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Chemotherapy versus surgery for initial treatment in advanced ovarian epithelial cancer (Review)

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[Intervention Review]

Chemotherapy versus surgery for initial treatment in advanced ovarian epithelial cancer

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ABSTRACT

Background

Epithelial ovarian cancer presents at an advanced stage in the majority of women. These women require surgery and chemotherapy for optimal treatment. Conventional treatment is to perform surgery first and then give chemotherapy. However, it is not yet clear whether there are any advantages to using chemotherapy before surgery.

Objectives

To assess whether there is an advantage to treating women with advanced epithelial ovarian cancer with chemotherapy before cytoreductive surgery (neoadjuvant chemotherapy (NACT)) compared with conventional treatment where chemotherapy follows maximal cytoreductive surgery.

Search methods

For the original review we searched, the Cochrane Central Register of Controlled Trials (CENTRAL, Issue 3, 2006), MEDLINE (Silver Platter, from 1966 to 1 Sept 2006), EMBASE via Ovid (from 1980 to 1 Sept 2006), CANCERLIT (from 1966 to 1 Sept 2006), PDQ (search for open and closed trials) and MetaRegister (most current search Sept 2006). For this update randomised controlled trials (RCTs) were identified by searching the Cochrane Central Register of Controlled Trials (CENTRAL, Issue 3, 2011) and the Cochrane Gynaecological Cancer Specialised Register (2011), MEDLINE (August week 1, 2011), EMBASE (to week 31, 2011), PDQ (search for open and closed trials) and MetaRegister (August 2011).

Selection criteria

RCTs of women with advanced epithelial ovarian cancer (Federation of International Gynaecologists and Obstetricians (FIGO) stage III/IV) who were randomly allocated to treatment groups that compared platinum-based chemotherapy before cytoreductive surgery with platinum-based chemotherapy following cytoreductive surgery.

Data collection and analysis

Data were extracted by two review authors independently, and the quality of included trials was assessed by two review authors independently.

Main results

One high-quality RCT met the inclusion criteria. This multicentre trial randomised 718 women with stage IIIc/IV ovarian cancer to NACT followed by interval debulking surgery (IDS) or primary debulking surgery (PDS) followed by chemotherapy. There were no significant differences between the study groups with regard to overall survival (OS) (670 women; HR 0.98; 95% CI 0.82 to 1.18) or progression-free survival (PFS) (670 women; HR 1.01; 95% CI 0.86 to 1.17).

Significant differences occurred between the NACT and PDS groups with regard to some surgically related serious adverse effects (SAE grade 3/4) including haemorrhage (12 in NACT group vs 23 in PDS group; RR 0.50; 95% CI 0.25 to 0.99), venous thromboembolism (none in NACT group vs eight in PDS group; RR 0.06; 95% CI 0 to 0.98) and infection (five in NACT group vs 25 in PDS group; RR 0.19; 95% CI 0.07 to 0.50). Quality of life (QoL) was reported to be similar for the NACT and PDS groups.

Three ongoing RCTs were also identified.

Authors' conclusions

We consider the use of NACT in women with stage IIIc/IV ovarian cancer to be a reasonable alternative to PDS, particularly in bulky disease. With regard to selecting who will benefit from NACT, treatment should be tailored to the patient and should take into account resectability, age, histology, stage and performance status. These results cannot be generalised to women with stage IIIa and IIIb ovarian cancer; in these women, PDS is the standard. We await the results of three ongoing trials, which may change these conclusions.

PLAIN LANGUAGE SUMMARY

Does giving chemotherapy before surgery improve survival or quality of life for women with advanced ovarian epithelial cancer?

Epithelial ovarian cancer is the seventh most common cancer worldwide in women under the age of 65 years, and is the most common form of ovarian cancer (approximately 90% of ovarian cancers). Unfortunately most women with ovarian cancer present at a late stage when their disease has spread throughout the abdomen. This is because symptoms are vague, often occur only after the cancer has spread, and can be misdiagnosed as being caused by other benign conditions. In Europe, just over a third of women diagnosed with ovarian cancer are alive five years after diagnosis.

Conventional treatment for ovarian cancer is to have surgery (laparotomy) to remove the womb, ovaries, the omentum (a fatty structure (apron) that hangs down from the stomach and drapes over the intestines in the upper abdomen) and to sample the lymph nodes (glands) in the pelvis and abdomen. The intention of surgery is to stage the disease (assess where the cancer has spread to) and remove as much of the cancer as possible (debulking or cytoreduction). However, since most women will have widespread disease, surgery alone does not cure the disease and further treatment is necessary, in the form of chemotherapy. Chemotherapy for ovarian cancer uses platinum-based drugs (carboplatin and cisplatin) to treat any cancer cells that cannot be removed by surgery or are too small to be seen (microscopic disease).

Chemotherapy can be used before surgery (also called neoadjuvant chemotherapy) with the aim of shrinking the cancer and making it easier to remove all of the cancer.

One good-quality study in women with advanced ovarian cancer was included in this review. This study compared 336 women who were given chemotherapy first with 334 women who underwent surgery first and found no difference between the two treatments with respect to the time to death or the time to progression of the disease, that is chemotherapy before surgery had a similar effect on survival as the conventional treatment. The study only enrolled women with stage IIIc/IV ovarian cancer. (Stage IIIc is when the tumour that has spread into the abdomen is greater than 2 cm in size.) A large proportion of women in the study had very bulky tumours. We therefore assessed the evidence to be of moderate quality and concluded that neoadjuvant chemotherapy is a reasonable alternative to primary surgery in women with bulky stage IIIc/IV disease. Three other studies are currently being conducted that will hopefully contribute more evidence to guide clinical practice in this area in the future.

BACKGROUND

This is an updated version of the review that was first published in the Cochrane Database of Systematic Reviews, Issue 4, 2007.

Description of the condition

Ovarian cancer is the seventh most common cancer in women under the age of 65 years. A woman's risk of developing ovarian cancer by age 65 years ranges from 0.36% in developing countries to 0.64% in developed countries (GLOBOCAN 2008). In Europe, just over a third of women with ovarian cancer are alive five years after diagnosis (EUROCARE 2003), largely because most women with ovarian cancer are diagnosed when the cancer is already at an advanced stage (Jemel 2008). Symptoms are often vague and of a short duration and, as yet, there are no effective screening programmes. However, initial results of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS), evaluating the effectiveness of annual CA-125 or transvaginal ultrasound, or both, screening in post-menopausal women, show promise in identifying early-stage disease (UKCTOCS 2009), although survival data are still pending. In early-stage disease (Federation of International Gynaecologists and Obstetricians (FIGO) stage I/IIa; Table 1) radical surgery will cure most women, although a minority of women will benefit from adjuvant chemotherapy (Trimbos 2003), especially those who are not adequately staged at primary surgery. Unfortunately, around 75% of women present when the disease has spread outside the pelvis (FIGO stage III/IV), when surgery alone cannot be curative and the role of surgery is less clear.

The standard treatment of advanced ovarian cancer (FIGO stage III/IV) is a staging laparotomy with primary debulking surgery (PDS) followed by platinum-based chemotherapy. The extent of tumour cytoreduction is considered the most important prognostic factor. Griffiths 1975 was the first to report a relationship between the size of residual disease and survival. Meta-analyses of non-randomised studies (NRS) have since concurred that survival correlates positively with the extent of tumour debulking achieved (Hunter 1992; Allen 1995; Bristow 2002). However, the extent of debulking achievable may be directly related to tumour biology, which would strongly bias results from non-RCTs. Tumours that have spread to the para-aortic or scalene lymph nodes may be less likely to be optimally debulked intra-abdominally (Burghardt 1991; Petru 1991). Thus, the ability to achieve successful debulking may reflect tumour biology rather than an independent effect on outcome. One exploratory analysis of three prospectively randomised trials in advanced ovarian cancer suggested that surgical debulking can partially overcome these biological factors (du Bois 2009). Other independent prognostic factors for overall survival (OS) were shown to be age, performance status, grade, FIGO stage and histology (du Bois 2009).

The definition of what constitutes 'optimal' or 'maximal' debulking has changed since the 1980s; originally considered to be no residual tumour deposit of greater than 2 cm in diameter, and more recently as residual tumour of $\leq$ 1 cm, the current aim is to leave no macroscopic disease (Thigpen 2011).

In contrast to the evidence for improved survival with PDS, some investigators have been unable to show a benefit to maximal debulking for women with high-volume disease (Hoskins 1992; Vergote 1998). Vergote 1998 introduced a policy of treating women with primary chemotherapy (neoadjuvant chemotherapy (NACT)) or primary surgery, depending on the extent of the patient's disease and performance status. Following the change in patient management, they reported an overall improvement in survival, despite a reduction in primary debulking rates from 82% to 57%. The role of so-called supra-radical surgery, with extensive surgical effort often involving the upper abdomen, in ovarian cancer is reviewed elsewhere (Ang 2011) and this review does not seek to question the value or extent of surgery, rather its timing in respect of chemotherapy.

Description of the intervention

NACT involves giving chemotherapy as the initial treatment of advanced ovarian cancer before attempting cytoreductive surgery. It has evolved from the practice of interval debulking surgery (IDS), a secondary attempt at tumour cytoreduction performed after a suboptimal attempt at primary cytoreduction and adjuvant chemotherapy. In a Cochrane review (Tangjitgamol 2010), IDS performed by gynaecological oncologists secondary to PDS and adjuvant chemotherapy was found to offer no additional survival benefit compared with standard treatment of advanced ovarian cancer. However, IDS may improve survival of women in whom primary surgery was not performed by gynaecological oncologists and who have had suboptimal PDS.

Bristow 2007 reviewed 26 NRSs comparing NACT with PDS and concluded that, while NACT might be a viable option for unresectable tumours, survival outcomes with NACT may be inferior to PDS. Thus, platinum-based NACT has become an alternative to PDS, particularly where complete cytoreduction at PDS is considered unlikely (Swart 2009). Tumour resectability depends on the patient's age, disease burden, co-morbidities, location of metastatic sites, performance status and stage (Vergote 2011a), as well as the skill of the surgical team (Kehoe 1994; Chi 2010; Vergote 2011b).

The goal of surgery (IDS and PDS) should be complete resection of all disease (Onda 2010). A review of 21 NRSs (Kang 2009) found that, compared with PDS, NACT improved the rate of optimal cytoreduction; however, this did not seem to influence survival.

How the intervention might work

There are several reasons why NACT may be preferable to PDS:

- NACT may decrease the size and extent of the tumour such that complete resection is more feasible;
- NACT may improve patient performance status;
- PDS necessitates hospital admission, whereas chemotherapy can be administered in an outpatient setting and started immediately;
- PDS delays starting chemotherapy as there is the potential for chemotherapy to interfere with wound healing;
- if surgery is not curative, residual tumour cells may multiply while the patient awaits recovery from surgery.

Concerns about using NACT include the following:

- NACT delays the removal of the tumour and, thereby, may compromise patient survival;
- Chemotherapy induces fibrosis, which may make complete cytoreduction more difficult;
- if too many cycles of NACT are given pre-surgery, there is a concern regarding the possibility of chemo-resistance post-surgery. One meta-analysis found a negative association between OS and the number of NACT cycles given (Bristow 2006);
- PDS reduces the tumour bulk and number of cancer cells, thereby reducing the chance of developing chemo-resistance.

Why it is important to do this review

There is considerable controversy in the literature surrounding the use of NACT in advanced ovarian cancer (Chi 2011; du Bois 2011; Vergote 2011a). In one overview, Onda 2011 stated "NACT is expected to become standard treatment for unselected patients with advanced ovarian cancer when favourable results are confirmed by Phase III studies and several problems are resolved". However, surveys among members of the US Society of Gynecologic Oncology (Dewdney 2010) and the European Society of Gynaecologic Oncology (Vergote 2011b) suggest a large discrepancy in acceptance and use of NACT as a treatment option for advanced ovarian cancer. Many investigators agree that NACT has a place, at the very least, in women with lesions that cannot be optimally resected (Bristow 2007; Swart 2009; Chi 2010; Vergote 2011a). To our knowledge, at least four randomised trials of NACT versus PDS have been underway in the past decade (EORTC 55971; CHORUS #; Onda #; Kumar #). Since RCTs are the 'gold standard' of evidence-based medical research, we hope that a review of randomised evidence may clarify what the benefits and risks are of using NACT for women with advanced ovarian cancer, compared with the standard treatment of PDS.

OBJECTIVES

To assess whether chemotherapy prior to surgery NACT is more effective for increasing survival, or improving quality of life (QoL) for women with advanced epithelial ovarian cancer, compared with standard debulking surgery followed by chemotherapy.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs).

Types of participants

Women with advanced epithelial ovarian cancer (FIGO stage III/IV).

Types of interventions

PDS, with the aim of complete resection or optimal debulking (as defined by the investigators), followed by platinum-based chemotherapy, compared to platinum-based NACT followed by debulking surgery.

Types of outcome measures

Primary outcomes

1. OS
2. Progression-free survival (PFS)

Secondary outcomes

1. QoL (as defined/measured by investigators).
2. Morbidity/adverse effects, including:

i) direct surgical morbidity (e.g. bladder injury, intestinal obstruction, haematoma, local infection, duration of operation, need for blood transfusion);

ii) surgically related systemic morbidity (e.g. deep vein thrombosis (DVT), pulmonary embolism (PE), chest infection, cardiac events);

iii) recovery, including duration of hospital stay;

iv) toxicity related to chemotherapy; grouped as haematological, gastrointestinal, genitourinary, skin and neurological toxicity.

3. Extent of surgical debulking achieved (e.g. optimal or suboptimal).

Search methods for identification of studies

Electronic searches

The following databases were searched:

- the Specialised Register of the Cochrane Gynaecological Cancer Group;
- EMBASE via Ovid (from 1980 to week 31, 2011) (Appendix 1);
- MEDLINE (Silver Platter, from 1966 to Sept 2006; and Ovid, from Sept 2006 to Aug week 1, 2011) (Appendix 2);
- the Cochrane Central Register of Controlled Trials (CENTRAL, Issue 3, 2011) (Appendix 3);
- PDQ and MetaRegister (August 2011).

For the original review we searched, the Cochrane Central Register of Controlled Trials (CENTRAL, Issue 3, 2006), MEDLINE (Silver Platter, from 1966 to 1 Sept 2006), EMBASE via Ovid (from 1980 to 1 Sept 2006), CANCERLIT (from 1966 to 1 Sept 2006), PDQ (search for open and closed trials) and MetaRegister (most current search Sept 2006).

Searching other resources

The reference lists of the relevant papers found were searched for further studies and the authors of relevant trials contacted to request information relating to their participation in unpublished trials. Papers in all languages were sought, and translations carried out if necessary.

All relevant articles found were entered into PubMed, and using the 'related articles' feature, a further search was carried out for any other published articles. Meta-register and links were searched for ongoing trials. The main investigators of relevant trials were contacted for further information.

Data collection and analysis

Selection of studies

Two review authors independently selected trials from the results of the searches according to the inclusion criteria specified above (JM and SC for the original review; TAL and KH for the updated review). Disagreements were resolved by discussion with a third review author (JM) for this update.

Data extraction and management

Two review authors (TAL and JM) independently extracted data from the included trial onto a specifically designed data-collection form. Where there were disagreements, these were resolved by discussion. No attempt was made to blind review authors to authors of articles or to journals.

For included studies, we recorded details of trial methodology, the study population and sample size, inclusion and exclusion criteria, intervention and comparison, duration of follow-up and risks of bias. We extracted data relating to participant characteristics (age, histology, grade, extent of disease, previous therapies) and outcomes. For each outcome, we extracted the outcome definition and unit of measurement.

Results were extracted as follows:

- for time to event data (survival and disease progression), we extracted the log of the hazard ratio [log(HR)] and its standard error. If these were not reported, we estimated the log (HR) and its standard error using the methods of Parmar 1998;
- for dichotomous outcomes (e.g. adverse events or deaths) we extracted the number of women in each treatment arm who experienced the outcome of interest and the number of women assessed at end point, in order to estimate a risk ratio (RR);
- for continuous outcomes (e.g. QoL measures), we extracted the final value and standard deviation of the outcome of interest and the number of women assessed at end point 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.

Where data were missing or methods were unclear, we contacted the authors for further information. We entered data into Review Manager software (RevMan 2011) and two review authors checked for accuracy.

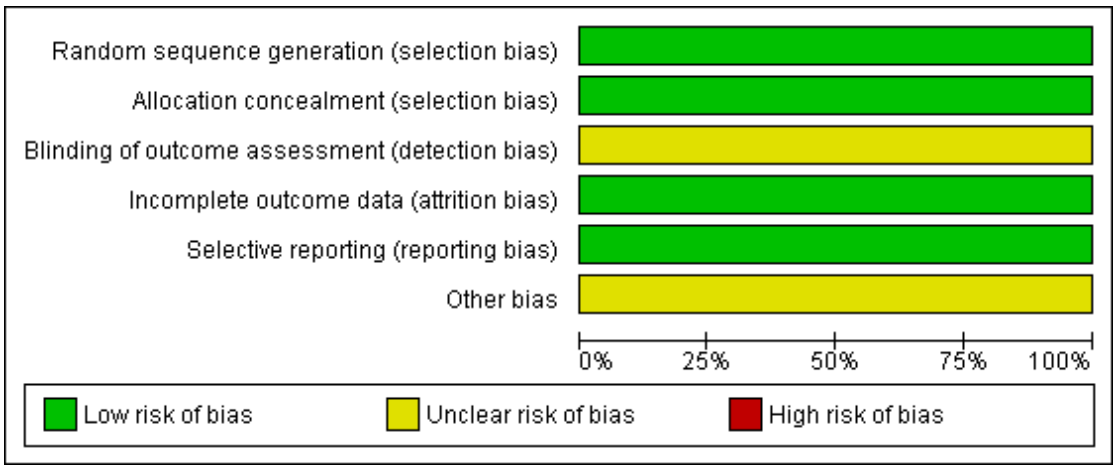
Assessment of risk of bias in included studies

Using The Cochrane Collaboration's tool (Higgins 2011), we assessed the following for the included study:

1. selection bias: random sequence generation and allocation concealment;
2. detection bias: blinding of outcome assessment;
3. attrition bias: incomplete outcome data;
4. reporting bias: selective reporting of outcomes;
5. other possible sources of bias.

The 'Risk of bias' tool (Appendix 4) was applied independently by two review authors (TAL and JM) and differences of opinion were resolved by discussion. Results were summarised in a 'Risk of bias' graph (Figure 1).

Figure 1. 'Risk of bias' graph: review authors' judgements about each 'Risk of bias' item presented as percentages across all included studies.



Measures of treatment effect

We used the following measures of the effect of treatment:

- for time to event data, we used the HR;
- for dichotomous outcomes, we used the RR and 95% confidence interval (CI);
- for continuous outcomes, we used the MD between treatment arms.

Dealing with missing data

We noted levels of attrition. In future, when we more trials are available for inclusion (see Ongoing studies), we will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis, where appropriate.

Assessment of heterogeneity

As only one study was included in this review, heterogeneity was not an issue. However, in future versions of this review, heterogeneity between studies will be assessed by visual inspection of forest plots, and by using the T^2, I^2 and Chi^2 statistics.

Data synthesis

We had planned to combine data from included trials in meta-analyses to calculate overall estimates of treatment efficacy; however, with data from only one trial, this was not possible. In future updates of the review, when the results of the ongoing trials are available (see Characteristics of ongoing studies), we will perform meta-analyses if more than one included study contributes data and if the trials are clinically homogeneous, as follows:

- for time-to-event data, HRs will be pooled using the generic inverse variance facility of RevMan 2011;
- for any dichotomous outcomes, RRs will be calculated for each study and these will then be pooled;
- for continuous outcomes, the MDs 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 MDs will be pooled.

Random-effects models will be used for all meta-analyses (DerSimonian 1986).

Subgroup analysis and investigation of heterogeneity

For this updated review, we included the following subgroup analyses:

1. age: 60 years or less and over 60 years;
2. extent of debulking achieved: complete debulking; residual tumour 1 cm or less; residual tumour greater than 2 cm.

These subgroups were not pre-specified in the protocol (see Differences between protocol and review) and were evaluated with respect to primary outcomes only. In future versions of this review, we plan to subgroup data by FIGO stage.

Sensitivity analysis

In future versions of this review, where more studies have been included, sensitivity analyses will be performed where there is a risk of bias associated with the quality of any of the included trials.

RESULTS

Description of studies

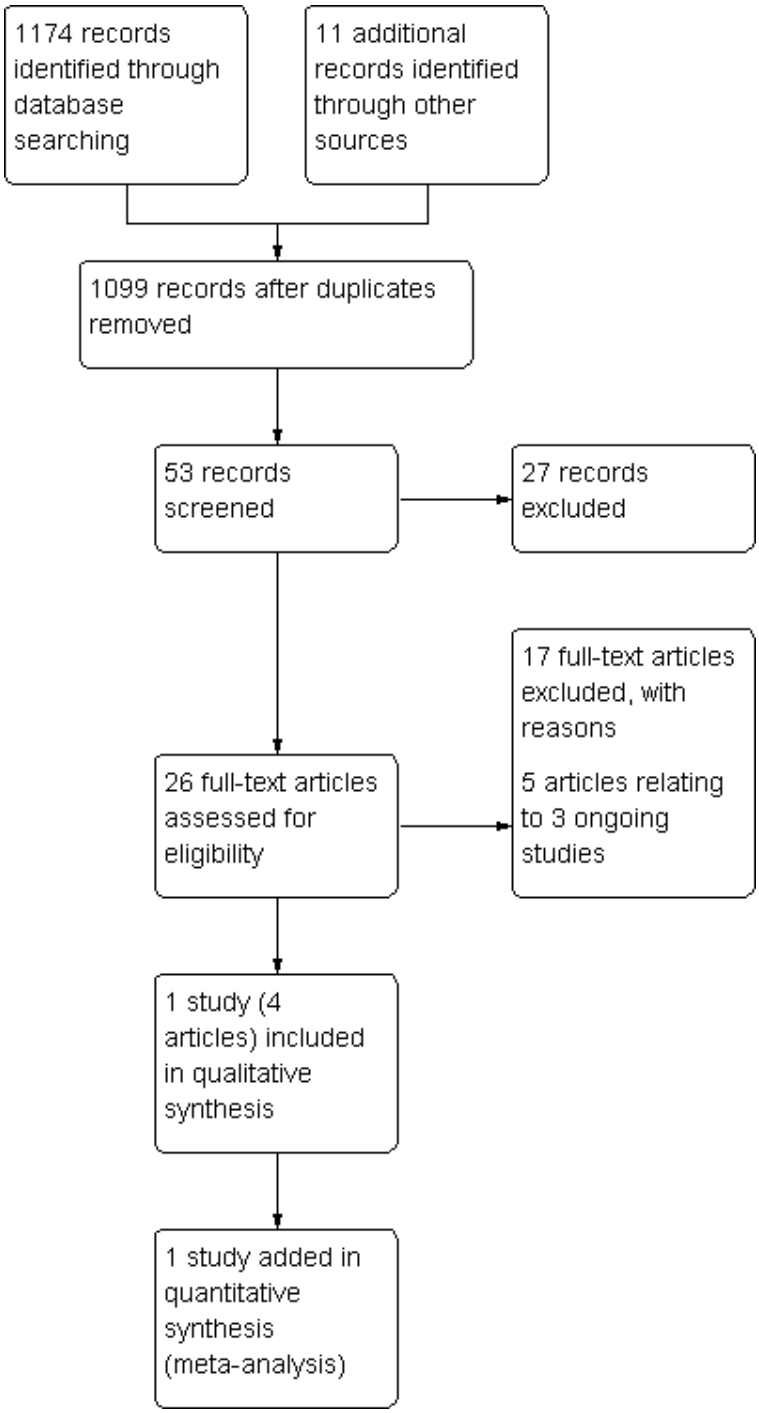
Results of the search

For details of the search strategies see Appendix 1 and Appendix 2.

The original broad free text search to Sept 2006 yielded approximately 2000 potential articles. Two review authors (JM and AS) independently read the abstracts; articles that obviously did not meet the inclusion criteria were excluded at this stage. Forty-eight articles were retrieved in full and translated into English where appropriate. We classified these studies as included (Liu 2004), ongoing (CHORUS #; Kumar # (three citations); EORTC 55971) and excluded (42 studies).

We updated the search in August 2011 to include studies from Sept 2006 to Aug 2011. This search identified 1099 studies, excluding duplicates (Figure 2). Two review authors (TAL and KH) independently sifted the search results and identified 26 studies as relevant to this review. On further evaluation, we classified these studies as included (EORTC 55971, four citations), ongoing (CHORUS #; Kumar # (three additional citations); Onda #) and excluded (17 studies). In addition, three review authors (TAL, JM and SK) re-evaluated a previously included trial (Liu 2004) and found that it did not meet the inclusion criteria for this review (see Differences between protocol and review).

Figure 2. Study flow diagram of the updated search (Sept 2006 to Aug 2011).



Included studies

See Characteristics of included studies.

EORTC 55971 was a large, multicentre, non-inferiority RCT conducted in 59 institutions in Belgium, Canada, the UK, Sweden, Netherlands, Italy, Norway, Spain, Austria, Portugal, Ireland and Argentina. In total, 718 women were enrolled between 1998 and 2006; however, 48 were excluded after randomisation owing to authorisation irregularities at the Argentinian centre. Thus 670 women with stage IIIc/IV epithelial ovarian cancer, primary peritoneal cancer or fallopian tube cancer were evaluated. For inclusion, extra-pelvic tumour needed to be 2 cm or more and treatment needed to begin within three weeks of the initial biopsy. The experimental group (334 women) were allocated to receive three cycles of platinum-based NACT, followed by IDS and then at least three more cycles of NACT. The control group (336 women) received 'standard' treatment (i.e. PDS plus at least six cycles of platinum-based chemotherapy ± IDS). The primary outcome was OS. Secondary outcomes were PFS, surgical morbidity and mortality, QoL and adverse effects. The investigators performed subgroup analyses on OS with respect to age, FIGO stage and extent of residual tumour. Subgroups of age were: age under 50 years, age 50 to 70 years and age over 70 years; subgroups of extent of residual tumour were: no residual tumour, residual tumour of 1 to 10 mm, and residual tumour greater than 10 mm.

Excluded studies

See Characteristics of excluded studies.

Sixty studies/reports were excluded for the following reasons:

- non-RCTs (45);
- RCTs without a surgical arm comparison (Lotze 1987; Bertelsen 1990; Trope 1997; Deval 2003; Dutta 2005; Mahner 2006; Polcher 2009; Mackay 2011);
- RCTs of IDS (Redman 1994; van der Burg 1995);
- RCTs of non-platinum-based NACT versus surgery (Evdokimova 1982);
- RCTs of chemotherapy plus iliac artery embolisation versus surgery (Liu 2004);
- reviews (Bristow 2001; Baekelandt 2003; Lyngstadaas 2005).

Liu 2004, an RCT comparing NACT plus iliac artery embolisation versus PDS, was originally an 'included study' in the 2006 version of this review. The main findings of this study were that there was no significant difference in survival between the two arms; however, optimal cytoreduction was achieved more often in the NACT/embolisation group (30 vs 21 women; P < 0.005) and this group had a shorter operating time (P < 0.01), less blood loss (665 ± 38 mL vs 849 ± 41 mL; P < 0.001) and fewer blood transfusions (16 vs 29; P < 0.05). For the update, we revised our assessment of this study and excluded it, as the study findings might have been attributable to NACT, the iliac artery embolisation, or the combination.

Risk of bias in included studies

Two review authors (JM and TAL) independently assessed EORTC 55971 according to the pre-defined criteria stated in the methods section. We considered this multicentre trial to be at a low risk of bias as randomisation and allocation concealment were performed centrally, all pre-specified outcomes were reported and there was minimal loss to follow-up (Figure 1). Data from 48 women from Argentina were excluded owing to "potential authorisation irregularities"; however, the investigators state that their results were similar when these excluded data were included. The exclusions appear erroneously as pre-randomisation exclusions on the published study-flow diagram.

EORTC 55971 was an open-label study and outcome assessment was not blind. This is not an issue for primary outcomes (i.e. survival); however, it may lead to detection bias with regard to other outcomes or subgroups (e.g. extent of debulking achieved). The importance of blinding of outcome assessment in ovarian cancer trials had been raised in a Gynecologic Cancer InterGroup (GCIG) consensus statement (Thigpen 2011). Data for such outcomes are thus interpreted with caution.

Effects of interventions

No meta-analyses were possible as only one study was included. Data from this one included study (EORTC 55971) gave the following results:

Overall survival (Analyses 1.1 to 1.3)

There was no significant difference in OS between the NACT and PDS groups (670 women; HR 0.98; 95% CI 0.82 to 1.18; Analysis 1.1). Neither were there any significant differences in OS subgrouped by age (tests for subgroup differences: P = 0.89; I^2 = 0%; Analysis 1.2) or residual disease (P = 0.48; I^2 = 0%; Analysis 1.3). (EORTC 55971 presented age data subgrouped as under 50 years, 50 to 70 years and over 70 years. Since there were no other studies to include, we adhered to these subgroups, although we had planned to subgroup age as 60 years or less and over 60 years.)

Progression-free survival (Analysis 1.4)

EORTC 55971 data showed no significant difference in PFS between the NACT and PDS groups (670 women; HR 1.01; 95% CI 0.87 to 1.17; Analysis 1.4).

Extent of residual disease (Analysis 1.5)

Significantly more lesions were completely resected in the NACT group compared with the PDS group (RR 2.56; 95% CI 2.00 to 3.28; Analysis 1.5). These results should be interpreted with caution as they are potentially at a high risk of bias (Risk of bias in included studies)

Surgically related severe adverse effects (SAEs) and mortality (Analyses 1.6 and 1.7)

The following grade 3/4 (CTCAE 2009) SAEs were reported in the EORTC 55971 trial (632 women - per protocol; Analysis 1.6):

- haemorrhage: 12 in NACT group versus 23 in PDS group; RR 0.50; 95% CI 0.25 to 0.99;
- venous thromboembolism: none in NACT group versus eight in PDS group; RR 0.06; 95% CI 0 to 0.98;
- infection: five in NACT group versus 25 in PDS group; RR 0.19; 95% CI 0.07 to 0.50;
- gastrointestinal SAEs: one in NACT group versus three in PDS group; RR 0.32; 95% CI 0.03 to 3.07;
- urinary SAEs: one in NACT group versus one in PDS group; RR 0.96; 95% CI 0.06 to 15.32.

Peri/post-operative death within 28 days of surgery occurred in 2/322 women in NACT group versus 8/310 women in PDS group in the EORTC 55971 trial (RR 0.24; 95% CI 0.05 to 1.12).

Blood transfusions (Analysis 1.8)

In the EORTC 55971 trial, the need for blood transfusions and mean blood loss were not reported. However, investigators provided unpublished data with respect to the number of women who received blood transfusions in the NACT and PDS groups and these did not differ significantly (Analysis 1.8).

Duration of operation

Operating times in EORTC 55971 for PDS and IDS (NACT) were 3 hours (range 0.5 to 9.3 hours) and 2.75 hours (range 0.17 to 12 hours), respectively (standard deviations not reported).

Quality of life

Data for QoL in EORTC 55971 were not reported. However, in the published paper it states that there were no significant advantages of NACT or PDS with respect to QoL.

DISCUSSION

Summary of main results

There was no significant difference in OS or PFS in women with stage IIIc/IV ovarian cancer who were treated with NACT plus IDS compared with PDS plus chemotherapy. Surgically related morbidity (grade 3/4) was significantly higher in the PDS group with respect to haemorrhagic, infective and thromboembolic adverse effects.

Overall completeness and applicability of evidence

The evidence for the non-inferiority of NACT versus PDS for advanced ovarian cancer is not widely applicable as only participants with stage IIIc/IV ovarian tumours (extra-pelvic spread larger than 2 cm) were included in the EORTC 55971 trial and the majority of participants had extensive disease (metastatic lesions larger than 10 cm were present in 61.6% of women). In the subgroup of women with pre-operative extra-pelvic tumour of less than 5 cm in diameter (189 women), PDS significantly improved OS compared with NACT (HR 0.64; 95% CI 0.44 to 0.93) (EORTC 55971 Supplementary appendix). Furthermore, when subgrouped by FIGO stage, there was a trend for women with stage IV disease to survive for longer with NACT than with PDS (HR 0.72; 95% CI 0.50 to 1.02).

Possibly as a result of the extensive disease (Vergote 2011a), median survival times are low compared with other studies. In the PDS group, median survival time for no residual disease, 1 to 10 mm' residual disease and greater than 10 mm' residual disease was 45, 32 and 26 months, respectively, compared with NACT, which was 38, 27 and 25 months, respectively. While these differences were not statistically significant, du Bois 2011 argues that they are clinically significant differences in favour of PDS.

Chi 2011 maintain that the majority of women should be able to tolerate a major debulking procedure. They suggest that the problem lies with a lack of skills among gynaecological oncologists (or a willingness to perform lengthy surgery) and that the assembly of multidisciplinary surgical teams would improve survival figures in advanced ovarian cancer.

Vergote 2011b has recommended selection criteria for utilising NACT in stage IIIc/IV disease: the Leuven selection criteria for NACT and IDS in stage IIIc/IV ovarian cancer include the following:

- tumours greater than 2 cm around the superior mesenteric artery or behind the porta hepatis; or
- intrahepatic metastases or extra-abdominal metastases (excluding resectable inguinal or supraclavicular lymph nodes); or
- poor general condition (e.g. over 80 years of age); or
- extensive serosal invasion necessitating bowel resections of greater than 1.5 m; or
- women who cannot be easily debulked to no residual tumour (e.g. more than one bowel resection, expected operating time greater than four hours).

According to Vergote 2011b, these criteria select about 50% of women with stage IIIc and IV disease. While agreeing that surgical skills are important, the authors stress that aggressive surgery should be tailored to the general condition and extent of disease of the patient, in order to decrease post-operative morbidity and mortality.

Of further interest, EORTC 55971 investigators performed post hoc multivariate analyses on their data. Complete cytoreduction was the strongest independent predictor of prolonged survival (P = 0.001) followed by stage IIIc disease (P = 0.001), small tumour size before randomisation (P = 0.001), endometrioid histological type (P = 0.005) and younger age (P = 0.005). This is in keeping with findings of du Bois 2009 and other studies.

In EORTC 55971, complete cytoreduction occurred more frequently in the NACT group than the PDS group; however, this finding did not translate into improved survival in the NACT group. Preliminary data from Kumar # appear to support this observation (see Characteristics of ongoing studies). The reasons for this are not known and may include bias in the assessment of complete cytoreduction. We refer the reader to the literature (e.g. du Bois 2011) for more insight into this debate.

Results from the EORTC 55971 trial will benefit by corroboration from ongoing studies (CHORUS #; Kumar #; Onda #).

Quality of the evidence

We consider the current evidence for primary outcomes to be of moderate quality. Further research is likely to have an important impact on our confidence in the estimates of effects and may change the estimates, overall and/or for subgroups of women with advanced ovarian cancer. We consider the evidence with regard to surgical morbidity to be of low quality owing to small number of events and the lack of blinding; further research is likely to change these estimates.

Potential biases in the review process

To our knowledge there are no biases in the review process, other than the introduction of subgroup analyses (i.e. stage, age and residual disease) that were not specified in the original protocol. We do not consider this risk to be substantial as there is only one included study in the review at this stage.

We had hoped to include data from the Kumar # trial. However, at the time of writing, the investigators had not completed their final analyses and advised us that they hoped to publish these data in 2012 (see below). We made the decision to await these data, rather than to include provisional data from past conference presentations (e.g. Kumar 2009). Therefore, once these data are published, we plan to update this review again.

Agreements and disagreements with other studies or reviews

Investigators of the ongoing trial Kumar #, have presented interim results over the past few years, including at the ACSO 2006 and 2007 conferences. Data from Kumar 2009 appear to corroborate the findings of the EORTC 55971 study. In the 2009 abstract, the investigators reported no significant differences in OS and PFS with HRs for OS and PFS of 0.94 (95% CI 0.56 to 1.56) and 1.1 (95% CI 0.71 to 1.86), respectively (PDS vs NACT). Blood loss, peri-operative mortality, post-operative infections and length of hospital stay were all reduced in the NACT group; in addition, QoL scores were significantly better in the NACT group "at the end of treatment" (P < 0.001). We understand from correspondence with Professor Kumar (from Sept 2011 to January 2012) that this trial is now closed, that new analyses are being undertaken and that data will be presented in manuscript form during the course of 2012. Owing to insufficient data in the 2009 report and discrepancies in some of the reported findings over time, we took the decision to await the final statistical analyses before including the interim data in meta-analyses (see Characteristics of ongoing studies).

AUTHORS' CONCLUSIONS

Implications for practice

PDS is the standard treatment for advanced (stage III/IV) ovarian cancer. NACT is a reasonable alternative for women with bulky stage IIIc/IV disease. Compared to PDS, NACT may increase the rate of complete cytoreduction but this does not translate into an increase in OS. More evidence is needed to show which women are most likely to benefit from NACT. We consider the Leuven selection criteria (Vergote 2011b) to be a reasonable guide to patient selection until further evidence is available, although these criteria still need to be validated.

Implications for research

There are currently three ongoing RCTs (CHORUS #; Kumar #; Onda #) aimed at addressing the role of NACT in ovarian cancer and we await these results. According to the investigators, data from Kumar # should be published soon. Collection of QoL data is an important patient-centred outcome in advanced ovarian disease, especially if there is minimal difference in survival between treatment options. The GCIG consensus statement recommends PFS as the preferred primary end point of Phase III trials in advanced ovarian cancer as OS is confounded by the treatment on detection of progression (Thigpen 2011).

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

EORTC 55971

Methods	Multicentre non-inferiority RCT; 59 institutions in Belgium, Canada, the UK, Sweden, Netherlands, Italy, Norway, Spain, Austria, Portugal, Ireland and Argentina Recruitment period: 1998 to 2006 Median follow-up: 56.4 months
Participants	718 women enrolled, 48 excluded post-randomisation owing to authorisation irregularities at the Argentinian centre leaving 670 women Inclusion criteria: evidence of stage IIIc/IV EOC, primary peritoneal cancer or fallopian tube cancer by intraperitoneal biopsy or FNA plus presence of extra-pelvic tumour of at least 2 cm (excluding ovaries) on laparoscopy or CT scan; WHO performance status of 0 to 2; no other serious disabling diseases contraindicating PDS or NACT; no prior primary malignancies; no brain metastases; adequate haematological, renal and hepatic function; absence of other factors that could affect compliance; CA-125:CEA ratio higher than 25. Treatment had to start within 3 weeks of initial biopsy/FNA
Interventions	Experimental: NACT (334 women) - 3 cycles of platinum-based NACT, followed by IDS within 6 weeks of third cycle, then at least 3 more cycles of NACT Control: PDS (336 women) plus at least 6 cycles of platinum-based chemotherapy ± IDS All surgery was performed by gynaecological oncologists
Outcomes	OS, PFS, QoL (QLQ-C30 and QLQ-Ov28), surgical morbidity and mortality, toxicity, optimal debulking
Notes	Baseline characteristics were similar: stage IIIc (75.7% vs 76.5%) or stage IV (22.9% vs 24.3%); mean age 63 years (NACT) vs 62 years (PDS); at least 6 cycles received by 276/322 (85.8%) of NACT group and 253/310 (81.6%) of PDS group The number of women with metastases > 5 cm at the time of surgery in the NACT group was half that of the PDS group (37.2% vs 74.5%) suggesting NACT-related tumour shrinkage. Optimal debulking (80.6% vs 41.6%) and complete debulking were achieved more often in NACT group, but this did not translate into improved survival, even though complete debulking was a prognostic indicator for OS Median OS was 30 vs 29 months (NACT vs PDS) and median PFS was 12 months for both groups Intervention effects on OS differed significantly between participating countries

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation done centrally. Minimisation used to stratify for institution, biopsy method, tumour stage and largest pre-operative tumour size

EORTC 55971 (*Continued*)

Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unblinded, therefore high risk for some outcomes assessed by investigators involved with patient care (e.g. optimal debulking). Low risk for survival outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	3/336 vs 5/334 lost to follow-up
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported. Analysis by ITT and per-protocol
Other bias	Unclear risk	48 post-randomisation exclusions from the Argentinian centre owing to "authorisation irregularities" were indicated erroneously as pre-randomisation exclusions on the study-flow diagram. The investigators state that "The results of the study were similar whether the 48 patients...were included or excluded"

CEA: carcinoembryonic antigen; CT: computer tomography; EOC: epithelial ovarian cancer; FNA: fine needle aspiration; IDS: interval debulking surgery; ITT: intention to treat; NACT: neoadjuvant chemotherapy; OS: overall survival; PDS: primary debulking surgery; PFS: progression-free survival; QoL: quality of life; WHO: World Health Organization.

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

Study	Reason for exclusion
Ansquer 2001	Retrospective study of 54 women with unresectable disease at primary laparotomy
Baekelandt 2003	Review article
Bertelsen 1990	RCT of chemotherapy (cisplatin vs cisplatin, cyclophosphamide, doxorubicin) no surgery randomisation
Bidzinski 2005	Retrospective study
Bristow 2001	Meta-analysis of the impact of optimal debulking. no surgical randomisation in any trial included
Chambers 1990	Retrospective case series of 17 women
Chan 2003	Prospective case control series of 17 women

(*Continued*)

Colombo 2009	Not an RCT. Retrospective review of 203 women with stage IIIc/IV EOC; 142 received PDS and 61 received NACT. Overall median survival was 35 months. Concludes that PDS is management of choice. NACT is indicated in non-operable tumours or in women with poor performance status
Deval 2003	RCT of different chemotherapy regimens. No surgical randomisation. 102 women with stage IV ovarian cancer. 53% primary surgery, 15% secondary surgery, 32% no surgery. No significant differences in survival
Dutta 2005	RCT but comparing surgery after 3 or 6 cycles of chemotherapy, with no up-front surgery arm. Small study (24 women). No details of how women were randomised. No assessment of survival outcomes
Evdokimova 1982	RCT of NACT then surgery vs surgery then chemotherapy. Chemotherapy - alternating cycles of cyclophosphamide/5-fluorouracil and cyclophosphamide hexamethylmelamine, therefore non-platinum based. Survival advantage for up-front surgery
Everett 2006	Not an RCT. Retrospective study in which 200 women with advanced ovarian cancer received NACT (98 women) or PDS (102 women). Optimal cytoreduction achieved more frequently in the NACT group. Optimal cytoreduction was associated with better survival
Fanfani 2003	Retrospective case-control series of 73 women with unresectable disease receiving NACT compared with 184 women with resectable disease undergoing conventional treatment
Feng 1998	Retrospective case series of 18 women with advanced ovarian cancer treated with NACT
Ghaemmaghami 2008	Not an RCT. Retrospective study of 92 women with advanced ovarian cancer. Compared 24 women with unresectable disease and NACT/IDS with 68 women with PDS and chemotherapy. PDS was associated with longer survival. Extent of residual tumour associated with poorer prognosis
Giannopoulos 2006	Not an RCT. Prospective cohort study of 64 women with stage IIIc/IV ovarian cancer. 35 women were considered unresectable and received NACT with IDS and 29 received PDS. Concluded that there was less morbidity in the IDS group. Optimal cytoreduction higher in NACT group (NS)
Hanker 2010	Not an RCT. Exploratory meta-analysis on the impact of surgical debulking, using individual patient data from 3 RCTs that investigated platinum/taxane-based regimens after primary surgery for advanced ovarian cancer. Concluded that the goal of 'optimal debulking' in PDS should be complete resection
Hegazy 2005	Not an RCT. Prospective study of 59 women with advanced ovarian cancer who received NACT if optimal cytoreduction was not feasible (27 women) or PDS (32 women) if it was feasible
Hou 2007	Not an RCT. Retrospective study of 172 women with advanced ovarian cancer: 109 received PDS and 63 received NACT. NACT was associated with less peri-operative morbidity, more 'optimal cytoreduction' and less need for further aggressive surgery
Inciura 2006	Not an RCT. Retrospective study of 574 women; 213 received NACT and 361 received PDS. No significant differences in survival rates or 'optimal cytoreduction' rates
Jacob 1991	Retrospective case-control series

(*Continued*)

Kayikcioglu 2000	Retrospective series of 189 women. No randomisation
Kayikcioglu 2001	Retrospective series of 205 women. No randomisation
Kuhn 2001	Prospective NRS of 31 women treated with NACT vs 32 women with conventional treatment
Lawton 1989	Prospective case series of 23 women with suboptimally debulked disease at primary surgery
Lee 2006	Not an RCT. Prospective study of 40 women with advanced EOC. Compared 18 women who received NACT with 22 who received PDS. No significant survival differences between groups
Lim 1993	Non-randomised prospective case series of 30 women with untreated FIGO stage III and IV ovarian carcinoma given carboplatin (400 mg/m^2) and ifosfamide (5 g/m^2) with mesna. No surgical randomisation
Liu 1995	Retrospective case series
Liu 2004	Randomised 85 women with advanced ovarian cancer to NACT plus ovarian artery embolisation or PDS. 42 women received 1 cycle of neoadjuvant platinum-based chemotherapy (cisplatin, doxorubicin and cyclophosphamide) directly into the ovarian artery, followed by ovarian artery embolisation. These women then had debulking surgery followed by 7 cycles of intravenous platinum-based chemotherapy. The 43 women in the control arm underwent debulking surgery and then received 8 cycles of intravenous platinum-based chemotherapy. The results may have been attributable to the chemotherapy, embolisation or the combination
Loizzi 2005	Retrospective case-control study of 30 women
Lotze 1987	RCT of intra-arterial chemotherapy, not surgery
Lyngstadaas 2005	Systematic review. No RCTs identified for NACT
Mackay 2011	Ongoing RCT of intravenous NACT vs intraperitoneal NACT (NCIC CTG OV.21 protocol)
Mahner 2006	Conference presentation of Polcher 2009
Malzoni 1993	Case report
Mazzeo 2003	Retrospective case series of 45 women
Morice 2003	Retrospective study of 57 women with unresectable disease undergoing chemotherapy then surgery with 28 women with resectable disease following surgery then chemotherapy
Negretti 1988	Retrospective case series of 27 women
Oe 2011	Not an RCT but methods not clear. More details requested from authors

(*Continued*)

Onda 2009	Not an RCT. A cohort of 56 women with advanced mullerian tumours underwent a diagnostic laparoscopy, NACT and IDS. The aim of the study was to determine whether diagnostic laparoscopy was necessary before NACT. Clinical diagnosis plus cytology/histology yielded a positive predictive value > 95% for advanced mullerian tumours. Concluded that diagnostic laparoscopy not necessary before giving NACT
Onnis 1996	Retrospective case series of 88 women with NACT then surgery
Polcher 2009	Phase II RCT comparing 2 NACT treatment schedules, namely 3/6 cycles (40 women) or 2/6 cycles (43 women) of carboplatin/docetaxel followed by optimal debulking surgery. Primary outcome was pre-operative reduction in ascites volume. Secondary outcomes were residual tumour, peri-operative morbidity and mortality. Concluded that 2 NACT cycles is a reasonable option. Any residual disease associated with survival rates
Rafii 2007	Not an RCT. Retrospective study on the benefit of debulking surgery in Stage IV ovarian cancer using data from GINECO randomised studies of platinum/taxane regimens
Recchia 2001	Prospective non-randomised Phase II study of primary chemotherapy in 34 women with stage IV ovarian cancer. No surgical randomisation
Redman 1994	RCT comparing IDS vs no further surgery in women suboptimally debulked at primary surgery
Robova 2003	Not an RCT. Treated 87 women with inoperable EOC with NACT. Conference abstract only
Salzer 1990	Prospective non-randomised cohort study of different chemotherapy regimens and IDS
Schwartz 1994	Retrospective case-control study of 11 women treated with NACT followed by surgery
Schwartz 1999	Retrospective case-control study of 59 women treated with NACT followed by surgery. Included long-term follow-up of 28 women from 2 other studies (Schwartz 1994 and Chambers 1990)
Shibata 2003	Retrospective, NRS
Shimizu 1993	Retrospective case series of 138 women with ovarian cancer. 77 women had conventional treatment, 82 had exploratory laparotomy alone with 74 then receiving chemotherapy
Steed 2006	Not an RCT. Retrospective analysis of 116 women with advanced ovarian cancer who received NACT (50 women) or primary surgery (66 women)
Sun 2000	Retrospective study. 95 women managed by traditional surgery-chemotherapy (76 women) or chemotherapy-surgery-chemotherapy (17 women)
Surwit 1999	Retrospective case series of 39 women receiving NACT prior to surgery
Trope 1997	RCT study of chemotherapy regimens. No randomisation arm for surgery
Ushijima 2002	Retrospective case-control study of 65 women with unresectable ovarian cancer treated with NACT and surgery

(*Continued*)

van der Burg 1995	RCT of IDS following suboptimal primary surgery (319 women)
Vergote 1998	Retrospective longitudinal study of 285 women: 112 in first cohort all underwent surgery; of second cohort (173 women) 43% received primary chemotherapy and 57% received PDS
Vergote 2000	Retrospective analysis of 338 women, including longer-term follow-up of those in Vergote 1998 paper
Vrscaj 2002	Retrospective case-control study of 75 women with advanced ovarian cancer

EOC: epithelial ovarian cancer; FIGO: Federation of International Gynaecologists and Obstetricians; GINECO: Group d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens; IDS: interval debulking surgery; NACT: neoadjuvant chemotherapy; NCIC CTG: NCIC Clinical Trial Group; NRS: non-randomised study; NS: not significant; PDS: primary debulking surgery; RCT: randomised controlled trial

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

CHORUS

Trial name or title	CHORUS (Chemotherapy or Upfront Surgery). A randomised feasibility trial to determine the impact of timing of surgery and chemotherapy in newly diagnosed patients with advanced epithelial ovarian, primary peritoneal or fallopian tube carcinoma. ISRCTN number: 74802813
Methods	RCT
Participants	550 women with stage IIIc/IV epithelial ovarian cancer
Interventions	Primary surgery then 6 cycles of platinum-based chemotherapy or 3 cycles of platinum-based chemotherapy, surgery, then a further 3 cycles of platinum-based chemotherapy
Outcomes	OS, PFS, QoL
Starting date	March 2004
Contact information	Professor S. Kehoe sean.kehoe@obs-gyn.ox.ac.uk
Notes	www.ctu.mrc.ac.uk/plugins/StudyDisplay/protocols/CHORUS protocol Version 2.0 - 05 June 2008.pdf Expected end date: Jan 2013

Kumar #

Trial name or title	Neoadjuvant chemotherapy in stage IIIc & IV epithelial ovarian carcinoma (EOC)
Methods	RCT; open-label
Participants	180 women Included if: age 20 to 65 years; EOC stage IIIc & IV (pleural effusion only); ECOG PS 0-2; cytology/biopsy-positive women; good compliance; previously untreated women Excluded if: any medical contraindication to surgery; psychiatric illness; cardiac, liver or renal dysfunction
Interventions	Upfront surgery followed by 6 cycles of paclitaxel + carboplatin (chemotherapy) (arm A) or upfront chemotherapy - 3 cycles chemotherapy followed by surgery then 3 more cycles of chemotherapy
Outcomes	Optimal debulking rate (≤ 1 cm), OS, PFS, clinical CR, QoL, operating time, blood loss, stay in ICU, duration of hospital stay, infections, chemo-toxicity
Starting date	Oct 2001. Accrual is closed. Results expected in 2012
Contact information	lalitaiims@yahoo.com www.asco.org/ASCOv2/MultiMedia/Virtual+Meeting?&vmview=vm_session_presentations_view&confID=47&sessionID=2214
Notes	Clinical Trials Register: NCT00715286 Interim results presented at 2007 ASCO meeting: 113/139 women evaluable, 20% optimally debulked in PDS group vs 85% in the NACT group. NACT group also experienced less blood loss (P = 0.01), shorter hospital stay (P = 0.04), less post-operative infection (2 cases vs 7 cases; P = 0.06) and less operative mortality (1 deaths vs 5 deaths; P = 0.08). Median OS was 29 months in PDS group vs 41 months in NACT group Interim results presented in Kumar 2009: 128/133 women evaluable, 62 in PDS group, 66 in NACT group. Optimum debulking was achieved in 22.6% and 86.2% (P < 0.0001), respectively. The NACT group experienced less blood loss (413 mL vs 600 mL; P < 0.0001), reduced post-operative infections (1.54% vs 14.5%; P < 0.025), reduced operating time (75.4 minutes vs 89.2 minutes; P < 0.001) and shorter hospital stay (7.6 days vs 11.5 days; P < 0.001). Median follow-up at 42 months found similar OS of 42 months and 41 months in the PDS and NACT group, respectively (the 2007 results presented showed significantly better OS in the NACT group). HR for OS (PDS vs NACT) was 0.94; 95% CI 0.56 to 1.56. HR for PFS (PDS vs NACT) was 1.1; 95% CI 0.71 to 1.86. QoL score was significantly better in the NACT group 'at the end of treatment' (P < 0.001) There are some discrepancies in these data when compared with the 2007 interim results (e.g. OS data). Furthermore, the denominators used to create these data were not stated in Kumar 2009, and continuous data were presented without standard deviations. We were unable to obtain clarification from the authors, but understand that complete results will be published soon

Onda #

Trial name or title	Phase III trial of upfront debulking surgery versus neoadjuvant chemotherapy for stage III/IV ovarian, tubal and peritoneal cancers: Japan Clinical Oncology Group Study JCOG0602
Methods	Multicentre, non-inferiority, Phase III RCT; minimisation method of randomisation balanced by stage, PS and age

Onda # (*Continued*)

Participants	300 women with stage III/IV ovarian, tubal and peritoneal cancers
Interventions	PDS arm: PDS is performed within 4 weeks of enrolment followed by 8 cycles of paclitaxel (175 mg/m^2, day 1) and carboplatin (AUC = 6, day 1) every 3 to 5 weeks. IDS was required when any of the standard procedures was not completed at PDS or if residual tumour > 1 cm after PDS NACT arm: 4 cycles of paclitaxel (175 mg/m^2, day 1) and carboplatin (AUC = 6, day 1) every 3 weeks. IDS is performed 4 to 7 weeks after fourth cycle of NACT. 4 additional cycles of chemotherapy were administered 3 to 5 weeks after IDS
Outcomes	Primary: OS Secondary: complete remission rate; PFS; response rate; safety and peri-operative morbidity including adverse events, duration of surgery, blood loss, blood transfusion or other infusions
Starting date	Nov 2006. Accrual of 301 women was completed in Oct 2011. Follow-up planned to extend to 5 years from completion of accrual
Contact information	Takashi Onda: takashi-tky@umin.ac.jp
Notes	UMIN Clinical Trials Registry as UMIN000000523 (www.umin.ac.jp/ctr/index.htm) upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&type=summary&recptno=R000000633&language=E

ASCO: American Society of Clinical Oncology; AUC: area under curve; CI: confidence interval; CR: complete response; ECOG PS: Eastern Cooperative Oncology Group Performance Scale; EOC: epithelial ovarian carcinoma; HR: hazard ratio; ICU: intensive care unit; NACT: neoadjuvant chemotherapy; OS: overall survival; PDS: primary debulking surgery; PFS: progression-free survival; QoL: quality of life; RCT: randomised controlled trial.

DATA AND ANALYSES

Comparison 1. NACT vs PDS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	1		Hazard Ratio (Random, 95% CI)	Subtotals only
2 Overall survival by age	1		Hazard Ratio (Random, 95% CI)	Subtotals only
2.1 Age < 50 years	1	84	Hazard Ratio (Random, 95% CI)	0.91 [0.54, 1.55]
2.2 Age 50-70 years	1	439	Hazard Ratio (Random, 95% CI)	0.96 [0.77, 1.19]
2.3 Age > 70 years	1	147	Hazard Ratio (Random, 95% CI)	1.05 [0.72, 1.53]
3 Overall survival by residual disease	1		Hazard Ratio (Random, 95% CI)	Subtotals only
3.1 No residual tumour	1	214	Hazard Ratio (Random, 95% CI)	1.17 [0.82, 1.67]
3.2 Residual tumour 1-10 mm	1	161	Hazard Ratio (Random, 95% CI)	1.22 [0.84, 1.77]
3.3 Residual tumour > 1 cm	1	222	Hazard Ratio (Random, 95% CI)	0.91 [0.64, 1.30]
4 Progression-free survival	1		Hazard Ratio (Random, 95% CI)	Subtotals only
5 Extent of residual disease	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 No residual disease	1	597	Risk Ratio (M-H, Random, 95% CI)	2.56 [2.00, 3.28]
5.2 Residual disease ≤ 10 mm	1	597	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.94, 1.60]
5.3 Residual disease > 10 mm	1	597	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.25, 0.43]
6 Surgically related severe adverse effects (grade 3/4)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Haemorrhage	1	632	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.25, 0.99]
6.2 Venous thromboembolism	1	632	Risk Ratio (M-H, Random, 95% CI)	0.06 [0.00, 0.98]
6.3 Infection	1	632	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.07, 0.50]
6.4 Gastrointestinal	1	632	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.03, 3.07]
6.5 Urinary	1	632	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.06, 15.32]
7 Post-operative mortality	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8 Blood transfusions	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Analysis 1.1. Comparison 1 NACT vs PDS, Outcome 1 Overall survival.

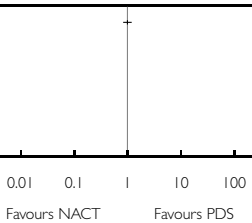
Review: Chemotherapy versus surgery for initial treatment in advanced ovarian epithelial cancer

Comparison: 1 NACT vs PDS

Outcome: 1 Overall survival

Study or subgroup	NACT N	PDS N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Random,95% CI	Weight	Hazard Ratio IV,Random,95% CI
EORTC 55971 (1)	334	336	-0.0202 (0.0937)			0.98 [0.82, 1.18]

Test for subgroup differences: Not applicable



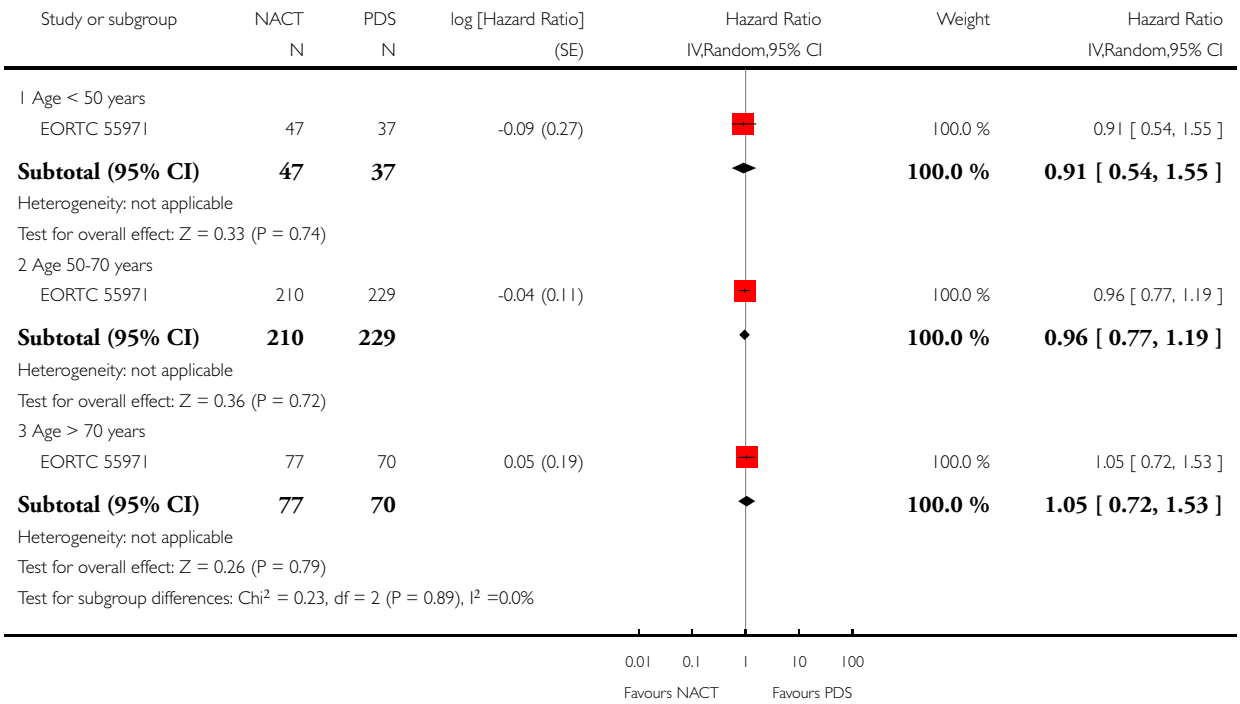
(1) We have applied 95% CIs (investigators report 90% CIs).

Analysis 1.2. Comparison 1 NACT vs PDS, Outcome 2 Overall survival by age.

Review: Chemotherapy versus surgery for initial treatment in advanced ovarian epithelial cancer

Comparison: 1 NACT vs PDS

Outcome: 2 Overall survival by age



Analysis 1.3. Comparison 1 NACT vs PDS, Outcome 3 Overall survival by residual disease.

Review: Chemotherapy versus surgery for initial treatment in advanced ovarian epithelial cancer

Comparison: 1 NACT vs PDS

Outcome: 3 Overall survival by residual disease

Study or subgroup	NACT N	PDS N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Random,95% CI	Weight	Hazard Ratio IV,Random,95% CI
1 No residual tumour						
EORTC 55971	152	62	0.16 (0.18)		100.0 %	1.17 [0.82, 1.67]
Subtotal (95% CI)	**152**	**62**			**100.0 %**	**1.17 [0.82, 1.67]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.89 (P = 0.37)						
2 Residual tumour 1-10 mm						
EORTC 55971	87	74	0.2 (0.19)		100.0 %	1.22 [0.84, 1.77]
Subtotal (95% CI)	**87**	**74**			**100.0 %**	**1.22 [0.84, 1.77]**
Heterogeneity: not applicable						
Test for overall effect: Z = 1.05 (P = 0.29)						
3 Residual tumour > 1 cm						
EORTC 55971	53	169	-0.09 (0.18)		100.0 %	0.91 [0.64, 1.30]
Subtotal (95% CI)	**53**	**169**			**100.0 %**	**0.91 [0.64, 1.30]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.50 (P = 0.62)						
Test for subgroup differences: Chi^2 = 1.49, df = 2 (P = 0.48), I^2 =0.0%						

Analysis 1.4. Comparison 1 NACT vs PDS, Outcome 4 Progression-free survival.

Review: Chemotherapy versus surgery for initial treatment in advanced ovarian epithelial cancer

Comparison: 1 NACT vs PDS

Outcome: 4 Progression-free survival

Study or subgroup	NACT N	PDS N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Random,95% CI	Weight	Hazard Ratio IV,Random,95% CI
EORTC 55971 (1)	334	336	0.01 (0.0769)			1.01 [0.87, 1.17]

Test for subgroup differences: Not applicable

(1) We have applied 95% CIs (Investigators used 90% CIs)

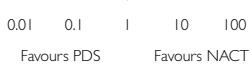
Analysis 1.5. Comparison 1 NACT vs PDS, Outcome 5 Extent of residual disease.

Review: Chemotherapy versus surgery for initial treatment in advanced ovarian epithelial cancer

Comparison: 1 NACT vs PDS

Outcome: 5 Extent of residual disease

Study or subgroup	NACT n/N	PDS n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 No residual disease					
EORTC 55971	152/292	62/305		100.0 %	2.56 [2.00, 3.28]
Subtotal (95% CI)	**292**	**305**		**100.0 %**	**2.56 [2.00, 3.28]**
Total events: 152 (NACT), 62 (PDS)					
Heterogeneity: not applicable					
Test for overall effect: Z = 7.43 (P < 0.00001)					
2 Residual disease ≤ 10 mm					
EORTC 55971	87/292	74/305		100.0 %	1.23 [0.94, 1.60]
Subtotal (95% CI)	**292**	**305**		**100.0 %**	**1.23 [0.94, 1.60]**
Total events: 87 (NACT), 74 (PDS)					
Heterogeneity: not applicable					



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Study or subgroup	NACT n/N	PDS n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Test for overall effect: Z = 1.52 (P = 0.13)					
3 Residual disease > 10 mm					
EORTC 55971	53/292	169/305		100.0 %	0.33 [0.25, 0.43]
Subtotal (95% CI)	**292**	**305**		**100.0 %**	**0.33 [0.25, 0.43]**
Total events: 53 (NACT), 169 (PDS)					
Heterogeneity: not applicable					
Test for overall effect: Z = 8.30 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 126.04, df = 2 (P = 0.00), I^2 =98%					

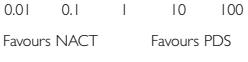
Analysis 1.6. Comparison 1 NACT vs PDS, Outcome 6 Surgically related severe adverse effects (grade 3/4).

Review: Chemotherapy versus surgery for initial treatment in advanced ovarian epithelial cancer

Comparison: 1 NACT vs PDS

Outcome: 6 Surgically related severe adverse effects (grade 3/4)

Study or subgroup	NACT n/N	PDS n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Haemorrhage					
EORTC 55971 (1)	12/322	23/310		100.0 %	0.50 [0.25, 0.99]
Subtotal (95% CI)	**322**	**310**		**100.0 %**	**0.50 [0.25, 0.99]**
Total events: 12 (NACT), 23 (PDS)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.98 (P = 0.047)					
2 Venous thromboembolism					
EORTC 55971	0/322	8/310		100.0 %	0.06 [0.00, 0.98]
Subtotal (95% CI)	**322**	**310**		**100.0 %**	**0.06 [0.00, 0.98]**
Total events: 0 (NACT), 8 (PDS)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.98 (P = 0.048)					



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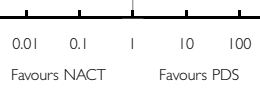
Study or subgroup	NACT n/N	PDS n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
3 Infection					
EORTC 55971	5/322	25/310		100.0 %	0.19 [0.07, 0.50]
Subtotal (95% CI)	**322**	**310**		**100.0 %**	**0.19 [0.07, 0.50]**
Total events: 5 (NACT), 25 (PDS)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.41 (P = 0.00065)					
4 Gastrointestinal					
EORTC 55971	1/322	3/310		100.0 %	0.32 [0.03, 3.07]
Subtotal (95% CI)	**322**	**310**		**100.0 %**	**0.32 [0.03, 3.07]**
Total events: 1 (NACT), 3 (PDS)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.99 (P = 0.32)					
5 Urinary					
EORTC 55971	1/322	1/310		100.0 %	0.96 [0.06, 15.32]
Subtotal (95% CI)	**322**	**310**		**100.0 %**	**0.96 [0.06, 15.32]**
Total events: 1 (NACT), 1 (PDS)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.03 (P = 0.98)					
Test for subgroup differences: Chi^2 = 4.70, df = 4 (P = 0.32), I^2 =15%					



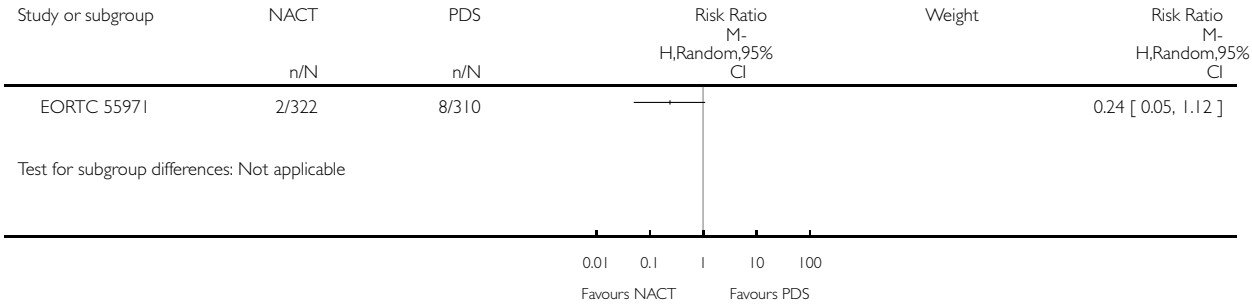
(1) Results for all SAEs in this trial are per protocol, not ITT.

Analysis 1.7. Comparison 1 NACT vs PDS, Outcome 7 Post-operative mortality.

Review: Chemotherapy versus surgery for initial treatment in advanced ovarian epithelial cancer

Comparison: 1 NACT vs PDS

Outcome: 7 Post-operative mortality

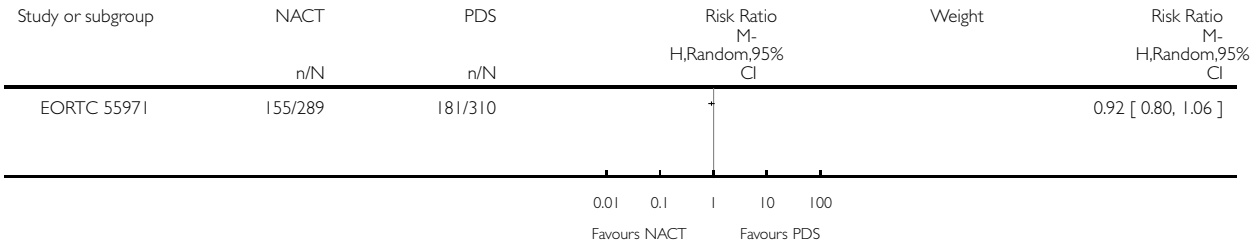


Analysis 1.8. Comparison 1 NACT vs PDS, Outcome 8 Blood transfusions.

Review: Chemotherapy versus surgery for initial treatment in advanced ovarian epithelial cancer

Comparison: 1 NACT vs PDS

Outcome: 8 Blood transfusions



ADDITIONAL TABLES

Table 1. Carcinoma of the ovary: FIGO* nomenclature

Stage	Extent of tumour	Substage	Details
I	Limited to ovaries	Ia	Limited to 1 ovary, no tumour on surface or capsule rupture, no positive ascites
		Ib	Limited to both ovaries, no tumour on surface or capsule rupture, no positive ascites
		Ic	Stage Ia or Ib but with capsule ruptured, tumour on ovarian surface or positive peritoneal washings/ascites
II	Limited to 1 or both ovaries with pelvic extension	IIa	Extension, metastases to uterus, tubes, or a combination
		IIb	Extension to other pelvis tissues
		II c	Stage IIa or IIb with tumour on the surface of 1 or both ovaries, or with capsule ruptured, or with positive peritoneal washings/ascites
III	Limited to abdomen with histologically confirmed peritoneal implants outside the pelvis or positive nodes, or both, or extension to small bowel or omentum	IIIa	Tumour grossly limited to the true pelvis with negative regional lymph nodes, microscopic seeding of abdominal peritoneal surfaces or extension to small bowel or mesentery
		IIIb	Macroscopic metastases < 2 cm; negative regional lymph nodes
		IIIc	Macroscopic metastases > 2 cm or positive regional lymph nodes, or both
IV	Distant metastases		Growth outside the abdominal cavity (e.g. lung, liver parenchyma (superficial liver metastases is stage III))

FIGO: Federation of International Gynaecologists and Obstetricians. * From FIGO 2009.

APPENDICES

Appendix 1. EMBASE search strategy

EMBASE (R) 1980 to Sept 2006 via Ovid:
The search: (ovar*) and (cancer* or carcinoma* or malignan* or neoplas* or tumour* or tumor*) and (chemotherap*) and (surg*) and (rct or random* or study or studies or trial* or investigation*) and (advanced or stage III or stage IV)
EMBASE Sept 2006 to Aug 2011 via Ovid:

1. exp ovary tumor/
2. (ovar* adj5 (neoplas* or tumor* or tumour* or cancer* or malignan* or carcinoma*)).mp.
3. 1 or 2
4. chemotherap*.mp.
5. dt.fs.
6. exp antineoplastic agent/
7. exp cancer chemotherapy/
8. adjuvant chemotherapy/
9. 4 or 5 or 6 or 7 or 8
10. surg*.mp.
11. su.fs.
12. exp surgery/
13. 10 or 11 or 12
14. 3 and 9 and 13
15. random*.ti,ab.
16. factorial*.ti,ab.
17. (crossover* or cross over* or cross-over*).ti,ab.
18. placebo*.ti,ab.
19. (doubl* adj blind*).ti,ab.
20. (singl* adj blind*).ti,ab.
21. assign*.ti,ab.
22. allocat*.ti,ab.
23. volunteer*.ti,ab.
24. crossover procedure/
25. double blind procedure/
26. randomised controlled trial/
27. single blind procedure/
28. 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
29. 14 and 28

Appendix 2. MEDLINE search strategy

The full MEDLINE search strategy via Silver Platter, from 1966 to Sept 2006 was: (ovar*) and (cancer* or carcinoma* or malignan* or neoplas* or tumour* or tumor*) and (chemotherap*) and (surg*) and (rct or random* or study or studies or trial* or investigation*) and (advanced or stage III or stage IV)
It contained free text (including alternative spellings) and MeSH terms, and MeSH headings were exploded. For databases other than MEDLINE we adapted the search strategy accordingly.
MEDLINE Sept 2006 to Aug 2011 via Ovid;

1. exp Ovarian Neoplasms/
2. (ovar* adj5 (neoplas* or tumor* or tumour* or cancer* or malignan* or carcinoma*)).mp.
3. 1 or 2
4. chemotherap*.mp.
5. drug therapy.fs.
6. exp Antineoplastic Agents/
7. Antineoplastic Combined Chemotherapy Protocols/

8. Neoadjuvant Therapy/
9. 4 or 5 or 6 or 7 or 8
10. surg*.mp.
11. surgery.fs.
12. exp Surgical Procedures, Operative/
13. 10 or 11 or 12
14. 3 and 9 and 13
15. randomized controlled trial.pt.
16. controlled clinical trial.pt.
17. randomized.ab.
18. placebo.ab.
19. clinical trials as topic.sh.
20. randomly.ab.
21. trial.ti.
22. 15 or 16 or 17 or 18 or 19 or 20 or 21
23. 14 and 22

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

Appendix 3. CENTRAL search strategy

CENTRAL Issue 4 2010
#1 MeSH descriptor Ovarian Neoplasms explode all trees
#2 ovar* near/5 (neoplas* or tumor* or tumour* or cancer* or malignan* or carcinoma*)
#3 (#1 OR #2)
#4 chemotherap*
#5 Any MeSH descriptor with qualifier: DT
#6 MeSH descriptor Antineoplastic Agents explode all trees
#7 MeSH descriptor Antineoplastic Combined Chemotherapy Protocols explode all trees
#8 MeSH descriptor Neoadjuvant Therapy explode all trees
#9 (#4 OR #5 OR #6 OR #7 OR #8)
#10 surg*
#11 Any MeSH descriptor with qualifier: SU
#12 MeSH descriptor Surgical Procedures, Operative explode all trees
#13 (#10 OR #11 OR #12)
#14 (#3 AND #9 AND #13)

Appendix 4. Assessing 'Risk of bias' of included studies

We assessed the risk of bias of included studies according to the following criteria:
(1) Random sequence generation (checking for possible selection bias)
We described for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it produced comparable groups. We assessed the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We described for each included study the method used to conceal allocation to interventions prior to assignment and assessed whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment. We assessed the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3) Blinding of outcome assessment (checking for possible detection bias)
We described for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We assessed methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias owing to the amount, nature and handling of incomplete outcome data)
We described for each included study the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusions where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or could be supplied by the trial authors, we re-included missing data in the analyses that we undertook. We assessed methods as:

- low risk of bias (e.g. no missing outcome data or missing data < 20%; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)
We described for each included study how we investigated the possibility of selective outcome reporting bias and what we found. We assessed the methods as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review were reported);
- high risk of bias (where not all the study's pre-specified outcomes were reported; one or more reported primary outcomes were not pre-specified; outcomes of interest were reported incompletely and so could not be used; study failed to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other bias (checking for bias owing to problems not covered by 1 to 5 above)
We described for each included study any important concerns we had about other possible sources of bias. We assessed each study as:

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

WHAT'S NEW

Date	Event	Description
11 February 2015	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 3, 2005

Review first published: Issue 4, 2007

Date	Event	Description
27 March 2014	Amended	Contact details updated.
21 June 2012	New search has been performed	Search updated; 26 newly identified reports added to studies awaiting classification, including five reports of three ongoing studies (CHORUS #; Kumar #; Onda #).
21 June 2012	New citation required and conclusions have changed	One new trial (EORTC 55971) included. Conclusions changed.

CONTRIBUTIONS OF AUTHORS

- J Morrison: co-review author, wrote first draft of protocol, sifted original search results, assessed papers, evaluated included papers and co-wrote the review.
- T Lawrie: sifted updated search results, assessed new papers, performed data extraction and co-wrote the updated review.
- K Haldar: sifted searches for the updated review and provided critical appraisal.
- S Kehoe: initial idea, supervisor and approval of final version.

DECLARATIONS OF INTEREST

Sean Kehoe is lead investigator in the CHORUS # study.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- 10/4001/12 NIHR Cochrane Programme Grant Scheme, UK.

This review received methodological and statistical support as part of the 10/4001/12 NIHR Cochrane Programme Grant Scheme - Optimising care, diagnosis and treatment pathways to ensure cost effectiveness and best practice in gynaecological cancer: improving evidence for the NHS

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have updated the methodology of this review to be consistent with the latest Cochrane guidelines, therefore the method of assessing the risk of bias of included studies has changed from the protocol. We have also specified subgroup analyses to be performed in subsequent versions of this review, which were not in the protocol.

This updated version of the review differs from the original review in that a previously included trial, Liu 2004, has now been excluded. After much discussion, we decided that this trial does not strictly meet the inclusion criteria for this review as it compares chemotherapy plus internal iliac artery embolisation (and not chemotherapy alone) with surgery. Thus any effects seen in the chemotherapy group cannot be clearly attributable to the chemotherapy intervention and may, rather, be as a result of the internal iliac artery embolisation.

INDEX TERMS

Medical Subject Headings (MeSH)

Antineoplastic Agents [*therapeutic use]; Chemotherapy, Adjuvant [methods]; Disease-Free Survival; Drug Administration Schedule; Neoadjuvant Therapy [*methods]; Ovarian Neoplasms [*drug therapy; mortality; pathology; *surgery]; Postoperative Complications; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans