomes below will not be an eligibility criterion.

Primary outcomes

- Overall survival (OS): survival until death from all causes (survival from the time of randomisation).
- Intervention-related mortality. For the group receiving surgery, this will be assessed as any death, regardless of cause, occurring within 30 days. For the chemotherapy-alone group, this will be assessed as any reported death whilst on chemotherapy treatment or within 30 days from completion of chemotherapy.

Secondary outcomes

- Progression-free survival (PFS) (survival until progression of disease). We will assess survival from the time women were enrolled in the study (time of randomisation).
- Quality of life (QoL), measured using a scale that has been validated through reporting of norms in a peer-reviewed publication. We will use the Treatment Outcome Index (TOI) of the Functional Assessment of Cancer Therapy for ovarian cancer (FACT-O TOI); if this is not reported, we will use the European Organisation for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30) followed by the Functional Assessment of Cancer Therapy - General (FACT-G) (Aaronson 1993; Basen-Engquist 2001; Brucker 2005; Fayers 2001). We will assess QoL at baseline and 6 and 12 months from randomisation.
- Severe adverse events (grades 3 to 5), reported during the treatment period and up to 100 days after completion of study

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treatment, assessed using the Common Terminology Criteria for Adverse Events (CTCAE 2017):

- Direct surgical morbidity (e.g. death within 30 days, injury to bladder, ureter, vasculature, small bowel or colon), presence and complications of adhesions, febrile morbidity, intestinal obstruction, haematoma, local infection, need for bowel resection and/or stoma formation).
- Surgically related systemic morbidity (chest infection, thromboembolic events (deep vein thrombosis and pulmonary embolism), cardiac events (cardiac ischaemia and cardiac failure), cerebrovascular accident).
- Recovery: delayed discharge, unscheduled readmission.
- Chemotherapy-related severe adverse events (grade 3+ adverse events whilst on chemotherapy treatment or within 30 days from completion of chemotherapy).
- Chemotherapy toxicity. We will categorise grades of toxicity into the following groups:
  - haematological (leucopenia, anaemia, thrombocytopenia, neutropenia, haemorrhage);
  - gastrointestinal (nausea, vomiting, anorexia, diarrhoea, liver, proctitis);
  - genitourinary;
  - skin (stomatitis, mucositis, alopecia, allergy);
  - neurological (peripheral and central);
  - pulmonary.

Search methods for identification of studies

Electronic searches

We will search the following electronic databases based on terms related to the review topic:

- Cochrane Central Register of Controlled Trials (CENTRAL, latest issue), in the Cochrane library;
- MEDLINE Ovid (1946 to present);
- Embase Ovid (1974 to present).

The MEDLINE search strategy is presented in Appendix 1.

We will then identify the articles on PubMed and use the 'related articles' feature in order to carry out a further search for newly published articles. The search will be restricted from 2009 to current, considering that no RCTs were identified for inclusion in the previous version of the review, which was published in 2010. (Galaal 2010). We will consider publications in all languages as long as they meet the inclusion criteria.

Searching other resources

We will search the following resources for unpublished, ongoing trials and grey literature:

- World Health Organization International Clinical Trials Registry platform (WHO ICTRP) (www.apps.who.int/trialsearch);
- Physician Data Query (PDQ) (www.cancer.gov/publications/pdq);
- ClinicalTrials.gov (www.clinicaltrials.gov);
- National Cancer Institute Clinical Trials Information (www.cancer.gov/clinicaltrials);
- National Institutes of Health (NIH) Clinical Center Search the Studies site (www.clinicalstudies.info.nih.gov/).

If we identify ongoing trials that have not been published through these searches, we will approach the principal investigators and major co-operative groups active in this area to request relevant data.

Handsearching

We will handsearch the citation lists of included studies, key textbooks, and previous systematic reviews, and contact experts in the field to identify further reports of trials.

We will also handsearch the reports of conferences from the following sources:

- Gynecologic Oncology (Annual Meeting of the American Society of Gynecologic Oncology);
- International Journal of Gynaecological Cancer (Annual Meeting of the International Gynecologic Cancer Society and Meeting of the European Society of Gynaecological Oncology);
- British Journal of Cancer;
- British Cancer Research Meeting;
- Annual Meeting of the European Society of Medical Oncology;
- Annual Meeting of the American Society of Clinical Oncology.

Data collection and analysis

Selection of studies

We will download all titles and abstracts retrieved by the electronic searches to the reference management database EndNote and remove any duplicates (EndNote). Two review authors (CP, SS) will independently examine the titles and abstracts of the remaining references. We will obtain the full-text reports of references deemed potentially relevant, and two review authors (CP, SS) will independently assess the full-text reports for inclusion in the review. Any disagreements will be resolved by discussion with the senior author (MA). We will document in detail the reasons for exclusion of studies excluded at the full-text stage.

Data extraction and management

Two review authors (CP, SS) will independently extract study characteristics and outcome data from included studies onto a piloted data collection form. We will note in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. We will resolve disagreements by consensus or by involving a third person (MA). One review author (CP) will transfer data into RevMan software (RevMan 2024). We will double-check that data have been entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (SS) will 'spot-check' the accuracy of the study characteristics against the trial report.

We will extract the following data from the included studies.

- Author, year of publication and journal citation (including language)
- Country
- Setting
- Inclusion and exclusion criteria
- Study design, methodology
- Study population
- Total number randomised

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- Total number received assigned treatment
- Patient characteristics (ethnic origin, diagnosis details, tumour histology, FIGO stage, tumour grade, ascites)
- Age, body mass index (BMI)
- Comorbidities (Eastern Cooperative Oncology Group (ECOG) Performance Status)
- Other baseline characteristics (ethnicity, BRCA status, mutation germline/non-germline, homologous recombination deficiency (HRD) status)
- First-line surgical treatment (type of primary surgery, type of resection - no macroscopic residual disease (NMRD), small volume residual disease (SVRD < 1 cm), and large volume residual disease (LVRD > 1 cm), complications)
- First-line chemotherapy treatment (type of regimen, number of cycles, doses, any need for dose reduction, plus/minus PARBi/VEGF-A, side effects, toxicity)
- Response to chemotherapy
- Details of recurrence (time, organ, single-site or multiorgan, number of recurrent lesions)
- Intervention details
- Secondary CRS (type of surgery, type of resection - NMRD, SVRD < 1 cm, LVRD > 1 cm, complications)
- Chemotherapy following secondary CRS (type of regimen, number of cycles, doses, any need for dose reduction, plus/minus PARBi/VEGF-A, side effects, toxicity)
- Comparison (chemotherapy alone with or without PARBi/VEGF-A)
- Risk of bias in study
- Duration of follow-up (if present)
- Outcomes: for each outcome we will extract the outcome definition and unit of measurement. For adjusted estimates, we will record variables adjusted for analyses.
- Results: we will extract the number of participants allocated to each intervention group, the total number analysed for each outcome, and the missing participants.
- Notes: funding for trials and notable conflicts of interest of trial authors. Each will be given important consideration for risk of bias assessment.

We will extract results as follows.

- For time-to-event data (survival and disease progression), we will extract the log of the hazard ratio (log(HR)) and its standard error from the trial reports. If these are not reported, we will attempt to estimate the log(HR) and its standard error using the methods of Parmar 1998.
- For dichotomous outcomes, where each participant's outcome is one of only two possible categorical responses, if it is not possible to use HR, we will extract the number of participants in each treatment arm who experienced the outcome of interest and the number of participants assessed at endpoint, in order to estimate a risk ratio (RR).
- For continuous outcomes (e.g. QoL measures), we will extract the final value and standard deviation (SD) of the outcome of interest and the number of participants assessed at the endpoint in each treatment arm at the end of follow-up, in order to estimate the mean difference (MD) between treatment arms and its standard error.

We will extract both unadjusted and adjusted statistics if reported.

Where possible, all data extracted will be subject to an intention-to-treat analysis, in which participants will be analysed in the groups to which they were assigned.

We will note the time points at which outcomes were collected and reported.

Dealing with duplicate and companion publications

In the event of duplicate publications, companion documents, or multiple reports of a primary study, we will maximise the yield of information by collating all available data and using the most complete data set aggregated across all known publications. In case of doubt, we will give priority to the publication reporting the longest follow-up associated with our primary or secondary outcomes.

Assessment of risk of bias in included studies

We will evaluate risk of bias in included studies using Cochrane's RoB 1 tool, according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), which recommends the explicit reporting of the following individual elements for RCTs (Appendix 2).

- Selection bias: random sequence generation and allocation concealment
- Performance bias: blinding of participants and personnel (i.e. treatment providers)
- Detection bias: blinding of outcome assessment
- Attrition bias: incomplete outcome data
- Reporting bias: selective reporting of outcomes
- Other possible sources of bias, e.g. unpublished data regarding no effectiveness or safety, funding or conflict of interest

Two review authors (CP, SS) will apply the RoB 1 tool independently, resolving any differences by discussion or by appeal to a third review author (MA). We will judge each item as being at low, high, or unclear risk of bias as set out in the criteria provided by Higgins 2011, and provide a quote from the study report and/or a statement of justification for the judgement for each item in the risk of bias table. We will summarise results in both a risk of bias graph and risk of bias summary. When interpreting treatment effects and meta-analyses, we will take into account the risk of bias for the studies that contribute to that outcome. Where information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the risk of bias table.

Measures of treatment effect

We will use the following measures for the effect of treatment.

- For time-to-event data, we will use the HR with 95% confidence interval (CI) (e.g. oncologic survival outcomes).
- For dichotomous outcomes, (outcomes with only two distinct and mutually exclusive options), we will analyse data based on the number of events and the number of women assessed in the intervention and comparison groups. We will use these to calculate the RR and 95% CI.
- For continuous outcomes, we will analyse data based on the mean, SD, and number of women assessed for both the intervention and comparison groups to calculate the MD

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between treatment arms with 95% CI. If the MD is reported without individual group data, we will use this to report the study results. If more than one study measures the same outcome using different tools, we will calculate the standardised mean difference (SMD) and 95% CI using the inverse variance method in RevMan (RevMan 2024).

We will undertake meta-analyses only where this is meaningful, that is if the treatments, participants, and the underlying clinical question are similar enough for pooling to make sense. We will describe skewed data that are reported as median and interquartile ranges narratively. Where multiple trial arms are reported in a single trial, we will include only the relevant arms. If two comparisons (e.g. surgery versus chemotherapy alone and surgery versus chemotherapy alone + targeted agent) are combined in the same meta-analysis, we will halve the control group in each case to avoid double-counting.

Unit of analysis issues

We will evaluate studies for unit of analysis issues based on the criteria originally set by Whiting-O'Keefe (Whiting-O'Keefe 1984). We will examine any and all RCTs randomised in a cluster fashion for reporting of any statistical precautionary measures that could account for the clustering effect. If otherwise not found, the study will not be included in the final quantitative synthesis.

Two review authors (CP, SS) will review unit of analysis issues according to Higgins 2022, with any differences resolved by discussion. These include reports where:

- groups of women were randomised together to the same intervention (i.e. cluster-randomised trials). Inclusion of such data will depend on the method of analysis, e.g. multilevel modelling. If the analysis does not account for clustering, we will include an estimate of each cluster. Considering that the latter approach will reduce the statistical power for the study, where each cluster will be treated as an individual, we plan to conduct a sensitivity analysis where we exclude cluster-RCTs that were analysed without accounting for clustering;
- individual women undergo more than one intervention (e.g. in a cross-over trial, or simultaneous treatment of multiple sites on each woman). For cross-over RCTs, we will attempt to include them in the meta-analysis depending on the design and analysis used in each trial. If a cross-over trial is eligible, we will include the results from the phase parallel-group trial to avoid carry-over effects and loss to follow-up. We will then conduct a sensitivity analysis excluding cross-over trials from the meta-analysis;
- there were multiple observations of the same outcome (e.g. repeated measurements, recurring events, measurements on different body parts).

If a trial has more than one intervention arm and one control arm, we will include the relevant intervention comparison with the control group. If more than one intervention group is compared to the control group, and the intervention groups can be combined into one intervention group, we will do so and include one comparison. If, for example, two intervention groups are compared with the control group, and both comparisons are eligible for inclusion, we will include both comparisons but avoid double-counting by splitting the shared group.

Dealing with missing data

We will attempt to contact the original study authors (corresponding author and the senior author) to obtain missing data (participant, outcome or summary data). For participant data, where possible we will conduct analysis on an intention-to-treat basis; otherwise we will analyse data as reported. We will report on the levels of loss to follow-up and assess this as a source of potential bias.

For missing outcome or summary data, we will not impute missing data and report any assumptions in the review. We will investigate, through sensitivity analyses, the effects of any imputed data on pooled effect estimates. We will not impute missing outcome data for the primary outcome.

Assessment of heterogeneity

Where studies are considered similar enough based on several characteristics (e.g. age of participants, performance status, histopathology, stage and grade of disease, residual disease following secondary CRS, addition of PARPi or VEGF-A or both to platinum-based chemotherapy, time of follow-up, assessment of adverse events, and quality of life measurements) to allow pooling of data using meta-analysis, we will assess the degree of heterogeneity by visual inspection of forest plots; by estimation of the percentage heterogeneity (I^2 measurement) between trials which cannot be ascribed to sampling variation (Higgins 2003; Higgins 2022); by a formal statistical test of the significance of the heterogeneity (Chi^2) (Deeks 2001); and, if possible, by subgroup analyses. We will regard heterogeneity to be substantial if I^2 is greater than 30%, and either Tau^2 is greater than zero, or there is a low P value (< 0.10) in the Chi^2 test for heterogeneity.

If there is evidence of substantial clinical, methodological, or statistical heterogeneity across the included studies, we will not pool results for meta-analysis but will instead use a narrative approach to our data synthesis. In this event, we will investigate and report the possible clinical or methodological reasons for the heterogeneity.

It should be noted that when few trials are included in a meta-analysis, the Chi^2 test has little power to detect heterogeneity. Therefore, a non-significant result will not necessarily be interpreted as evidence of no heterogeneity and will instead be interpreted with care.

Furthermore, thresholds for the interpretation of I^2 can be misleading, since the importance of inconsistency depends on several factors.

A rough guide to interpretation is as follows:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;*
- 50% to 90%: may represent substantial heterogeneity;*
- 75% to 100%: represents considerable heterogeneity.*

*The importance of the observed value of I^2 depends on 1) the magnitude and direction of effects and 2) the strength of evidence for heterogeneity (e.g. P value from the Chi^2 test, or a CI for I^2).

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Assessment of reporting biases

We will examine funnel plots corresponding to meta-analysis of the outcome to assess the potential for small-study effects such as publication bias. We plan to assess funnel plot symmetry visually, and if asymmetry is suggested, we will perform exploratory analyses to investigate it. However, in the case of treatment effects, we will use a fixed-effect model to run a separate sensitivity analysis.

Data synthesis

If a sufficient number of clinically similar studies (regarding participants, settings, interventions, comparison, and outcome measures) are available to ensure meaningful conclusions, and statistical heterogeneity is low (I^2 < 30%), we will pool results in meta-analyses using the random-effects model in RevMan (RevMan 2024). If there is variability in participants, populations, interventions, primary and secondary outcomes of the included studies, or if statistical heterogeneity is substantial (I^2 > 30%), we will use the random-effects model with inverse variance for meta-analysis (DeSimonian 1986).

- For time-to-event data, we will pool HRs using the generic inverse variance facility in RevMan (RevMan 2024).
- For dichotomous outcomes, we will calculate the RR using the inverse variance method for each study, which will then be pooled.
- For continuous outcomes, we will pool the MDs between the treatment arms at the end of follow-up if all trials measure the outcome on the same scale; otherwise we will pool SMDs.

If any trials have multiple treatment groups, we will divide the 'shared' comparison group into the number of treatment groups and treat the split comparison group as independent comparisons.

If we are unable to pool the data statistically using meta-analysis, we will conduct a narrative synthesis of results. We will present the major outcomes and results, organised by intervention categories according to the major types and/or aims of the identified interventions. Depending on the assembled research, we may also explore the possibility of organising the data by population. Within the data categories we will explore the main comparisons of the review.

If we cannot conduct a meta-analysis, we will synthesise the data following the Synthesis Without Meta-analysis (SWiM) approach (Campbell 2020).

Subgroup analysis and investigation of heterogeneity

We will conduct subgroup analysis to explore the impact of prognostic factors, such as performance status, sites of recurrence (single-site versus recurrence in more than one site), and platinum-free interval (6 to 12 months versus more than 12 months after the last platinum infusion), in OS and PFS.

We will also conduct subgroup analysis for women having secondary CRS followed by chemotherapy with immunotherapy versus those having secondary CRS followed by chemotherapy without immunotherapy.

We will assess heterogeneity against the study's participant characteristics such as age, type of intervention, length of follow-up, hospitalisation duration, stage of disease, and risk of bias status. We will compare the subgroups using the formal test for subgroup differences in RevMan (RevMan 2024).

Sensitivity analysis

We will conduct sensitivity analysis for studies with high risk of bias or unadjusted results.

For eligible studies that include only a subset of relevant participants that is not analysed separately, we will perform a sensitivity analysis to assess the impact of the decision on the review's findings.

For eligible cross-over trials, we will include the results from the phase parallel-group trial to avoid carry-over effects and loss to follow-up. We will then conduct a sensitivity analysis excluding cross-over trials from the meta-analysis.

Summary of findings and assessment of the certainty of the evidence

We will present the overall certainty of the evidence for each outcome according to the GRADE approach, which takes into account issues not only related to internal validity (risk of bias, inconsistency, imprecision, publication bias) but also to external validity such as directness of results (Langendam 2013; Schünemann 2011; Schünemann 2020). Two review authors (CP, SS) will independently assess the certainty of the evidence, resolving any disagreements by discussion or by appeal to a third review author (MA).

We will create a summary of findings table based on the methods described in the *Cochrane Handbook* and using GRADEpro GDT software (GRADEpro GDT; Higgins 2022). We will use the GRADE checklist and GRADE Working Group certainty of evidence definitions (Meader 2014). We will downgrade the evidence from 'high' certainty by one level for serious (or by two levels for very serious) concerns for each limitation, as follows.

- High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

We will include the following outcomes in the summary of findings table (Appendix 3).

- Overall survival (OS) (survival until death from any cause from the time of randomisation).
- Intervention-related mortality. For the group receiving surgery, this will be assessed as any death, regardless of cause, occurring within 30 days. For the chemotherapy-alone group, this will be assessed as any reported death whilst on chemotherapy treatment or within 30 days from completion of chemotherapy.

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- Progression-free survival (PFS) (survival until progression of disease from the time of randomisation).
- Quality of life (QoL) measures with (FACT-O TOI) at six months.
- Surgical-related severe adverse events (grade 3+): bowel resection +/− stoma formation (within 30 days of surgery).
- Surgical-related severe adverse events (grade 3+): postoperative events (within 30 days of surgery).
- Chemotherapy-related severe adverse events (grade 3+ adverse events, whilst on chemotherapy treatment or within 30 days from completion of chemotherapy).

If meta-analysis is not possible, we will present the results in a narrative summary of findings table format, such as that used by Chan (Chan 2011).

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Editorial and peer-reviewer contributions

The following people conducted the editorial process for this article.

- Sign-off Editor (final editorial decision): Jo Morrison
- Managing Editor (selected peer reviewers, provided editorial guidance to authors, edited the article): Sam Hinsley, Cochrane Central Editorial Service
- Editorial Assistant (conducted editorial policy checks, collated peer-reviewer comments, and supported the editorial team): Leticia Rodrigues, Cochrane Central Editorial Service
- Copy Editor (copy editing and production): Lisa Winer, Cochrane Central Production Service
- Peer reviewers (provided comments and recommended an editorial decision): Nuala Livingstone, Cochrane Evidence Production and Methods Directorate (methods), Steve McDonald, Cochrane Australia (search), Sahar Salehi, Department of Women's and Children's Health, Division of Obstetrics and Gynaecology, Karolinska Institute and Department of Pelvic Cancer, Theme Cancer, Karolinska University Hospital, Stockholm, Sweden (clinical), Aditi Bhatt, MS, MCh., KD Hospital, Ahmedabad, India (clinical), and Ruth Payne (consumer)

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APPENDICES

Appendix 1. MEDLINE search strategy

1. exp Ovarian Neoplasms/
2. (ovar* adj5 (cancer* or tumor* or tumour* or neoplas* or carcinoma* or malignan* or adenocarcinoma*)).mp.
3. 1 or 2
4. exp Cytoreduction Surgical Procedures/
5. debulk*.mp.
6. cytoreduc*.mp.
7. 4 or 5 or 6
8. exp Antineoplastic Agents/
9. Antineoplastic Combined Chemotherapy Protocols/
10. chemotherap*.mp.
11. 8 or 9 or 10
12. 7 or 11
13. 3 and 12
14. randomized controlled trial.pt.
15. controlled clinical trial.pt.
16. randomized.ab.
17. placebo.ab.
18. clinical trials as topic.sh.
19. randomly.ab.
20. trial.ti.
21. 14 or 15 or 16 or 17 or 18 or 19 or 20
22. (animals not (humans and animals)).sh.
23. 21 not 22
24. 13 and 23
25. limit 24 to yr="2009 -Current"

key
mp=title, original title, abstract, name of substance word, subject heading word
fs= floating subheading
pt=publication type

Appendix 2. Risk of bias domains for RCTs

Random sequence generation

- Low risk of bias, e.g. participants assigned to treatments based on a computer-generated random sequence or a random numbers table
- High risk of bias, e.g. participants assigned to treatments based on date of birth, clinic identity number, or surname, or there was no attempt to randomise participants
- Unclear risk of bias, e.g. not reported; information not available

Allocation concealment

- Low risk of bias: the allocation sequence could not be foretold
- High risk of bias: allocation sequence could be foretold by participants, investigators, or treatment providers
- Unclear risk of bias: allocation concealment was not reported

Blinding of participants and personnel

- Low risk of bias: participants and personnel were adequately blinded
- High risk of bias: participants were not blinded to the intervention received
- Unclear risk of bias: this was not reported or unclear

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Blinding of outcomes assessors

- Low risk of bias: outcome assessors were adequately blinded
- High risk of bias: outcome assessors were not blinded to the intervention participants received
- Unclear risk of bias: this was not reported or unclear

Incomplete outcome data: we will record the proportion of participants whose outcomes were not reported at the end of the study. We will code a satisfactory level of loss to follow-up for each outcome as follows.

- Low risk of bias: less than 20% of participants were lost to follow-up, and reasons for loss to follow-up were similar in both treatment arms
- High risk of bias: more than 20% of participants were lost to follow-up, or reasons for loss to follow-up differed between treatment arms
- Unclear risk of bias: loss to follow-up was not reported

Selective reporting of outcomes

- Low risk of bias: the study reports all outcomes specified in the protocol
- High risk of bias: it is suspected that outcomes have been selectively reported
- Unclear risk of bias: it is unclear whether outcomes have been selectively reported

Other bias

- Low risk of bias: no other source of bias is suspected, and the trial appears to be methodologically sound
- High risk of bias: it is suspected that the trial was prone to other bias
- Unclear risk of bias: it is not clear whether other bias may have been present

We will define the following endpoints as subjective outcomes: progression-free survival, adverse events, quality of life.

We will define the following endpoints as objective outcomes: overall survival, extent of resection, adverse events (toxicity, intraoperative complications, death).

Appendix 3. Summary of findings table

Cytoreductive surgery plus chemotherapy versus chemotherapy alone for recurrent epithelial ovarian cancer

Patient or population: women diagnosed with platinum-sensitive recurrent epithelial ovarian cancer

Settings: inpatients and outpatients

Intervention: secondary cytoreductive surgery followed by platinum-based chemotherapy with or without PARPi or VEGF-A (bevacizumab) or both

Comparison: platinum-based chemotherapy with or without PARPi or VEGF-A (bevacizumab) or both

Outcomes	Illustrative comparative risks*		Relative effect (95% CI)	No. of participants (studies)	Certainty of evidence (GRADE)	Comment
	Assumed risk	Corresponding risk				
Overall survival (survival until death from any cause from the time of randomisation)						
Intervention-related mortality (For the group receiving surgery, this will be assessed as any death, regardless of cause, occurring within 30 days. For the chemotherapy-alone group, this will be assessed as any reported death whilst on						

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(Continued) chemotherapy treatment or within 30 days from completion of chemotherapy.)
Progression-free survival (survival until progression of disease from the time of randomisation)
Quality of life measures with FACT-O TOI at 6 months
Surgical-related severe adverse events (grade 3+): bowel resection +/− stoma formation (within 30 days of surgery)
Surgical-related severe adverse events (grade 3+): postoperative events (within 30 days of surgery)
Chemotherapy-related severe adverse events - grade 3+ adverse events (whilst on chemotherapy treatment or within 30 days from completion of chemotherapy)

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: confidence interval; **HR:** hazard ratio; **MD:** mean difference; **OR:** odds ratio; **RR:** risk ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

CONTRIBUTIONS OF AUTHORS

Mo'iad Alazzam, guarantor of the review, conceived the idea and contributed to writing the protocol. Christina Pappa wrote the first draft of the protocol. Khadra Galaal, Sarah Smyth, Ali Khashan, and Robert Bristow reviewed the manuscript and provided expert advice.

DECLARATIONS OF INTEREST

Christina Pappa: none known

Khadra Galaal: none known

Sarah Smyth: none known

Robert E Bristow: none known

Ali S Khashan: none known

Mo'iad Alazzam: none known

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  None

External sources

- There are no external sources of support in terms of funding for the review, Other

  None

NOTES

Khadra Galaal and Robert Bristow were authors of the original review. This is a new protocol to take into account methodological changes since the previous review was published.

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