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

Khadra Galaal¹, Raj Naik², Robert E Bristow³, Amit Patel⁴, Andrew Bryant⁵, and Heather O Dickinson⁵

¹Gynaecological Oncology, Princess Alexandra Wing, Royal Cornwall Hospital, Truro, UK.

²Northern Gynaecological Oncology Centre, Gateshead, UK.

³Division of Gynecologic Oncology, University of California - Irvine, Medical Center, Orange, CA, USA.

⁴Gynaecological Oncology, University Hospitals Bristol NHS Foundation Trust, Bristol, UK.

⁵Institute of Health & Society, Newcastle University, Newcastle upon Tyne, UK

Abstract

Background—Most women with advanced epithelial ovarian cancer will ultimately develop recurrent disease after completion of initial treatment with primary surgery and adjuvant chemotherapy. Secondary cytoreductive surgery may have survival benefits in selected patients. However, a number of chemotherapeutic agents are active in recurrent ovarian cancer and the standard treatment of patients with recurrent ovarian cancer remains poorly defined.

Objectives—To evaluate the effectiveness and safety of secondary surgical cytoreduction and chemotherapy compared to chemotherapy alone for women with recurrent epithelial ovarian cancer.

Search methods—We searched the Cochrane Gynaecological Cancer Group Trials Register, The Cochrane Register of Controlled Trials, (CENTRAL) Issue 1 2009, MEDLINE and EMBASE up to February 2009. We also searched registers of clinical trials, abstracts of scientific meetings, reference lists of review articles and contacted experts in the field.

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Contact address: Khadra Galaal, Gynaecological Oncology, Princess Alexandra Wing, Royal Cornwall Hospital, Truro, TR1 3LJ, UK. Khadra.Galaal@rcht.cornwall.nhs.uk.khadragalaal@yahoo.co.uk.

CONTRIBUTIONS OF AUTHORS

Khadra Galaal is guarantor of the review. She developed the protocol and wrote the review. Raj Naik developed the title, protocol and clinical sections of the review. Robert Bristow assisted in developing the clinical sections of the review and reviewed the final draft. Amit Patel sifted through the abstracts and assisted with the clinical sections of the review. Andrew Bryant and Heather Dickinson drafted the methodological sections of the protocol and contributed to the review. All authors agreed the final version.

Editorial group: Cochrane Gynaecological Cancer Group.

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DECLARATIONS OF INTEREST

None

Selection criteria—We searched for RCTs, quasi-randomised trials and non-randomised studies that compared secondary cytoreductive surgery and chemotherapy to chemotherapy alone in women with recurrent epithelial ovarian cancer.

Data collection and analysis—Three reviewers independently assessed whether potentially relevant studies met the inclusion criteria. No trials were found and therefore no data were analysed.

Main results—The search strategy identified 1431 unique references of which all were excluded on the basis of title and abstract.

Authors' conclusions—We found no evidence from RCTs to inform decisions about secondary surgical cytoreduction and chemotherapy compared to chemotherapy alone for women with recurrent epithelial ovarian cancer. Ideally, a large randomised controlled trial or, at the very least, well designed non-randomised studies that use multivariate analysis to adjust for baseline imbalances are needed to compare these treatment modalities. The results of the ongoing RCT AGO-OVAR OP.4 (DESKTOP III) is awaited.

Medical Subject Headings (MeSH)

Carcinoma [*drug therapy; pathology; *surgery]; Combined Modality Therapy [methods]; Neoplasm Recurrence, Local [*drug therapy; *surgery]; Ovarian Neoplasms [*drug therapy; pathology; *surgery]

MeSH check words

Female; Humans

BACKGROUND

Description of the condition

Ovarian cancer is the sixth most common cancer among women (GLOBOCAN 2002). Worldwide there are more than 200,000 new cases of ovarian cancer each year, accounting for around 4% of all cancers diagnosed in women. A woman's risk of developing cancer of the ovaries by age 75 years varies between countries, ranging from 0.5% to 1.6% (IARC 2002), corresponding to an age-standardised rate of ovarian cancer varying between countries from 5 to 14 cases per year in 100,000 women under 75 years. In Europe, 37-41% women with ovarian cancer are alive five years after diagnosis (EUROCARE 2003). The poor survival associated with ovarian cancer is largely because most women are diagnosed when the cancer is already at an advanced stage (Jemal 2008) Epithelial ovarian cancer is a disease in which malignant cells form in the tissue covering the ovary. It accounts for about 90% of ovarian cancers, the remaining 10% arise from germ cells and the sex cord and stroma of the ovary. Approximately 75 to 80% of epithelial ovarian cancers are of serous histological type, less common are mucinous (10%), endometrioid, clear cell, Brenner and undifferentiated cancers (Scully 1998).

Most women with ovarian cancer have widespread disease at presentation (FIGO stage III to IV) (Appendix 1). This may be due to relatively early spread and implantation of high grade

serous cancers to the rest of the peritoneal cavity. In addition presenting symptoms such as abdominal pain and swelling, gastrointestinal symptoms, and pelvic pain are often unrecognised leading to possible delay in diagnosis (Goff 2000; Smith 2005)

Description of the intervention

Surgery is the first step in the initial diagnosis and staging of ovarian cancer. The standard management of primary ovarian cancer is cytoreductive surgery usually defined as removal of all visible disease (complete cytoreduction) or reduction of residual disease to less than 1 cm (optimal cytoreduction) followed by platinum-based chemotherapy (Bristow 2002; Delgado 1988; Hacker 1983; Hoskins 1994; Piver 1988). Most women with primary ovarian cancer achieve remission on this combination therapy. The theoretical benefit from cytoreductive surgery relates to removing large tumour volumes that have a decreased growth fraction and poor blood supply, thereby improving the efficacy of chemotherapeutic agents (Boente 1998). Cytoreductive surgery is also thought to remove the chemoresistant clones of cancer cells.

For patients achieving clinical remission after completion of initial treatment, most women with advanced epithelial ovarian cancer will ultimately develop recurrent disease (Burke 1994; Munkarah 2004). Secondary cytoreductive surgery is defined as surgery after completion of the primary treatment to further debulking the recurrent tumour. It is commonly performed in cases where the disease has recurred more than six months after initial treatment (platinum sensitive).

Most of the evidence for surgical treatment in recurrent epithelial ovarian cancer are on platinum sensitive disease. Secondary cytoreductive surgery is usually not offered for resistant disease with evidence of progression during first line platinum chemotherapy (platinum refractory), or recurrent disease within less than six months of primary treatment (platinum resistant). These women usually have poor prognosis and do not benefit from further surgical attempts at cytoreduction (Eisenkop 2000; Scarabelli 2001; Tebes 2007).

The apparent benefits of optimal primary surgery in advanced ovarian cancer have prompted investigations into the role of secondary surgery for recurrent disease after a period of clinical remission. These studies, which included a heterogeneous group of patients, suggested that secondary cytoreductive surgery may have survival benefits in selected patients with overall survival of 37 to 66 months (Gadducci 2000; Gungor 2005; Harter 2006; Munkarah 2004; Santillan 2007; Tebes 2007). A recent met analysis on surgery for recurrent ovarian cancer suggested that complete cytoreduction is independently associated with increased overall post-recurrence survival time (Bristow 2009).

A number of chemotherapeutic agents are active in recurrent ovarian cancer including a combination of platinum and paclitaxel (Gonzalez-Martin 2003; Parmar 2003). Other chemotherapeutic agents with activity in recurrent ovarian cancer include topotecan, gemcitabine, Caelyx, Etoposide, Doxocycline, Docetaxel, Oxaliplatin and Bevacicamab (Avastin) (Bookman 1998; Ferrero 2009; Markman 2004; Monk 2009; Weber 2009). Newer chemotherapeutic agents have shown activity in recurrent ovarian cancer and response rates of 20 to 30% have been described (Harter 2006; Selinger 2009; Ozols 2005; Wright 2006).

These chemotherapeutic agents are sometimes given within research protocols. Response to these agents is often short lived and they have a significant toxicity profile (Munkarah 2004).

Why it is important to do this review

The standard treatment of patients with recurrent ovarian cancer remains poorly defined. Surgical debulking (cytoreduction) may be associated with improved outcomes in terms of survival in selected cases (platinum sensitive disease). Several chemotherapeutic agents have shown activity in recurrent ovarian cancer with some improvement in survival. A systematic review and meta-analysis is essential to make a reliable evaluation of the potential benefits and risks of surgery and chemotherapy versus chemotherapy alone in recurrent ovarian cancer. A recent systematic review on cytoreductive surgery for recurrent ovarian cancer suggested that complete cytoreduction confers survival benefit (Bristow 2009).

OBJECTIVES

To compare the effectiveness and safety of secondary cytoreductive surgery and chemotherapy to chemotherapy alone for women with platinum sensitive recurrent epithelial ovarian cancer.

METHODS

Criteria for considering studies for this review

Types of studies

- Randomised controlled trials (RCTs)

As we expected to find few RCTs of surgical interventions (Johnson 2008), non-randomised studies with concurrent comparison groups were also included:

- Quasi-randomised trials, non-randomised trials, prospective and retrospective cohort studies, and case series of 30 or more patients.
- Case-control studies and case series of fewer than 30 patients were excluded.

Types of participants

- Women diagnosed with recurrent epithelial ovarian cancer who received standard surgery and adjuvant platinum based chemotherapy in the primary setting.
- Women with other concurrent malignancies were excluded.

Types of interventions

Intervention

- Secondary cytoreductive surgery and chemotherapy

Comparison

- Chemotherapy

Types of outcome measures

Primary outcomes

Primary outcomes

1. Overall survival: survival until death from all causes (Survival from the time when women were diagnosed with recurrent disease).

Secondary outcomes

1. Progression-free survival
2. Quality of life (QoL), measured using a scale that has been validated through reporting of norms in a peer-reviewed publication
3. Adverse events, (CTCAE 2006):
 - i. direct surgical morbidity (e.g. death within 30 days, injury to bladder, ureter, vascular, small bowel or colon), presence and complications of adhesions, febrile morbidity, intestinal obstruction, haematoma, local infection)
 - ii. surgically related systemic morbidity (chest infection, thrombo-embolic events (deep vein thrombosis and pulmonary embolism), cardiac events (cardiac ischemias and cardiac failure), cerebrovascular accident)
 - iii. recovery: delayed discharge, unscheduled re-admission
 - iv. chemotherapy toxicity
 - v. other

Grades of chemotherapeutic toxicity were categorised into the following groups:

- i. haematological (leucopenia, anaemia, thrombocytopenia, neutropenia, haemorrhage)
- ii. gastrointestinal (nausea, vomiting, anorexia, diarrhoea, liver, proctitis)
- iii. genitourinary
- iv. skin (stomatitis, mucositis, alopecia, allergy)
- v. neurological (peripheral and central)
- vi. pulmonary

Search methods for identification of studies

Papers in all languages were sought and translations carried out if necessary.

Electronic searches—See: Cochrane Gynaecological Cancer Group methods used in reviews.

The following electronic databases were searched:

- The Cochrane Gynaecological Cancer Collaborative Review Group's Trial Register

- Cochrane Central Register of Controlled Trials (Central)
- MEDLINE
- EMBASE

The MEDLINE, EMBASE and CENTRAL search strategies based on terms related to the review topic are presented in Appendix 2, Appendix 3 and Appendix 4.

Databases were searched from 1950 until February 2009.

All relevant articles found were identified on PubMed and using the ‘related articles’ feature, a further search was carried out for newly published articles.

Searching other resources

Unpublished and Grey literature: Metaregister, Physicians Data Query, www.controlled-trials.com/rct, www.clinicaltrials.gov, www.cancer.gov/clinicaltrials and Gynaecologic Oncologists of Canada (<http://www.g-o-c.org>) were searched for ongoing trials. The main investigators identified one relevant ongoing trial which is in protocol stage AGO-OVAR OP.4

Handsearching: Reports of conferences were hand searched in the following sources:

- Gynecologic Oncology (Annual Meeting of the American Society of Gynecologic Oncologists)
- International Journal of Gynecological Cancer (Annual Meeting of the International Gynecologic Cancer Society)
- British Journal of Cancer
- British Gynaecological Cancer Society (BGCS)
- British Cancer Research Meeting
- Annual Meeting of European Society of Medical Oncology (ESMO)
- Annual Meeting of the American Society of Clinical Oncology (ASCO)
- BioMed (open text publisher); AACR conferences
- ESGO conference

We additionally searched the Journal of Ovarian Research: <http://www.ovarianresearch.com/home/>

Reference lists and Correspondence: The citation lists of included studies were checked and experts in the field contacted to identify further reports of trials.

Data collection and analysis

Selection of studies—All titles and abstracts retrieved by electronic searching were downloaded to the reference management database Endnote, duplicates were removed and the titles and abstracts of the remaining references were examined by two review authors

(KG, AP) independently. There were a number of retrospective and prospective studies on surgical cytoreduction for platinum sensitive recurrent ovarian cancer, however none had comparison with chemotherapy alone arm (Eisenkop 2000; Gungor 2005; Harter 2010; Tebes 2007). All were excluded at this stage as clearly not meeting the inclusion criteria. We have identified one ongoing RCT (AGO-OVAR OP.4) which meets our inclusion criteria and results of this trial is awaited. In future updates of the review, we will employ the following methods:

Copies of the full text of relevant references will be obtained. The eligibility of retrieved papers will be assessed independently by three review authors (KG, AB, AP). Disagreements will be resolved by discussion between the three review authors. Reasons for exclusion will be documented.

Data extraction and management—For included studies, data will be abstracted as recommended in Chapter 7 of the Cochrane Handbook 2008 (Higgins 2008). This will include data on the following:

- Author, year of publication and journal citation (including language)
- Country
- Setting
- Inclusion and exclusion criteria
- Study design, methodology
- Study population
 - Total number enrolled
 - Patient characteristics
 - Age
 - Co-morbidities
- Ovarian cancer details at diagnosis
 - FIGO stage
 - Histological cell type
 - Tumour grade
 - Primary surgery (complete cytoreduction, optimal cytoreduction)
 - Extent of disease
- Details at recurrence
 - Disease free interval (time to recurrence)
 - Method of detecting recurrence
 - Number of recurrences

- Presence of ascites
- Total number of intervention groups
- Intervention details
 - Details of secondary cytoreductive surgery
 - Type of surgeon (Gynaecologist, Gynaecologist, General surgeon)
 - Experience of surgeon
 - Details of chemotherapy
 - ◇ Dose
 - ◇ Cycle length
 - ◇ Combination
- Risk of bias in study (see below)
- Duration of follow-up
- Outcomes - Overall survival, recurrence-free survival, quality of life, patient satisfaction and adverse events.
 - For each outcome: Outcome definition (with diagnostic criteria if relevant);
 - Unit of measurement (if relevant);
 - For scales: upper and lower limits, and whether high or low score is good
 - Results: Number of participants allocated to each intervention group;
 - For each outcome of interest: Sample size; Missing participants

Data on outcomes will be extracted as below

- For time to event (overall survival) data, we will extract the log of the hazard ratio [log(HR)] and its standard error from trial reports; if these are not reported, we will attempt to estimate them from other reported statistics using the methods of Parmar 1998.
- For dichotomous outcomes (e.g. adverse events, or deaths if it was not possible to use a HR), we will extract the number of patients in each treatment arm who experienced the outcome of interest and the number of patients assessed at endpoint, in order to estimate a relative risk (RR).
- For continuous outcomes (e.g. QOL measures), we will extract the final value and standard deviation of the outcome of interest and the number of patients assessed at endpoint in each treatment arm at the end of follow-up, in order to estimate the mean difference (if trials measured outcomes on the same scale) or standardised mean differences (if trials measured outcomes on different scales) between treatment arms and its standard error.

Both unadjusted and adjusted statistics will be extracted, if reported.

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

The time points at which outcomes were collected and reported will be noted.

Data will be abstracted independently by two review authors (KG, RN) onto a data abstraction form specially designed for the review. Differences between review authors will be resolved by discussion or by appeal to a third review author (AB) if necessary.

Assessment of risk of bias in included studies—The risk of bias in included RCTs will be assessed using the following questions and criteria:

Sequence generation: Was the allocation sequence adequately generated?

- Yes: e.g. a computer-generated random sequence or a table of random numbers
- No: e.g. date of birth, clinic id-number or surname
- Unclear: e.g. not reported.

Allocation concealment: Was allocation adequately concealed?

- Yes: e.g. where the allocation sequence could not be foretold
- No: e.g. allocation sequence could be foretold by patients, investigators or treatment providers
- Unclear: e.g. not reported

Blinding: Assessment of blinding will be restricted to blinding of outcome assessors, since it is generally not possible to blind participants and treatment providers to surgical interventions.

Was knowledge of the allocated interventions adequately prevented during the study?

- Yes
- No
- Unclear.

Incomplete reporting of outcome data: We will record the proportion of participants whose outcomes were not reported at the end of the study; we will note if loss to follow-up was not reported.

Were incomplete outcome data adequately addressed?

- Yes, if fewer than 20% of patients were lost to follow-up and reasons for loss to follow-up were similar in both treatment arms
- No, if more than 20% of patients were lost to follow-up or reasons for loss to follow-up differed between treatment arms
- Unclear if loss to follow-up was not reported

Selective reporting of outcomes: Are reports of the study free of suggestion of selective outcome reporting?

- Yes e.g if review reports all outcomes specified in the protocol
- No
- Unclear

Other potential threats to validity: Was the study apparently free of other problems that could put it at a high risk of bias?

- Yes
- No
- Unclear

The risk of bias in non-randomised studies will be assessed in accordance with four additional criteria:

Cohort selection

1. Were relevant details of criteria for assignment of patients to treatments provided?
 - i. Yes
 - ii. No
 - iii. Unclear
2. Was the group of women who received the experimental intervention (secondary cytoreductive surgery) representative?
 - i. Yes, if they were representative of women with borderline ovarian tumours
 - ii. No, if group of patients was selected
 - iii. Unclear, if selection of group was not described
3. Was the group of women who received the comparison intervention (chemotherapy or best supportive care) representative?
 - i. Yes, if drawn from the same population as the experimental cohort
 - ii. No, if drawn from a different source
 - iii. Unclear, if selection of group not described

Comparability of treatment groups

1. Were there no differences between the two groups or differences controlled for, in particular with reference to age, FIGO stage, disease free interval, histology, type and experience of surgeon, number of recurrences and dose and duration of chemotherapy?

- i. Yes, if at least three of these characteristics were reported and any reported differences were controlled for
- ii. No, if the two groups differed and differences were not controlled for.
- iii. Unclear, if fewer than three of these characteristics were reported even if there were no other differences between the groups, and other characteristics had been controlled for.

The risk of bias tool will be applied independently by two review authors (KG, RN) and differences resolved by discussion or by appeal to a third reviewer (AB). Results will be presented in both a risk of bias graph and a risk of bias summary. Results of meta-analyses will be interpreted in light of the findings with respect to risk of bias.

Measures of treatment effect—We will use the following measures of the effect of treatment:

- For time to event data, we will use the HR.
- For dichotomous outcomes, we will use the RR.
- For continuous outcomes, we will use the mean difference between treatment arms (if trials measured outcomes on the same scale) or standardised mean differences (if trials measured outcomes on different scales).

Dealing with missing data—We will not impute missing outcome data for the primary outcome. If data are missing or only imputed data are reported we will contact trial authors to request data on the outcomes only among participants who were assessed.

Assessment of heterogeneity—Heterogeneity between studies will be assessed by visual inspection of forest plots, by estimation of the percentage heterogeneity between trials which cannot be ascribed to sampling variation (Higgins 2003), by a formal statistical test of the significance of the heterogeneity (Deeks 2001), and, if possible, by sub-group analyses (see below). If there is evidence of substantial heterogeneity, the possible reasons for this will be investigated and reported.

Assessment of reporting biases—Funnel plots corresponding to meta-analysis of the primary outcome will be examined to assess the potential for small study effects. When there is evidence of small-study effects, publication bias will be considered as only one of a number of possible explanations. If these plots suggest that treatment effects may not be sampled from a symmetric distribution, as assumed by the random effects model, sensitivity analyses will be performed using fixed effects models.

Data synthesis—If sufficient, clinically similar studies are available their results will be pooled in meta-analyses. Adjusted summary statistics will be used if available; otherwise unadjusted results will be used.

- For time-to-event data, HRs will be pooled using the generic inverse variance facility of RevMan 5.

- For dichotomous outcomes, the RR will be calculated for each study and these will then be pooled.
- For continuous outcomes, the mean differences between the treatment arms at the end of follow-up will be pooled if all trials measured the outcome on the same scale, otherwise standardised mean differences will be pooled.

If any trials have multiple treatment groups, the 'shared' comparison group will be divided into the number of treatment groups and comparisons between each treatment group and the split comparison group will be treated as independent comparisons. Random effects models with inverse variance weighting will be used for all meta-analyses (DerSimonian 1986).

If possible, indirect comparisons, using the methods of Bucher 1997 will be used to compare competing interventions that have not been compared directly with each other.

Subgroup analysis and investigation of heterogeneity—Sub-group analyses will be performed, grouping the trials by:

- Disease free interval
- Optimal cytoreduction achieved at the primary treatment

Factors such as age, stage, length of follow-up, adjusted/unadjusted analysis will be considered in interpretation of any heterogeneity.

Sensitivity analysis—Sensitivity analyses will be performed (i) excluding non-randomised studies if RCTs have been included (ii) excluding studies at high risk of bias and (iii) using unadjusted results.

RESULTS

Description of studies

Results of the search—The search strategy identified 1004 references in Medline, 1089 in Embase, 123 in Central and 77 in the specialised register. When the search results were merged into Endnote and duplicates were removed there were 1431 unique references. The abstracts of these were read independently by three reviewers and all were excluded. Two reviewers independently searched the grey literature; these searches also did not identify any relevant studies (KG, RN).

Risk of bias in included studies

No trials were found and therefore the risk of bias tool was not applied.

Effects of interventions

No data were available.

DISCUSSION

Summary of main results

We did not identify any studies that compared the effectiveness and safety of secondary surgical cytoreduction and chemotherapy for women with recurrent epithelial ovarian cancer. Therefore the questions of whether secondary cytoreductive surgery and chemotherapy is associated with a survival benefit when compared to chemotherapy alone in terms of overall and progression-free survival cannot be answered by this review.

We specified overall survival as the primary outcome of interest, as it is important to prolong life in patients who could, in theory, have a reasonable quality of life after surgery. However, this is likely to be conditional on women being disease-free for a long period of time, so progression-free survival is of similar importance as longer term progression-free disease is likely to lead to longer survival in patients.

Treatment-related morbidity may degrade the quality of the time that patients live, which is especially important after the completion of cancer treatment when patients will want to enjoy a comfortable standard of living during their final months. There is a definite need to address secondary cytoreductive surgery as a treatment modality that may impact on survival time, however it is also essential to investigate the effects of this type of surgery on quality of patient's life in terms of morbidity and minimising treatment toxicity.

Quality of the evidence

No studies met the inclusion criteria for this review, so there is no evidence to assess.

Potential biases in the review process

A comprehensive search was performed, including a thorough search of the grey literature and all studies were sifted and data extracted by two reviewers independently. We were not restrictive in our inclusion criteria with regards to types of studies as we planned to include non-randomised studies with concurrent comparisons groups as we suspected that we would not find any relevant RCTs. Therefore we attempted to ensure that we did not overlook any relevant evidence by searching a wide range of reasonable quality non-randomised study designs (case-control studies and case series of fewer than 30 patients were excluded).

The greatest threat to the validity of the review is likely to be publication bias i.e. studies that did not find the treatment to have been effective may not have been published. We were unable to assess this possibility as we did not find any studies that met the inclusion criteria.

Agreements and disagreements with other studies or reviews

We found no studies directly comparing the two modalities of treatment. There is however, a randomised controlled trial planned which is comparing the efficacy of cytoreductive surgery versus chemotherapy alone for recurrent platinum-sensitive ovarian cancer AGO-OVAR OP.4.

The influence of secondary cytoreduction on survival outcomes in recurrent ovarian cancer has been addressed in a substantial number of publications (Eisenkop 2000; Gadducci 2000;

Gungor 2005; Markman 2004; Scarabelli 2001; Tebes 2007; Tay 2000; Bristow 2009). However, these were non comparative prospective and retrospective surgical studies investigating the impact of secondary cytoreductive surgery with chemotherapy on survival. These studies suggested that in women who underwent secondary cytoreduction, recurrence more than 6 months, absence of ascites, performance status and size of residual disease had a significant impact on survival with complete cytoreduction being associated with significantly longer survival.

A recent systematic review on surgery for recurrent ovarian cancer suggested that for a select group of patients undergoing cytoreductive surgery complete cytoreduction is independently associated with overall post-recurrence survival time. For this select group of patients, the surgical objective should be resection of all macroscopic disease (Bristow 2009).

AUTHORS' CONCLUSIONS

Implications for practice

We found no current evidence from RCTs to guide clinical practice, however the results of an ongoing RCT AGO-OVAR OP.4 is awaited to determine the efficacy of secondary surgical cytoreduction with chemotherapy compared to chemotherapy alone for women with recurrent epithelial ovarian cancer.

Implications for research

To determine the effectiveness of surgical cytoreduction in recurrent ovarian cancer, a RCT is needed to compare secondary surgical cytoreduction with chemotherapy to chemotherapy alone.

In addition a trial investigating delayed surgical cytoreduction after a few cycles of chemotherapy for recurrent ovarian cancer should be considered. This trial may investigate the potential benefits and risks in terms of morbidity and QOL by the timing of surgery.

These trials need to be set up in gynaecological oncology centres with standardization of the level and expertise of the surgeons in order to obtain the best surgical outcomes

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External sources

- Department of Health, UK.

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Appendix 1. FIGO staging

Stage I

Stage I ovarian cancer is limited to the ovaries.

- Stage IA: Tumor limited to one ovary; capsule intact, no tumour on ovarian surface. No malignant cells in ascites or peritoneal washings.*
- Stage IB: Tumor limited to both ovaries; capsules intact, no tumour on ovarian surface. No malignant cells in ascites or peritoneal washings.*
- Stage IC: Tumor limited to one or both ovaries with any of the following: capsule ruptured, tumour on ovarian surface, malignant cells in ascites or peritoneal washings.[8]

* [Note: The term, malignant ascites, is not classified. The presence of ascites does not affect staging unless malignant cells are present.]

Stage II

Stage II ovarian cancer is tumour involving one or both ovaries with pelvic extension and/or implants

- Stage IIA: Extension and/or implants on the uterus and/or fallopian tubes. No malignant cells in ascites or peritoneal washings.
- Stage IIB: Extension to and/or implants on other pelvic tissues. No malignant cells in ascites or peritoneal washings.
- Stage IIC: Pelvic extension and/or implants (stage IIA or stage IIB) with malignant cells in ascites or peritoneal washings.

Different criteria for allotting cases to stage IC and stage IIC have an impact on diagnosis. To assess this impact, of value would be to know if rupture of the capsule was (1) spontaneous or (2) caused by the surgeon; and, if the source of malignant cells detected was (1) peritoneal washings or (2) ascites

Stage III

Stage III ovarian cancer is tumour involving one or both ovaries with microscopically confirmed peritoneal implants outside the pelvis. Superficial liver metastasis equals stage III. Tumor is limited to the true pelvis but with histologically verified malignant extension to small bowel or omentum

- Stage IIIA: Microscopic peritoneal metastasis beyond pelvis (no macroscopic tumour).
- Stage IIIB: Macroscopic peritoneal metastasis beyond pelvis 2 cm or less in greatest dimension.
- Stage IIIC: Peritoneal metastasis beyond pelvis more than 2 cm in greatest dimension and/or regional lymph node metastasis.

Stage IV

Stage IV ovarian cancer is tumour involving one or both ovaries with distant metastasis. If pleural effusion is present, positive cytologic test results must exist to designate a case to stage IV. Parenchymal liver metastasis equals stage IV (Shepherd 1989).

Appendix 2. MEDLINE Search Strategy

Medline Ovid 1950 to February week 4 2009

1. exp Ovarian Neoplasms/
2. (ovar* adj5 cancer*).mp.
3. (ovar* adj5 neoplas*).mp.
4. (ovar* adj5 carcinom*).mp.
5. (ovar* adj5 malignan*).mp.
6. (ovar* adj5 tumor*).mp.
7. (ovar* adj5 tumour*).mp.

8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. exp Surgical Procedures, Operative/
10. surg*.mp.
11. “surgery”.fs.
12. 9 or 10 or 11
13. debulk*.mp.
14. cytoreduc*.mp.
15. 13 or 14
16. 8 and 12 and 15
17. “randomized controlled trial”.pt.
18. “controlled clinical trial”.pt.
19. random*.mp.
20. trial*.mp.
21. group*.mp.
22. exp Cohort Studies/
23. cohort*.mp.
24. series.mp.
25. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26. 16 and 25
27. Animals/
28. Humans/
29. 27 not (27 and 28)
30. 26 not 29

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

Appendix 3. Embase search strategy

Embase Ovid 1980 to 2009 week 10

1. exp Ovary Tumor/
2. (ovar* adj5 cancer*).mp.
3. (ovar* adj5 neoplas*).mp. [
4. (ovar* adj5 carcinom*).mp.

5. (ovar* adj5 malignan*).mp.
6. (ovar* adj5 tumor*).mp.]
7. (ovar* adj5 tumour*).mp.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. exp Surgery/
10. surg*.mp.
11. su.fs.
12. 9 or 10 or 11
13. debulk*.mp.
14. cytoreduc*.mp.
15. 13 or 14
16. 8 and 12 and 15
17. exp Controlled Clinical Trial/
18. random*.mp.
19. trial*.mp.
20. group*.mp.
21. exp Cohort Analysis/
22. cohort*.mp.
23. series.mp.
24. 17 or 18 or 19 or 20 or 21 or 22 or 23
25. 16 and 24

key: mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name fs=floating subheading

Appendix 4. Central search strategy

CENTRAL Issue 1 2009

1. MeSH descriptor Ovarian Neoplasms explode all trees
2. ovar* near/5 cancer*
3. ovar* near/5 neoplas*
4. ovar* near/5 carcinom*
5. ovar* near/5 malignan*
6. ovar* near/5 tumor*

7. ovar* near/5 tumour*
8. (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)
9. MeSH descriptor Surgical Procedures, Operative explode all trees
10. surg*
11. Any MeSH descriptor with qualifier: SU
12. (#9 OR #10 OR #11)
13. debulk*
14. cytoreduc*
15. (#13 OR #14)
16. (#8 AND #12 AND #15)

CHARACTERISTICS OF STUDIES

Characteristics of ongoing studies *[ordered by study ID]*

AGO-OVAR OP.4

Trial name or title	A randomized multicenter study to compare the efficacy of additional tumor debulking surgery versus chemotherapy alone for recurrent platinum-sensitive ovarian cancer
Methods	
Participants	Patients with first recurrence of platinum sensitive ovarian cancer defined as a progression free interval of at least 6 months after end of primary therapy
Interventions	Chemotherapy will be a platinum based combination chemotherapy up to the investigators choice
Outcomes	OS
Starting date	May 2010
Contact information	p.harter@gmx.de
Notes	

DATA AND ANALYSES

This review has no analyses.

HISTORY

Protocol first published: Issue 2, 2009

Review first published: Issue 6, 2010

Date	Event	Description
12 December 2013	Amended	This review will not be updated until the publication of the DESKTOP III trial in December 2016. ClinicalTrials.gov Identifier: NCT01166737 (AGO-OVAR OP.4)

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Once detailed search and review of current evidence was carried out, it became apparent that the majority of studies addressing outcomes of surgery for recurrent ovarian cancer did not have direct comparison arm with the conventional chemotherapy treatment. We therefore came to the conclusion that there are two questions to address;

1. How does surgery in comparison to chemotherapy. (The current review addresses this first question, the title and relevant sections in the objectives and intervention were changed)
2. How effective is surgery in platinum sensitive recurrent ovarian cancer (We plan to complete a separate review addressing this)

WHAT'S NEW

Last assessed as up-to-date: 11 May 2010.

Date	Event	Description
26 February 2014	Amended	Contact details updated.

References to ongoing studies

AGO-OVAR OP4 {published and unpublished data} . Harter, P.; Kurzeder, C.; du Bois, A. A randomized multicenter study to compare the efficacy of additional tumor debulking surgery versus chemotherapy alone for recurrent platinum-sensitive ovarian cancer. 2012. ClinicalTrials.gov ClinicalTrials.gov Identifier: NCT01166737

Additional references

- Boente 1998 . Boente MP, Chi DS, Hoskins WJ. The role of surgery in the management of ovarian cancer: primary and interval cytoreductive surgery. *Seminars in Oncology*. 1998; 25:326–34. [PubMed: 9633844]
- Bookman 1998 . Bookman MA, Malmström H, Bolis G, Gordon A, Lissoni A, Krebs JB, et al. Topotecan for the treatment of advanced epithelial ovarian cancer: an open-label phase II study in patients treated after prior chemotherapy that contained cisplatin or carboplatin and paclitaxel. *Journal of Clinical Oncology*. 1998; 16(10):3345–52. [PubMed: 9779711]
- Bristow 2002 . Bristow RE, Tomacruz RS, Armstrong DK, Timble EL, Montz FJ. Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. *Journal of Clinical Oncology*. 2002; 20:1248–59. [PubMed: 11870167]
- Bristow 2009 . Bristow RE, Puri I, Chi DS. Cytoreductive surgery for recurrent ovarian cancer: a meta-analysis. *Gynecologic Oncology*. 2009; 112(1):265–74. [PubMed: 18937969]

- Bucher 1997 . Bucker HC, Guyatt GH, Griffith LE, Walter SD. The Results of Direct and Indirect Treatment Comparisons in Meta-Analysis of Randomized Controlled Trials. *Journal of Clinical Epidemiology*. 1997; Vol. 50(No. 6):683–91.
- Burke 1994 . Burke TW, Morris M. Secondary cytoreductive surgery for ovarian cancer. *Obstetrics and Gynecology Clinics of North America*. 1994; 21:167–78. [PubMed: 8015762]
- CTCAE 2006 . Common Terminology Criteria for Adverse Events v3.0 (CTCAE). Aug 9th. 2006 <http://ctep.cancer.gov/forms/CTCAEv3.pdf><http://ctep.cancer.gov/forms/CTCAEv3.pdf>
- Deeks 2001 . Deeks, JJ.; Altman, DG.; Bradburn, MJ. Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. In: Egger, M.; Davey Smith, G.; Altman, DG., editors. *Systematic Reviews in Health Care: Meta-Analysis in Context*. 2nd Edition. BMJ Publication Group; London: 2001.
- Delgado 1988 . Delgado G, Oram DH, Petril ES. Stage III epithelial ovarian cancer: the role of maximal surgical reduction. *Gynecologic Oncology*. 1984; 18:293–8. [PubMed: 6745731]
- DerSimonian 1986 . DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clinical Trials*. 1986; 7:177–88. [PubMed: 3802833]
- Eisenkop 2000 . Eisenkop SM, Friedman RL, Spirtos NM. The role of secondary cytoreductive surgery in the treatment of patients with recurrent epithelial ovarian carcinoma. *Cancer*. 2000; 88:144–53. [PubMed: 10618617]
- EUROCARE 2003 . Sant M, Aareleid T, Berrino F, Bielska Lasota M, Carli PM, Faivre J, et al. the EUROCARE Working Group. EUROCARE-3: survival of cancer patients diagnosed 1990-94 - results and commentary. *Annals of Oncology*. 2003; 14(Supplement 5):v61–v118. [PubMed: 14684501]
- Ferrero 2009 . Ferrero A, Logripo V, Fuso L, Perotto S, Daniele A, Zola P. Gemcitabine and vinorelbine combination in platinum-sensitive recurrent ovarian cancer. *International Journal of Gynecologic Cancer*. 2009; 19(9):1529–34.
- Gadducci 2000 . Gadducci A, Lacconi P, Cosio S, Fanucchi A, Cristofani R, Riccardo Genazzani A. Complete salvage surgical cytoreduction improves further survival of patients with late recurrent ovarian cancer. *Gynecologic Oncology*. 2000; 79(3):344–9. [PubMed: 11104603]
- GLOBOCAN 2002 . Ferlay, J.; Bray, F.; Pisani, P.; Parkin, DM.; GLOBOCAN 2002. IARC CancerBase No. 5. version 2.0. IARC Press; Lyon: 2004. Cancer Incidence, Mortality and Prevalence Worldwide.
- Goff 2000 . Goff BA, Mander L, Muntz HG. Ovarian carcinoma diagnosis. *Cancer*. 2000; 89(10): 2068–75. [PubMed: 11066047]
- Gonzalez-Martin 2003 . Gonzalez-Martin AA, Clavo E, Bover I, Rubio J, Arcusa A, Casado A. Randomized phase II study of carboplatin versus paclitaxel-carboplatin in platinum sensitive recurrent advanced ovarian carcinoma with assessment of quality of life. *Proceedings of the American Society of Clinical Oncology*. 2003; 22 abs 1812.
- Gungor 2005 . Gungor M, Ortac F, Arvas M, Kosebay D, Sonmezer M, Kose K. The role of secondary cytoreductive surgery for recurrent ovarian cancer. *Gynecologic Oncology*. 2005; 97(1):74–9. [PubMed: 15790440]
- Hacker 1983 . Hacker NF, Berek JS, Lagasse CD, Neiberg RK, Elashoff RM. Primary cytoreductive surgery for epithelial ovarian cancer. *Obstetrics and Gynecology*. 1983; 61:413–20. [PubMed: 6828269]
- Harter 2006 . Harter P, du Bois A, Hahmann M, Hasenburg A, Burges A, Loibl S, et al. Surgery in Recurrent Ovarian Cancer: The Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) DESKTOP OVAR Trial. *Annals of Surgical Oncology*. 2006; 13(12):1702–10. [PubMed: 17009163]
- Harter 2010 . Harter P, Hilpert F, Mahner S, Heitz F, Pfisterer J, du Bois A. Systemic therapy in recurrent ovarian cancer: current treatment options and new drugs. *Expert Reviews in Anticancer Therapy*. 2010; 10(1):81–8.
- Higgins 2003 . Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003; 327:557–60. [PubMed: 12958120]

- Higgins 2008 . Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.0 [updated February 2008]. The Cochrane Collaboration. 2008 Available from www.cochrane-handbook.org.
- Hoskins 1994 . Hoskins WJ, McGuire WP, Brady MF, Homesley HD, Creasman WT, Berman M, et al. The effect of diameter of largest residual disease on survival after primary cytoreductive surgery in patients with sub optimal residual epithelial ovarian carcinoma. *American Journal of Obstetrics and Gynecology*. 1994; 70:974–80. [PubMed: 8166218]
- IARC 2002 . Parkin, DM.; Whelan, SL.; Ferlay, J.; Teppo, L.; Thomas, DB. Cancer Incidence in Five Continents, Volume VIII. In: Parkin, DM.; Whelan, SL.; Ferlay, J.; Teppo, L.; Thomas, DB., editors. IARC Scientific Publication No. 155. IARC Scientific Publication; Lyon: 2002.
- Jemal 2008 . Jemal, A.; Siegel, R.; Ward, E.; Hao, Y.; Xu, J.; Murray, T. Cancer Statistics. Vol. 58. *A Cancer Journal for Clinicians*; CA: 2008. p. 71–96.
- Johnson 2008 . Johnson NP, Selman T, Zamora J, Khan KS. Gynaecologic surgery from uncertainty to science: evidence-based surgery is no passing fad. *Reproduction Advanced Access*. 2008
- Markman 2004 . Markman M, Markman J, Webster K, Zanotti K, Kulp B, Peterson G, et al. Duration of response to second-line, platinum-based chemotherapy for ovarian cancer: implications for patient management and clinical trial design. *Journal of Clinical Oncology*. 2004; 22(15):3120–5. [PubMed: 15284263]
- Monk 2009 . Monk BJ, Coleman RL. Changing the paradigm in the treatment of platinum-sensitive recurrent ovarian cancer: from platinum doublets to nonplatinum doublets and adding antiangiogenesis compounds. *International Journal of Gynecological Cancer*. 2009; S2:S63–7. [PubMed: 19955917]
- Munkarah 2004 . Munkarah AR, Coleman RL. Critical evaluation of secondary cytoreduction in recurrent ovarian cancer. *Gynecologic Oncology*. 2004; 95(2):273–280. [PubMed: 15491746]
- Ozols 2005 . Ozols, RF.; Rubin, SC.; Thomas, GM.; Robboy, SJ. Epithelial ovarian cancer. In: Hoskins, WJ.; Perez, CA.; Young, RC.; Barakat, R.; Markman, M.; Randall, M., editors. *Principles and Practice of Gynecologic Oncology*. 4th Edition. Lippincott-Raven Publishers; Philadelphia, PA: 2005. p. 895–987.
- Parmar 1998 . Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Statistics in Medicine*. 1998; 17(24): 2815–34. [PubMed: 9921604]
- Parmar 2003 . Parmar MK, Ledermann JA, Colombo N, du Bois A, Delaloye JF, Kristensen GB. Paclitaxel plus platinum-based chemotherapy versus conventional platinum-based chemotherapy in women with relapsed ovarian cancer. the ICON4/AGO-OVAR-2-2 trial. *Lancet*. 2003; 361:2099–2106. [PubMed: 12826431]
- Piver 1988 . Piver MS, Lele SB, Marchetti DL, Baker TR, Tsukaso Y, Emrich LJ. The impact of aggressive debulking surgery and cisplatin-based chemotherapy on progression-free survival in Stage III and IV ovarian carcinoma. *Journal of Clinical Oncology*. 1988; 6:983–9. [PubMed: 3373267]
- Santillan 2007 . Santillan A, Karam AK, Li AJ, Giuntoli R, Gardner GJ, Cass L, et al. Secondary cytoreductive surgery for isolated nodal recurrence in patients with epithelial ovarian cancer. *Gynecologic Oncology*. 2007; 104:686–90. [PubMed: 17141302]
- Scarabelli 2001 . Scarabelli C, Gallo A, Carbone A. Secondary cytoreductive surgery for patients with recurrent epithelial ovarian carcinoma. *Gynecologic Oncology*. 2001; 83:504–12. [PubMed: 11733963]
- Scully 1998 . Scully, RE.; Young, RH.; Clement, PB. Atlas of tumor pathology. Vol. fascicle 23 3rd series. Armed Forces Institute of Pathology; Washington: 1998. Tumors of the ovary, maldeveloped gonads, fallopian tube, and broad ligament; p. 1–168.
- Selinger 2009 . Selinger G, Muelier LP, Kegal T, Kantekhardt EJ, Grothey A, Gros R, et al. Phase 2 trial of docetaxel, gemcitabine and oxliplatin combination in platinum-pretreated epithelial ovarian cancer. *International Journal of Gynecological Cancer*. 2009; 19(9):1529–34. [PubMed: 19955931]
- Shepherd 1989 . Shepherd JH. Revised FIGO staging for gynaecological cancer. *British Journal of Obstetrics and Gynaecology*. 1989; 96(8):889–92. [PubMed: 2775686]

- Smith 2005 . Smith LH, Morris CR, Yasmeen S. Ovarian cancer: can we make the clinical diagnosis earlier. *Cancer*. 2005; 104(7):1398–407. [PubMed: 16116591]
- Tay 2000 . Tay E-H, Grant PT, GebSKI V, Hacker NF. Secondary Cytoreductive Surgery for Recurrent Epithelial Ovarian Cancer. *Obstetrics and Gynecology*. 2002; 99:1008–13. [PubMed: 12052591]
- Tebes 2007 . Tebes SJ, Sayer RA, Palmer JM, Tebes CC, Martino MA, Hoffman MS. Cytoreductive surgery for patients with recurrent epithelial ovarian carcinoma. *Gynecologic Oncology*. 2007; 106(3):482–87. [PubMed: 17590420]
- Weber 2009 . Weber B, Lortholary A, Mayer F, Bourgeois H, Orfeuvre H, Combe M, et al. Pegylated liposomal doxorubicin and carboplatin in late-relapsing ovarian cancer: a GINECO group phase II trial. *Anticancer Research*. Oct; 2009 29(10):4195–200. [PubMed: 19846972]
- Wright 2006 . Wright JD, Hagemann A, Rader JS, Viviano D, Gibb RK, Norris L, et al. Bevacizumab combination therapy in recurrent, platinum-refractory, epithelial ovarian carcinoma: A retrospective analysis. *Cancer*. 2006; 107(1):83–9. [PubMed: 16736514]

* *Indicates the major publication for the study*

PLAIN LANGUAGE SUMMARY

Secondary surgical efforts to remove recurrent ovarian cancer in women who are no longer in remission

Ovarian cancer is the sixth most common cancer among women. Epithelial ovarian cancer is a disease in which malignant cells form in the tissue covering the ovary. It accounts for about 90% of ovarian cancers., the remaining 10% arise from germ cells and the sex cord and stroma of the ovary. Women with epithelial ovarian cancer that has returned after primary surgery (recurrent disease) may need secondary surgery to remove all or part of the cancer. The option of surgery (debulking or cytoreductive surgery) is currently offered to a select group of women with recurrent ovarian cancer. It is important to ascertain whether this surgery helps women with recurrent disease to survive for longer than if they only got chemotherapy.

We searched for studies that compared secondary cytoreductive surgery and chemotherapy with chemotherapy alone in women with recurrent epithelial ovarian cancer. Although we checked 1431 possible articles, we found no relevant studies. Therefore there is currently no evidence to determine if secondary cytoreductive surgery is better or worse than chemotherapy alone in terms of prolonging life.

The review highlights the need for good quality studies comparing secondary cytoreductive surgery to chemotherapy. The results of the ongoing RCT AGO-OVAR OP.4 (DESKTOP III) is awaited.