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Neoadjuvant chemotherapy before surgery versus surgery followed by chemotherapy for initial treatment in advanced ovarian epithelial cancer (Review)

Coleridge SL, Bryant A, Kehoe S, Morrison J

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[Intervention Review]

Neoadjuvant chemotherapy before surgery versus surgery followed by chemotherapy 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 a combination of surgery and chemotherapy for optimal treatment. Conventional treatment has been to perform surgery first and then give chemotherapy. However, there may be 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 debulking surgery (neoadjuvant chemotherapy (NACT)) compared with conventional treatment where chemotherapy follows debulking surgery (primary debulking surgery (PDS)).

Search methods

We searched the following databases up to 9 October 2020: the Cochrane Central Register of Controlled Trials (CENTRAL), Embase via Ovid, MEDLINE (Silver Platter/Ovid), PDQ and MetaRegister. We also checked the reference lists of relevant papers that were identified to search for further studies. The main investigators of relevant trials were contacted for further information.

Selection criteria

Randomised controlled trials (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

Two review authors independently extracted data and assessed risk of bias in each included trial. We extracted data of overall (OS) and progression-free survival (PFS), adverse events, surgically-related mortality and morbidity and quality of life outcomes. We used GRADE methods to determine the certainty of evidence.

Main results

We identified 2227 titles and abstracts through our searches, of which five RCTs of varying quality and size met the inclusion criteria. These studies assessed a total of 1774 women with stage IIIc/IV ovarian cancer randomised to NACT followed by interval debulking surgery (IDS) or PDS followed by chemotherapy. We pooled results of the four studies where data were available and found little or no difference with regard to overall survival (OS) (Hazard Ratio (HR) 0.96, 95% CI 0.86 to 1.08; participants = 1692; studies = 4; high-certainty evidence) or progression-free survival in four trials where we were able to pool data (Hazard Ratio 0.98, 95% CI 0.88 to 1.08; participants = 1692; studies = 4; moderate-certainty evidence).

Adverse events, surgical morbidity and quality of life (QoL) outcomes were variably and incompletely reported across studies. There are probably clinically meaningful differences in favour of NACT compared to PDS with regard to overall postoperative serious adverse effects (SAE grade 3+): 6% in NACT group, versus 29% in PDS group, (risk ratio (RR) 0.22, 95% CI 0.13 to 0.38; participants = 435; studies = 2; heterogeneity index (I^2) = 0%; moderate-certainty evidence). NACT probably results in a large reduction in the need for stoma formation: 5.9% in NACT group, versus 20.4% in PDS group, (RR 0.29, 95% CI 0.12 to 0.74; participants = 632; studies = 2; I^2 = 70%; moderate-certainty evidence), and probably reduces the risk of needing bowel resection at the time of surgery: 13.0% in NACT group versus 26.6% in PDS group (RR 0.49, 95% CI 0.30 to 0.79; participants = 1565; studies = 4; I^2 = 79%; moderate-certainty evidence). NACT reduces postoperative mortality: 0.6% in NACT group, versus 3.6% in PDS group, (RR 0.16, 95% CI 0.06 to 0.46; participants = 1623; studies = 5; I^2 = 0%; high-certainty evidence). QoL on the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) scale produced inconsistent and imprecise results in three studies (MD -0.29, 95% CI -2.77 to 2.20; participants = 524; studies = 3; I^2 = 81%; very low-certainty evidence) but the evidence is very uncertain and should be interpreted with caution.

Authors' conclusions

The available high to moderate-certainty evidence suggests there is little or no difference in primary survival outcomes between PDS and NACT. NACT probably reduces the risk of serious adverse events, especially those around the time of surgery, and reduces the risk of postoperative mortality and the need for stoma formation. These data will inform women and clinicians (involving specialist gynaecological multidisciplinary teams) and allow treatment to be tailored to the person, taking into account surgical resectability, age, histology, stage and performance status. Data from an unpublished study and ongoing studies are awaited.

PLAIN LANGUAGE SUMMARY

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

What is the issue?

Epithelial ovarian cancer, arising from the surface layer of the ovaries or lining of the fallopian tubes, is the ninth most common cancer worldwide in women, 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 ovarian cancer often arises from the ends of the fallopian tubes, from where single cells can drop out into the abdominal cavity even when the primary tumour is microscopic. These tumour cells circulate around the abdominal cavity in the lubricating peritoneal fluid, implant on other surfaces and grow over time until they cause symptoms. Even then, symptoms, such as bloating and bowel disturbance (most commonly constipation), are nonspecific and easily attributed to more common benign conditions. In Europe and the UK, just over a third of women diagnosed with ovarian cancer are alive five years after diagnosis.

Conventional treatment for ovarian cancer involves two modalities of treatment: surgery and chemotherapy. The intention of surgery is to stage the disease (assess where the cancer has spread to) and remove as much of the visible (macroscopic) cancer as possible (known as debulking or cytoreduction), preferably to the point where the surgical team is not able to see any visible residual disease in the abdominal cavity. However, since most women will have widespread disease, surgery alone is unlikely to cure the disease and most will also need chemotherapy. Chemotherapy for ovarian cancer uses platinum-based drugs to treat cells that cannot be removed by surgery (macroscopic disease) or are too small to be seen (microscopic disease). Traditionally, chemotherapy was given after surgery (primary debulking surgery (PDS) and adjuvant chemotherapy) . However, chemotherapy can be used before surgery (known as neoadjuvant chemotherapy (NACT) and interval debulking surgery (IDS)) with the aim of shrinking the cancer and allowing women to get better prior to undertaking major surgery. Women who receive NACT and IDS complete the remaining cycles of chemotherapy following surgery.

What did we do?

We searched electronic databases up to October 2020 and conducted handsearches for unpublished reports of trials. We included randomised controlled trials (RCTs) of NACT and IDS versus surgery (primary debulking surgery (PDS)) followed by chemotherapy in women diagnosed with advanced stage epithelial ovarian cancer and pooled study outcome data, where appropriate.

What did we find?

We identified 2227 titles and abstracts from the search. From these, we found five RCTs which met our inclusion criteria, including a total of 1774 women with advanced ovarian cancer. We were able to pool data from four studies. These trials compared women who were given chemotherapy prior to surgery (NACT) with women who underwent surgery first (PDS) prior to chemotherapy. We found little or no difference between the two treatments with respect to the time to death and probably little or no difference in the time to progression of the disease. We found that giving NACT reduces the risk of postoperative mortality and need for stoma formation, for which we have

high certainty. NACT probably reduces the risk of some severe complications of surgery, but some of these data were less well reported in the included studies and so we have moderate to low certainty about these results. The studies only enrolled women with stage IIIc/IV ovarian cancer i.e. those who had advanced disease; a large proportion of women in this review had very bulky tumours. We are currently awaiting results of three ongoing studies and one unpublished full publication of a study that is awaiting classification that will hopefully contribute more evidence to guide clinical practice in this area in the future.

What does this mean?

Overall, the evidence was of moderate to high certainty. There is little or no difference in how long women with advanced epithelial ovarian cancer will survive, if they have chemotherapy or surgery first, where both treatments are planned. There is probably little or no difference in how long it will take for the cancer to regrow after initial treatment. NACT probably reduces some of the risks of surgery, probably halves the risk of needing the bowel removed, and probably has a large reduction in the risk of needing the bowel diverted through the abdominal wall via a stoma (a bag attached to the abdominal wall to collect bowel contents). NACT/IDS is an alternative to PDS followed by chemotherapy in women with bulky stage IIIc/IV disease. Individual decisions about which treatment to have first will depend on the individual woman's wishes, how well she is at the time of diagnosis, the risks of surgery and the burden and distribution of disease.

SUMMARY OF FINDINGS

Summary of findings 1. Neoadjuvant chemotherapy prior to interval surgery (NACT) compared to surgery followed by chemotherapy (PDS) for initial treatment in advanced ovarian epithelial cancer

NACT/IDS compared to PDS/adjuvant chemotherapy for initial treatment in advanced ovarian epithelial cancer

Women or population: women with advanced ovarian epithelial cancer

Settings: hospital-based care in countries including Algeria, Argentina, Austria, Belgium, Canada, Ireland, Italy, Japan, Norway, the Netherlands, Portugal, Spain, Sweden, the UK and New Zealand

Intervention: platinum-based chemotherapy followed by debulking surgery (neoadjuvant chemotherapy)

Comparison: primary debulking surgery followed by platinum-based chemotherapy (adjuvant chemotherapy)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with PDS	Risk with NACT				
Overall survival (follow-up 4.4 to 6 years)	Study population 757 per 1,000	743 per 1000 (704 to 783)	HR 0.96 (0.86 to 1.08)	2000 (4 RCTs)	⊕⊕⊕⊕ HIGH	NACT results in little to no difference in overall survival. Absolute risk of death at 4 years demonstrated for absolute effects using formula of corresponding intervention risk per 1000 = 1000 - (exp[ln(1 - proportion of patients with event) x HR]) x 1000 (Tierney 2007). Baseline risk of death at 4 years taken from PDS outcomes for combined Vergote 2010 and Kehoe 2015 data published in Vergote 2018
Progression-free survival (follow-up 4.4 to 6 years)	Study population 858 per 1,000	852 per 1000 (821 to 879)	HR 0.98 (0.88 to 1.08)	1847 (4 RCTs)	⊕⊕⊕⊖ MODERATE [2]	NACT probably results in little to no difference in progression-free survival. Absolute risk of recurrence at 1 year demonstrated for absolute effects using formula of corresponding intervention risk per 1000 = 1000 - (exp[ln(1 - proportion of patients with event) x HR]) x 1000 (Tierney 2007). Baseline risk of recurrence in PDS taken from combination of Vergote 2010 and Kehoe 2015 data published in Vergote 2018
Surgically-related severe adverse effects (grade 3+) - stoma for-	Study population 204 per 1,000	59 per 1000 (24 to 151)	RR 0.29 (0.12 to 0.74)	632 (2 RCTs)	⊕⊕⊕⊖ MODERATE [2]	NACT probably results in a large reduction in rate of stoma formation.

mation (within 30 days of surgery)						
Surgically-related severe adverse effects (grade 3+) - bowel resection (within 30 days of surgery)	Study population 266 per 1,000	130 per 1000 (80 to 210)	RR 0.49 (0.30 to 0.79)	1565 (4 RCTs)	⊕⊕⊕⊖ MODERATE	NACT probably reduces surgically-related severe adverse effects (grade 3+) - bowel resection.
Surgically-related severe adverse effects (grade 3+) - postoperative G3+ events (within 30 days of surgery)	Study population 294 per 1,000	65 per 1,000 (38 to 112)	RR 0.22 (0.13 to 0.38)	435 (2 RCTs)	⊕⊕⊕⊖ MODERATE [2]	NACT probably reduces surgically-related severe adverse effects (grade 3+) - postoperative G3+ events.
Surgically-related postoperative mortality (28 days to 6 months of surgery[4])	Study population 36 per 1,000	6 per 1000 (2 to 17)	RR 0.16 (0.06 to 0.46)	1623 (5 RCTs)	⊕⊕⊕⊕ HIGH	NACT reduces postoperative mortality.
EORTC QLQ-C30 QoL at 6 months - global health	The mean EORTC QLQ-C30 QoL at 6 months - global health was 66.5	MD 0.29 lower (2.77 lower to 2.2 higher)	-	524 (3 RCTs)	⊕⊖⊖⊖ VERY LOW [2]	NACT may reduce/have little to no effect on EORTC QLQ-C30 QoL at 6 months - global health but the evidence is very uncertain.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Outcome unlikely to have been seriously affected by lack of blinding in the study and so not downgraded for risk of bias due to lack of blinding
[2] Downgraded by 1 level for risk of bias due to unblinded study designs, which may have had an effect on some outcomes
[3] Downgraded by 3 levels due to concerns about overall risk of bias, concerns about imprecision, inconsistencies in results and general heterogeneity. QoL outcome was based on a selected number of institutions with better QoL compliance in largest study. While the trial authors offer justification for their approach, several differences were found when comparing the outcomes of the 404 selected women (of which only 212 were assessed in QoL domains) to the overall populations of 670 women. Women from the selected institutions had significantly better OS and PFS when compared to women treated in institutions which were excluded because of poor compliance rates.

4 Most postoperative deaths were within 28-30 days of surgery, but there were four late surgically-related deaths in Fagotti 2016. Definition of postoperative period varied between studies.

BACKGROUND

Description of the condition

Ovarian cancer is now the ninth most common cancer in females, affecting 313,959 women globally in 2020 (GLOBOCAN 2020). In Europe and the UK, just over a third of women with ovarian cancer are alive five years after diagnosis (CRUK 2018; EUROCARE 2015), largely because most women with ovarian cancer are diagnosed when the cancer is already at an advanced stage (Siegel 2018). Symptoms are often vague and of short duration and, as yet, there are no effective screening programmes. In early-stage disease (Federation of International Gynaecologists and Obstetricians (FIGO) stage I/IIa; Table 1), radical surgery will cure most women, although a proportion of women benefit from adjuvant chemotherapy (Lawrie 2015). In advanced cancer, even radical surgery cannot remove all microscopic disease and so survival is dependent upon chemo sensitivity. 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 nonrandomised studies (NRS) have since concurred that survival correlates positively with the extent of tumour debulking achieved (Allen 1995; Bristow 2002; Hunter 1992). The extent of debulking achievable, however, may be directly related to tumour biology, which would strongly bias results from nonrandomised controlled trials (RCTs). Tumours that have also spread to the para-aortic or scalene lymph nodes may be less likely to be optimally debulked intra-abdominally at surgery (Burghardt 1991; Petru 1991). Thus, the ability to achieve successful debulking may in part reflect tumour biology. 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). Interestingly, a recent study demonstrated that routinely removing non-bulky lymph nodes in epithelial ovarian cancer (EOC) does not improve survival (Harter 2019).

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 ≤ 1 cm; the current aim is to leave no macroscopic disease (no disease left visible to the naked eye - so called 'complete' or 'R0' surgery) (Thigpen 2011). This is somewhat misleading in advanced ovarian cancer, since in other cancers an 'R0 resection' indicates that the tumour has been removed with proven microscopically normal margins. In advanced ovarian cancer, due the pattern of spread via the intra-abdominal cavity, microscopic disease is likely to remain, even after a macroscopic debulk is achieved, hence the terms 'complete' and 'R0' will not be used in this review.

In the past, some investigators had not shown a benefit to maximal debulking in women with high-volume, advanced disease (Hoskins 1992; Vergote 1998). However, this may have been because some were very unwell prior to surgery and not fit enough at that stage to withstand a major operation. Vergote 1998, therefore, introduced a policy of treating women with primary chemotherapy (neoadjuvant chemotherapy (NACT)) or primary debulking surgery (PDS), depending on the extent of the 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 ultra-radical surgery in ovarian cancer, with extensive surgical effort often involving the upper abdomen, is a separate question and this review does not seek to question the value or extent of surgery, rather its timing in respect to its combination with chemotherapy. However, a nonrandomised study demonstrated the importance of the combination of surgery and chemotherapy, with a reduced survival in those who had chemotherapy alone and did not go on to have interval debulking surgery (IDS) (Hall 2019). This is supported by findings from a recent cohort study from Sweden, which demonstrated no improvement in survival with system-wide introduction of ultra-radical surgery for ovarian cancer, associated with a reduction in those undergoing surgery by around 10% (Falconer 2020). Studies that do not use whole population cohorts are at critical risk of bias and may overestimate the benefits of upfront surgery (e.g. Mueller 2016).

Description of the intervention

NACT involves giving chemotherapy before attempting cytoreductive surgery for advanced ovarian cancer and is a rationale used in other tumour types. It has evolved from the practice of IDS, a secondary attempt at tumour cytoreduction performed after a suboptimal attempt at primary cytoreduction and adjuvant chemotherapy. In a Cochrane Review (Tangjitgamol 2010), additional 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 with cytoreductive intent by a gynaecological oncologist and in those who have had suboptimal PDS.

Bristow 2007 reviewed 26 nonrandomised studies (NRS) comparing NACT with PDS and concluded that, while NACT might be a viable option for those unsuitable for an attempt at primary cytoreduction, because of significant comorbidities, current poor performance status or impossibility of surgery, survival outcomes with NACT may be inferior to PDS. However, this was based on highly selected data, at critical risk of bias, as women with worse disease were more likely to have received NACT/IDS rather than PDS. Thus, platinum-based NACT may be 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, comorbidities, location of metastatic sites, performance status and stage (Vergote 2011a), as well as the skill and philosophy of the surgical team (Chi 2010; Kehoe 1994; Vergote 2011b). Retrospective data suggest that the optimal time for IDS may be after three cycles of chemotherapy, followed by a further three cycles, and that delaying to four cycles might worsen OS (Bogani 2017). However, these data are based on retrospective analysis of NRS data and are therefore at critical risk of bias, as women who are less well are more likely to have delayed surgery. On multivariate analysis, only the Eastern Co-operative

Oncology Group performance status correlated with OS (hazard ratio (HR), 1.76; 95% confidence interval (CI), 1.2 to 2.49; P = 0.001).

The goal of surgery, whether IDS or PDS, should be complete resection of all disease (Onda 2010). A review of 21 NRS (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 individual awaits recovery from surgery.

Concerns about using NACT include the following:

- NACT delays the removal of the tumour and, thereby, may compromise women's survival;
- chemotherapy induces fibrosis, which may make complete cytoreduction more difficult;
- NACT may effectively shrink cancer deposits but leave microscopic disease that is then not surgically removed, whereas the whole deposit might have been removed had it been visible;
- 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 has been 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 women 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, or in those too unwell to undergo major surgery at diagnosis (Bristow 2007; Chi 2010; Swart 2009; Vergote 2011a). To our knowledge, nine randomised trials of NACT versus PDS have been started or completed in the past two decades (Fagotti 2016; Kumar 2009; Kehoe 2015; Mahner 2017; NCT04257786; NCT04515602; Onda 2016; SUNNY; Vergote 2010). 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.

This review updates previous analyses in this area, incorporating additional data from previously published studies.

OBJECTIVES

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

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs).

Types of participants

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

Types of interventions

Primary debulking surgery (PDS), with the aim of macroscopic resection or optimal debulking (as defined by the investigators), followed by platinum-based chemotherapy, compared to platinum-based neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS), with the aim of resecting disease to the same degree as the PDS group.

Types of outcome measures

We extracted data for direct outcome measures, relevant to patients and clinicians, including benefits, harms and quality of life data, as detailed below.

Primary outcomes

- Overall survival (OS): defined as death from any cause from time of randomisation
- Progression-free survival (PFS): defined as time free of disease progression or death from time of randomisation

Secondary outcomes

- Morbidity/adverse effects classified according to CTCAE 2017:
  - direct surgical morbidity (e.g. bladder injury, intestinal obstruction, haematoma, local infection, duration of operation, need for blood transfusion; need for bowel resection and/or stoma formation);
  - surgically-related systemic morbidity and mortality (e.g. deep vein thrombosis (DVT), pulmonary embolism (PE), chest infection, cardiac events, need for blood transfusion);
  - recovery, including duration of hospital stay;
  - toxicity related to chemotherapy; grouped as haematological, gastrointestinal, genitourinary, skin and neurological toxicity.
- QoL measured using a validated scale (e.g. QLQ-C30 (Osaba 1994), QLQ-OV28 (Greimel 2003)).

- Extent of surgical debulking achieved (e.g. macroscopic, 0.1 to ≤ 1 cm, > 1 cm and combined macroscopic and 0.1 to ≤ 1 cm, i.e. 'optimal').

We will present a summary of findings table reporting the following outcomes listed in order of priority:

1. Overall survival
2. Progression-free survival
3. Surgically-related side effects: need for blood transfusion
4. Surgically-related side effects: stoma formation
5. Surgically-related side effects: bowel resection
6. Surgically-related side effects: postoperative grade 3+ events
7. Postoperative mortality ; postoperative grade 5 event
8. EORTC QLQ-C30 QoL at 6 months

Search methods for identification of studies

Electronic searches

The following electronic databases were searched on 9th October 2020:

- Embase via Ovid (1980 to 2020 week 40) (Appendix 1);
- MEDLINE (Silver Platter/Ovid, 1966 to October week 1 2020) (Appendix 2);
- Cochrane Central Register of Controlled Trials (CENTRAL; 2020, Issue 10) (Appendix 3);
- PDQ and MetaRegister (October 2020).

Searching other resources

The reference lists of the relevant papers found were searched for further studies and we contacted the authors of relevant trials 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 PDQ were searched for ongoing trials. We contacted the main investigators of relevant trials 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 this update). Disagreements were resolved by discussion and referral to a third author (AB), if required.

Data extraction and management

Two review authors (SC and JM) independently extracted data from the included trials 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 would have 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 the end point, in order to estimate a risk ratio (RR);
- for continuous outcomes (e.g. quality of life (QoL) measures), we extracted the final value and standard deviation of the outcome of interest and the number of women assessed at the end point in each treatment arm, 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 2014) and three review authors (SC, AB, JM) checked the data for accuracy.

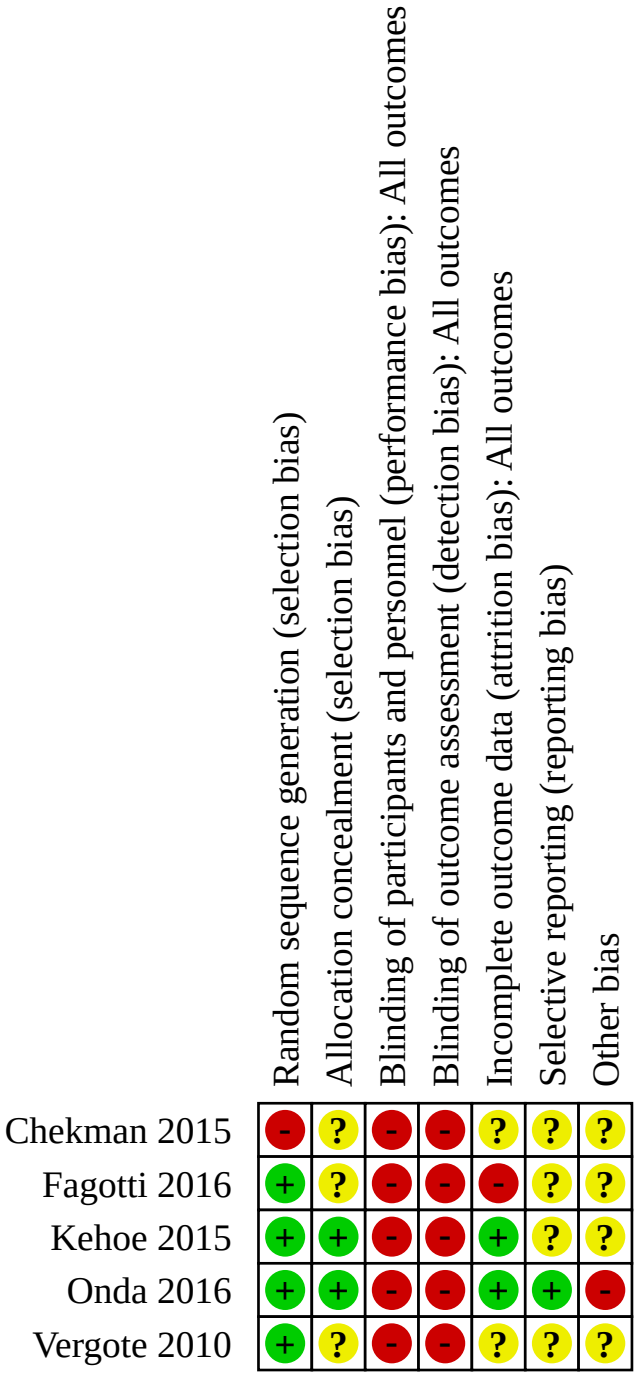
Assessment of risk of bias in included studies

Using Cochrane's risk of bias tool (Higgins 2011), we re-assessed the following for the included studies:

- selection bias: random sequence generation and allocation concealment;
- Blinding of patietns and assessors: performance and detection bias;
- attrition bias: incomplete outcome data;
- reporting bias: selective reporting of outcomes;
- other possible sources of bias.

The risk of bias tool (Appendix 4) was applied independently by up to two review authors (SC 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 summary: review authors' judgements about each risk of bias item for each included study.



Measures of treatment effect

We used the following measures of the effect of treatment:

- for time-to-event data, we used the hazard ratio (HR);
- for dichotomous outcomes, we used the risk ratio (RR);

- for continuous outcomes, we used the mean difference (MD) between treatment arms.

Unit of analysis issues

No issues were noted.

Dealing with missing data

We noted levels of attrition. We did not impute missing outcome data for any of the outcomes.

Assessment of heterogeneity

We assessed heterogeneity between studies by visual inspection of forest plots, by estimation of the percentage heterogeneity between trials that could not be ascribed to sampling variation (Higgins 2003), by a formal statistical test of the significance of the heterogeneity (Deeks 2001) and, where possible, by subgroup analyses (see below). If there was evidence of substantial heterogeneity, the possible reasons for this were investigated and reported.

Assessment of reporting biases

We did not produce funnel plots to assess the potential for small-study effects as there were only five included trials.

Data synthesis

If sufficient clinically similar studies were available, their adjusted results were pooled in meta-analyses.

- for time-to-event data, hazard ratios (HRs) were pooled using the generic inverse variance facility of RevMan 5;
- for any dichotomous outcomes, RRs were calculated for each study and these were then pooled;
- for continuous outcomes, the MDs between the treatment arms at the end of follow-up were pooled as all trials measured the outcome on the same scale, otherwise standardised MDs would have been pooled.

Random-effects models with inverse variance weighting were used for all meta-analyses (DerSimonian 1986).

Subgroup analysis and investigation of heterogeneity

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

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

These subgroups were not prespecified in the original 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 (Stage 3c versus 4).

Sensitivity analysis

In future versions of this review, where possible and with the inclusion of additional studies, sensitivity analyses will be performed where there is a risk of bias associated with the quality of any of the included trials.

Summary of findings and assessment of the certainty of the evidence

We presented the overall certainty of the evidence for each outcome (Types of outcome measures) according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, which takes into account issues not only related to internal validity (risk of bias, inconsistency, imprecision, publication bias) but also to external validity such as directness of results (Langendam 2013). We created a summary of findings table (Summary of findings 1) based on the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2020) and using GRADEpro GDT 2015 (GRADEpro GDT). We used the GRADE checklist and GRADE Working Group certainty of evidence definitions (Meader 2014). We downgraded the evidence from 'high' certainty by one level for serious (or by two for very serious) concerns for each limitation.

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

RESULTS

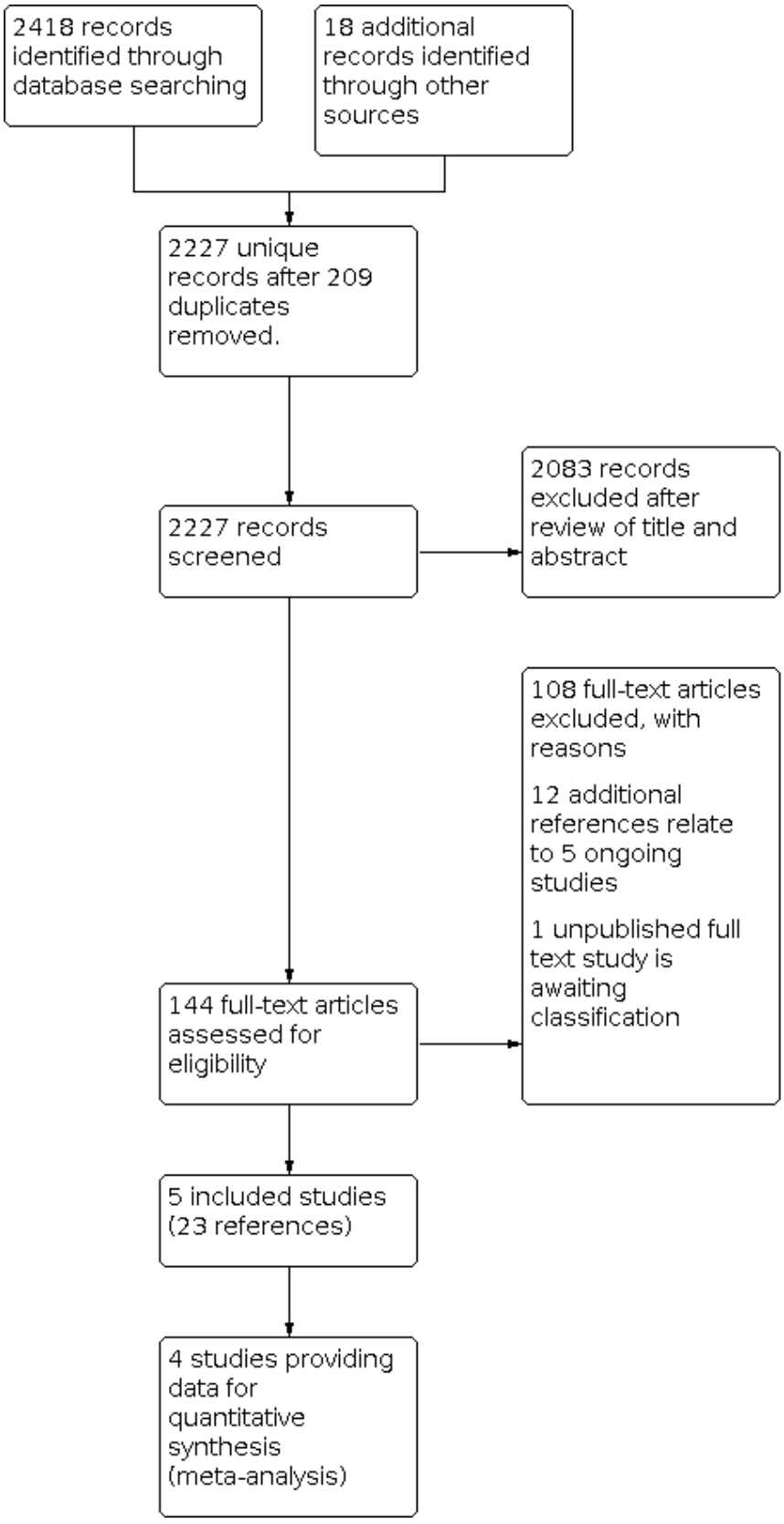
Description of studies

Results of the search

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

Our search identified 2227 unique references, excluding duplicates (Figure 2). At least two review authors (JM, SC) independently screened each abstract in this update of the review; 2083 articles that obviously did not meet the inclusion criteria were excluded at this stage. We retrieved 144 references in full and translated these into English, where appropriate. We found 23 references, reporting on five randomised controlled trials (RCTs), that met our inclusion criteria (Chekman 2015; Fagotti 2016; Kehoe 2015; Onda 2016; Vergote 2010); 12 references reporting on five ongoing trials (Kumar 2009, Mahner 2017 NCT04257786; NCT04515602; SUNNY). We excluded the remaining 108 references (see Excluded studies).

Figure 2. Study flow diagram of the search (up to October 2020).



Kumar 2009 had reported interim analyses in abstract form, but the outcomes were inadequately reported and the risk of bias profile was unclear, so we briefly discussed this trial in the Agreements and disagreements with other studies or reviews in the Discussion and included it with the list of ongoing studies (see Ongoing studies) rather than give it any weight in the main body of the review. Despite contacting the author, unfortunately, no further data have been provided to date for inclusion in the review.

One full-text study (Jiang 2018) is awaiting classification (see Characteristics of studies awaiting classification). Jiang 2018 described the study as a retrospective, cross-sectional study. However, the two groups (NACT versus PDS) were described as 'randomised' and ethical approval and informed consent were sought from study participants. There were significant differences in surgical outcomes between the two groups, but no significant differences in survival outcomes. Despite contacting the author, unfortunately, no further data have been provided to date for inclusion in the review.

Included studies

See Characteristics of included studies.

Chekman 2015 was a randomised controlled trial (RCT), conducted in Algeria between 2008 and 2014. The study enrolled 90 women with FIGO stage IIIc ovarian carcinoma who were randomised to either primary debulking surgery (PDS) followed by chemotherapy or neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS). The same surgeon operated on all women in both intervention arms. It would appear that all women had surgery as well as chemotherapy. Nine women were excluded (reasons not stated) and only data for those who had their disease resected to < 1 cm (including no macroscopic residual disease) were reported, i.e. there did not appear to be an intention-to-treat analysis. The diagnosis of stage IIIC ovarian carcinoma was confirmed by laparoscopic exploration in all but three cases. The number of cycles of chemotherapy in the NACT arm was six cycles (Carboplatin AU5/7.5 mg/mL/minute + Paclitaxel 175 mg/m^2/3 hours every three weeks) on average with 44% having six cycles (range 3 to 7 cycles). Women in the PDS arm had six cycles of chemotherapy on average (78%) (range: 4 to 9) and followed the same chemotherapy protocol as in the NACT arm. The mean duration of follow-up was 254.2 months (range: 69 to 480 months). The trial reported on < 1 cm residual tumour nodules (optimal debulk) or macroscopic resection, overall survival (OS), recurrence-free survival (RFS), morbidity and discussed the role of lumboaortic lymphadenectomy. The study was in abstract form only, but Professor Chekman kindly provided us with more information on request. Unfortunately, survival outcomes could not be analysed, as data for time-to-event outcomes were not provided in an appropriate format for inclusion.

Kehoe 2015 (CHORUS) was a multicentre, non-inferiority phase III RCT, conducted in 87 institutions in the UK and New Zealand. Inclusion criteria were women with clinical or radiological evidence of a pelvic mass with extra-pelvic disease compatible with stage III or IV ovarian, fallopian tube or primary peritoneal cancer who were fit for surgery and chemotherapy. All women had clinical assessment including serum tumour markers and radiological imaging and 552 women were randomised to undergo treatment; two women were subsequently excluded due to being randomised in error. In the PDS arm, 276 women were assigned to undergo PDS followed by six cycles of platinum-based chemotherapy within six weeks of surgery. In the PDS arm, women with residual tumour deposits > 1 cm were eligible to undergo an additional cytoreductive surgery after three cycles of chemotherapy. In the NACT arm, 274 women were assigned to undergo NACT for three cycles with platinum-based chemotherapy and then have IDS and to recommence chemotherapy within six weeks of surgery. Women in the NACT arm had histological or cytological confirmation of diagnosis before commencing chemotherapy. The primary outcome measure was OS; secondary outcomes were progression-free survival and quality of life (QoL). QLQC-30 and QLQ-Ov28 QoL questionnaires were used. The published QoL data provided only the global score at baseline (pretreatment), six months and 12 months post-treatment.

In the NACT arm, 253 (92%) of 274 women started treatment as allocated and 217/274 (79%) had IDS. Nineteen of the 274 (6.9%) women in the NACT arm had no treatment; 36 women had no surgery following chemotherapy; 17 women had no postoperative chemotherapy (one of whom had primary surgery). In the PDS arm, 251 (91%) of 276 women started treatment as allocated; 212 (77%) had adjuvant chemotherapy. Ten of the 276 (3.6%) women had no treatment; 11 women had chemotherapy first with no surgery afterwards; 39 women had no postoperative chemotherapy (one of whom had preoperative chemotherapy); one woman had an unknown postoperative treatment status. See Characteristics of included studies for further details.

Vergote 2010 (EORTC 55971/NCIC OV13) was a large, international, multicentre, non-inferiority phase III RCT. 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 (EOC), primary peritoneal cancer or fallopian tube cancer were evaluated. For inclusion, an 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 chemotherapy (CT). The control group (336 women) received 'standard' treatment (i.e. PDS plus at least six cycles of platinum-based CT ± IDS). The primary outcome was OS. Secondary outcomes were progression-free survival (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 mm to 10 mm, and residual tumour greater than 10 mm. QoL data from the Vergote 2010 trial were subsequently reported by Greimel 2013 (see nested references in Vergote 2010).

Of the 334 women assigned to NACT, 326 (98%) started chemotherapy and 295 (88%) underwent IDS. Of the 336 women assigned to the PDS group, 315 (94.3%) had PDS and 88.4% started chemotherapy. See Characteristics of included studies for further details.

Onda 2016 (JCOG0602) was a multicentre, non-inferiority, phase III RCT conducted in Japan. The authors enrolled 301 women between 2006 and 2011. For inclusion, women had stage III/IV ovarian, tubal and peritoneal cancers diagnosed by clinical findings, radiological imaging and cytology. CA125 had to be > 200 U/mL and CEA < 2

ng/mL to exclude malignancies of other anatomical sites. Women assigned to the control group (149) underwent PDS followed by eight cycles of platinum-based chemotherapy. An additional debulking operation was performed after PDS, if PDS left > 1 cm of residual tumour. An additional debulking operation was mandatory if the uterus, adnexa or omentum had not been removed at PDS, unless disease progression occurred. Women assigned to the experimental group (152) received four cycles of platinum-based NACT, then underwent IDS followed by a further four cycles of chemotherapy. The primary outcome of the study was OS, with survival data published in a peer reviewed journal in 2020, having previously been presented in conference proceedings. Secondary outcomes were invasiveness of surgery in terms of adverse events; these data have been published. No QoL assessment was performed.

Fagotti 2016 (SCORPION) was a single institution, superiority, phase III RCT. In total, 280 women with advanced ovarian cancer were enrolled into the study but, in order to be eligible for randomisation to the study arms, women had to undergo a staging laparoscopy. This was to obtain histology and confirm diagnosis, as well as assess the tumour load. Tumour load was assessed using a predictive index (PI). Only women with a PI score >/= to 8 and </ = 12, corresponding to a high tumour load, were eligible for randomisation. If it was deemed not possible to perform a staging laparoscopy due to large masses occupying the abdominal cavity infiltrating the abdominal wall or the presence of mesenteric retraction, women were withdrawn from the study. After recruitment reached 110 women in order to achieve statistical power for the analysis of the first co-primary end point of major perioperative morbidity, further women were recruited to attain statistical power on PFS (more details are given in Risk of bias in included studies). Two hundred and twenty-five women underwent staging laparoscopy in total, but only 171 went on to be randomised. In the control group, 84 women were assigned to PDS followed by six cycles of platinum-based chemotherapy started within four weeks of surgery. Once women in the control arm had undergone PDS they were not allowed to have an additional cytoreductive procedure. In the experimental group, 87 women were assigned to three or four cycles of platinum-based NACT and to undergo surgery within four weeks of the last cycle, if disease progression was excluded on imaging. The final cycles of chemotherapy in the experimental arm were resumed within four weeks of IDS. The mean and median time to the start of chemotherapy was 42.7 (SD = 18.3) and 41 days (range: 18-169) in the PDS arm, respectively. In the NACT arm, the mean time to chemotherapy was 26.4 days (SD = 11.5) and the median was 26 days (range: 3-79). The mean and median time to start adjuvant treatment after IDS in the NACT arm was 39 (SD = 10.8) and 37 (range: 14-71) days, respectively. Co-primary outcomes were PFS survival and postoperative complications. Secondary outcomes were OS and QoL. Further data were kindly provided by Professor Fagotti. Some outcomes were reported based on the initially published cohort of 110 patients, whereas others were reported for the final 171 participants in the randomised cohort.

Excluded studies

See Characteristics of excluded studies.

One hundred and eight references were excluded for the following reasons:

- Non-RCTs (77);
- Eleven RCTs without a surgical arm comparison (Bertelsen 1990; Chan 2017; Deval 2003; Dutta 2005; Liu 2017; Lotze 1987; Mackay 2011; Mahner 2006; Polcher 2009; Rutten 2012; Trope 1997);
- Three RCTs of IDS following PDS (Redman 1994; Van der Burg 1995; Varma 1990);
- One RCT of non-platinum-based NACT versus surgery (Evdokimova 1982);
- One RCT of chemotherapy plus iliac artery embolisation versus surgery (Liu 2004);
- Fourteen reviews or systematic reviews (Baekelandt 2003; Bristow 2001; Dai-yuan 2013; Fujiwara 2013; Kumar 2015; Lyngstadaas 2005; Mahner 2014; Makar 2016; Qin 2018; Sato 2014; Schorge 2014; Xiao 2018; Yang 2017; Zeng 2016);
- Two pooled analyses of studies included in the review (Vergote 2018; Vergote 2019);
- One RCT comparing early IDS after 3 cycles of NACT with late IDS after 6 cycles of NACT (Kumari 2020).

Liu 2004, an RCT comparing NACT plus iliac artery embolisation versus PDS, was originally an 'included study' in the 2006 version of this review. In a previous update of the review, we revised our assessment of this study and excluded it, as the study findings might have been attributable to NACT versus PDS, iliac artery embolisation, or the combination, because NACT versus PDS was not the only variable in the study and iliac artery embolisation was not delivered in both arms.

Risk of bias in included studies

For this update of the review, a combination of two out of three review authors (from SC, AB, JM) independently re-assessed the risk of bias in each included trial according to pre-defined criteria stated in the methods section (Figure 1).

Allocation

The Chekman 2015 study selection bias was judged to be at high risk, especially when compared to other studies with centralised randomisation, although allocation concealment was unclear due to lack of information. Ninety women with FIGO stage IIIc ovarian carcinoma were enrolled and underwent surgery, but only 82 women were randomised: 41 to PDS/chemotherapy and 41 to NACT/IDS. The randomisation was performed in the operating room by random draw by someone other than the surgeon, once verification of inclusion criteria and resectability under laparoscopy or laparotomy had been confirmed.

The Fagotti 2016 study was deemed to be at low risk of selection bias, albeit from a highly selected population. A centrally-performed, computer-generated list for block randomisation (1:1 ratio) was used. Women were randomly (maximum allowable percentage deviation = 10%) allocated to PDS + systemic adjuvant chemotherapy (arm A, control) or to NACT + IDS (arm B, experimental). Women were only eligible for randomisation into the study once they had undergone a staging laparoscopy to assess disease burden. The staging laparoscopy was used as a triage tool to assess eligibility for the study. If a staging laparoscopy was unfeasible, women were removed from the study. If the staging laparoscopy was successful, a predictive index (PI) value was calculated based upon seven parameters: presence or absence of omental cake, extensive carcinomatosis of the peritoneal or

diaphragmatic surfaces, mesenteric retraction, infiltration of the stomach, spleen or bowel and or superficial liver metastases. If the PI score was ≥ 8 or ≤ 12, this was considered to be a high tumour load, related to lower chances of optimal cytoreduction and worse prognosis. The PI scoring system was based upon earlier work by the same group (Fagotti 2006; Fagotti 2013; Vizzielli 2014).

The initial phase of the Fagotti 2016 study identified 280 women, of whom 14.3% (40) were excluded: seven due to refusal to participate; 15 due to PS score > 2; and 18 due to age > 75 years. A further 15 women (6.25%) had an unsuccessful attempt at a staging laparoscopy, leaving 225 women who underwent a successful staging laparoscopy. Of those 225 women, a further 115 (51.1%) were excluded following staging laparoscopy: 69 due to a PI score < 8; 31 due to mesenteric retraction or PI score > 12; and 15 had non-EOC histology. This left 110 women, with 55 allocated to each arm of the study. These complexities in trial design introduce potential sources of bias and may limit the applicability to the general advanced ovarian cancer population.

The risk of selection bias in the Kehoe 2015 study was deemed to be low risk as the randomisation was performed centrally using a minimisation method based on randomising centre, largest radiological tumour size, clinical FIGO stage, and prespecified chemotherapy regimen.

The Onda 2016 study was deemed to be at low risk of selection bias. The Japan Clinical Oncology Group (JCOG) data centre randomly assigned treatment to each woman via a minimisation method based on institution, stage (III versus IV), performance status (0 to 1 versus 2 to 3) and age (< 60 versus > 60).

In Vergote 2010, randomisation and allocation were performed centrally and the study appeared to be at low risk of allocation bias, although details of the process of randomisation method and concealment were lacking in published data.

Blinding

The five included studies were open-label studies and outcome assessment were not blinded. This is probably 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 studies had been raised in a Gynecologic Cancer InterGroup (GCIG) consensus statement (Thigpen 2011). Data for such outcomes are thus to be interpreted with caution and all studies were deemed to be at high risk of bias.

Incomplete outcome data

Chekman 2015 was at unclear risk of attrition bias due to lack of reported details.

Fagotti 2016 was judged to be at high risk of attrition bias. After the recruitment of 110 women was achieved for the analysis of the first co-primary end point of major perioperative morbidity, further women were recruited to attain statistical power on PFS. The final trial cohort consisted of 171 women, with 84 randomised to PDS and 87 randomised to NACT. Information was not available for two patients who were lost during treatment, one for each arm. The initial published data reported QoL outcomes and short-term surgical outcomes. There were substantial missing data for QoL outcomes, but relative results (hazard ratios (HRs)) for survival (OS and PFS) were adequately reported and analysed. Of the women included in the analysis, 82/84 women in the PDS arm required upper abdominal surgical procedures compared to 28/74 women who underwent IDS (42.3%). Median duration of entire treatment from randomisation to completion of medical treatment was also longer in the PDS arm (38 weeks versus 28 weeks). This was due to an almost two-week difference in time to start post-surgery chemotherapy (median time post-PDS 40 days; median time post-IDS 27 days; P = 0.0001).

Kehoe 2015 and Onda 2016 were deemed to be at low risk of attrition bias, as all trial participants were accounted for and the results were analysed on an intention-to-treat basis.

In the Vergote 2010 study, data from 48 women from Argentina were excluded owing to "potential authorisation irregularities"; however, the investigators stated that their results were similar when these excluded data were included. The exclusions appeared erroneously as pre-randomisation exclusions on the published study-flow diagram. The study was, therefore, at unclear risk of attrition bias.

Selective reporting

Chekman 2015 was at unclear risk of reporting bias due to lack of detail.

Fagotti 2016 was at unclear risk of reporting bias due to the differences in numbers reported for different outcomes, as described above, and lack of quality of life data to date.

In Kehoe 2015, the risk of reporting bias was unclear. All prespecified outcome measures have been reported in some capacity, but QoL data were provided only in the form of a global score at baseline, six months and 12 months post-treatment.

The potential for reporting bias in the Onda 2016 study is now deemed to be low risk; surgical morbidities were reported in the initial publication and survival outcomes have now been published .

There was an unclear risk of selective reporting bias for QoL data in the Vergote 2010 study. Vergote 2010 (including Greimel and colleagues) subsequently published the QoL data from the Vergote 2010 study (see additional reference under Vergote 2010). They reported that compliance for all women was too restrictive and changes to the protocol-defined analysis plan were made. The dataset for QoL data was then restricted to institutions with the best compliance. The authors stated that the sample size of the Vergote 2010 was overpowered to detect clinically meaningful differences in QoL between the two study arms and they therefore decreased the sample size for QoL data to 400 participants. They further restricted QoL data collection to institutions that had 50% compliance at baseline and at least 35% on further follow-up over all enrolled women. Twenty-seven institutions out of 59 contributed 404 women (60.3% of the total 670 trial participants). The participants in institutions that were included in the QoL data had statistically significant differences compared to those participants not included: they had larger tumours (P < 0.01) and optimal debulking rates were 20% higher (P = 0.001). Those participants in institutions selected for inclusion in QoL data analysis had a greater median OS (nine months longer; P = 0.001) and a greater median progression-free survival (PFS) (2.4 months longer; P < 0.001) than the participants in the institutions that were

not included in the QoL data collection. In addition, as well as selecting institutions with the highest compliance with QoL data, the overall compliance from those institutions was still relatively poor over time. Compliance rates were 83.4% at baseline, 58.7% at chemotherapy cycle 3, 74% at chemotherapy cycle 6, 59.4% at six-month follow-up and 45.7% at 12-month follow-up.

The authors concluded that there were no differences in the QoL functioning or symptoms scales, other than for pain and dyspnoea.. At baseline, the PDS group had higher pain scores (P = 0.046; PDS mean 36.7; NACT mean 29.9) and lower dyspnoea scores (P = 0.049; PDS mean 22.9; NACT mean 27.9). As the difference between the groups was less than 10 points, the authors concluded that this did not represent a "clinically relevant difference".

There was, therefore, unclear risk of reporting bias for the QoL data, given the differences in disease that those participants selected for measurement of this outcome had in comparison with participants in the institutions not selected.

Other potential sources of bias

Due to lack of detail, Chekman 2015 was judged to be at unclear risk of other potential sources of bias.

The complexity of the inclusion criteria in Fagotti 2016, as described above, mean that we were unclear about other potential sources of bias and the study design limits the applicability of the study to a wider, less selected, cohort of women with ovarian cancer.

Supplementary data in Kehoe 2015 table 7 show that hysterectomy/bilateral salpingo-oophorectomy (BSO) and omentectomy were performed in varying proportions in the different arms. It is unclear what effect this might have on outcomes and this could be a potential source of bias.

In the Onda 2016 study, 14 women (one in PDS and 13 in NACT) underwent some type of additional surgery (off-protocol treatment). These off-protocol operations were not included as PDS or IDS in the analysis. There appeared to be more off-protocol surgery in the NACT group. No intention-to-treat analysis was performed. These issues could be another potential source of bias.

Effects of interventions

See: **Summary of findings 1** Neoadjuvant chemotherapy prior to interval surgery (NACT) compared to surgery followed by chemotherapy (PDS) for initial treatment in advanced ovarian epithelial cancer

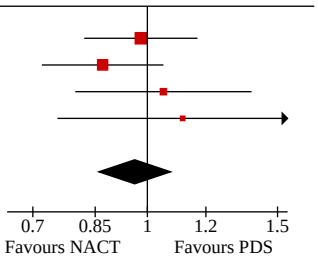
Overall survival (OS) (Analyses 1.1 to 1.4)

Meta-analysis of four studies (Fagotti 2016; Kehoe 2015; Onda 2016; Vergote 2010), assessing 1692 participants, demonstrated little or no difference in OS between neoadjuvant chemotherapy (NACT) and primary debulking surgery (PDS) for initial treatment in advanced ovarian cancer (hazard ratio (HR) = 0.96, 95% CI 0.86 to 1.08; high-certainty evidence); Analysis 1.1; Figure 3 and Figure 4).

Figure 3. Forest plot of comparison: 1 NACT vs PDS, outcome: 1.1 Overall survival.

Study or Subgroup	log[Hazard Ratio]	SE	Favours NACT Total	PDS Total	Weight	Hazard Ratio IV, Random, 95% CI
Vergote 2010 (1)	-0.0202	0.09	334	336	40.2%	0.98 [0.82 , 1.17]
Kehoe 2015	-0.1393	0.0966	274	276	34.9%	0.87 [0.72 , 1.05]
Onda 2016	0.05	0.14	152	149	16.6%	1.05 [0.80 , 1.38]
Fagotti 2016	0.11	0.199	87	84	8.2%	1.12 [0.76 , 1.65]
Total (95% CI)			**847**	**845**	**100.0%**	**0.96 [0.86 , 1.08]**

Heterogeneity: Tau² = 0.00; Chi² = 2.09, df = 3 (P = 0.55); I² = 0%
Test for overall effect: Z = 0.69 (P = 0.49)
Test for subgroup differences: Not applicable



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

Figure 4. In the PDS group 757 people out of 1000 had died over 4 years compared to 743 (95% CI 704 to 783) out of 1000 for the NACT group. Green = alive at 4 years with PDS/chemo; yellow = additional people alive at 4 years with NACT/IDS; red = people who had died by 4 years with either NACT/PDS or PDS/chemo.

The results were also robust (i.e. no meaningful difference between subgroups) in terms of OS when three trials (Fagotti 2016; Kehoe 2015; Vergote 2010) were subgrouped by age (< 50, 50 to 70 and 70+ years) (Analysis 1.2), and extent of residual disease in two studies (Kehoe 2015; Vergote 2010) (up to 0.5 mm, 0.5-1 cm, > 1 cm) (Analysis 1.3). The results were also robust when three trials (Kehoe 2015; Onda 2016; Vergote 2010) were subgrouped by stage (III and IV) (Analysis 1.4). Survival data by stage were not yet available for one study (Fagotti 2016).

We were not able to extract time-to-event data for OS from the Chekman 2015 study. However, in total, 24 women died during the study period; 15 women (62.5%) in the PDS arm compared to nine women (37.5%) in the NACT arm.

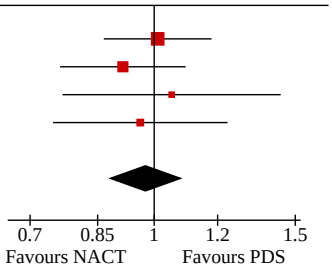
Progression-free survival (PFS) (Analysis 1.5)

Meta-analysis of four studies (Fagotti 2016; Kehoe 2015; Onda 2016; Vergote 2010), assessing 1692 participants, found there is probably little or no difference in risk of disease progression between NACT and PDS for initial treatment in advanced ovarian cancer (HR = 0.98, 95% CI 0.88 to 1.08; I^2 = 0%; moderate-certainty evidence) (Analysis 1.5; Figure 5 and Figure 6).

Figure 5. Forest plot of comparison: 1 NACT vs PDS, outcome: 1.4 Progression-free survival.

Study or Subgroup	log[Hazard Ratio]	SE	NACT Total	PDS Total	Weight	Hazard Ratio IV, Random, 95% CI
Vergote 2010 (1)	0.01	0.079	334	336	42.3%	1.01 [0.87 , 1.18]
Kehoe 2015 (2)	-0.09	0.092	274	276	31.2%	0.91 [0.76 , 1.09]
Fagotti 2016	0.05	0.16	87	84	10.3%	1.05 [0.77 , 1.44]
Onda 2016	-0.04	0.128	152	149	16.1%	0.96 [0.75 , 1.23]
Total (95% CI)			**847**	**845**	**100.0%**	**0.98 [0.88 , 1.08]**

Heterogeneity: Tau² = 0.00; Chi² = 0.93, df = 3 (P = 0.82); I² = 0%
Test for overall effect: Z = 0.49 (P = 0.62)
Test for subgroup differences: Not applicable



Footnotes
(1) We have applied 95% CIs (Investigators used 90% CIs)
(2) 0.09

Figure 6. In the PDS group 858 people out of 1000 had ovarian cancer that had recurred by 2 years compared to 852 (95% CI 821 to 879) out of 1000 for the NACT group. Green = not had recurrent disease by 2 years with PDS/chemo; yellow = additional people without recurrent disease by 2 years with NACT/IDS; red = peopel with recurrent disease by 2 years with either NACT/PDS or PDS/chemo.

From the Chekman 2015 study, we were not able to extract time-to event data for PFS. However, there were 36 recurrences (44%); 20 participants with progressive disease (55.5%) in the control arm (PDS) and 16 (44.5%) in the experimental (NACT) arm.

Of the 12 women in Chekman 2015 who were still alive with confirmed recurrence, five (41.6%) were in the PDS arm and seven (58.3%) were in the NACT arm. Peritoneal recurrence was reported to be most common. Further details about recurrence are given in the table Characteristics of included studies.

Extent of residual disease

In Kehoe 2015, 79/219 women (36%) and 39/255 women (15%) had no macroscopic residual disease in the NACT and PDS arms, respectively; 68/219 (31%) and 57/255 (22%) had 'optimal debulking' (defined as 0.1 cm to 1 cm residual disease) in the NACT and PDS arms, respectively; and 54/219 (25%) and 137/255 (54%) had suboptimal debulking (defined as > 1 cm) in the NACT and PDS arms, respectively. Overall, 147/219 (67%) women and 96/255 (38%) women in the NACT and PDS arms, respectively, had < 1 cm residual disease. Data on degree of resection were missing for 18 women in the NACT group and 22 in the PDS group.

In the NACT arm, 55/274 (20%) women did not have debulking surgery. In the PDS arm, 251 women had PDS and another four had surgery after NACT, so 21 of the 276 allocated to PDS women did not have debulking surgery (7.6%).

In Vergote 2010, of those who had debulking surgery, 151/295 women (51.2%) and 61/315 women (19.4%) had no macroscopic residual disease in the NACT and PDS arms, respectively; 87/295 (29.5%) and 70/315 (22.2%) had 1 mm to 10 mm residual disease in the NACT and PDS arms, respectively; and 52/295 (17.6%) and 167/315 (53%) had suboptimal debulking (> 1 cm residual disease) in the NACT and PDS arms, respectively. Data on debulking status were stated as missing for five (1.7%) women in the NACT group and 17 (5.4%) women in the PDS group. See Characteristics of included studies table for further details. Therefore, of those who had NACT and interval debulking surgery (IDS), 238 women (80.7%) had debulking to < 1 cm residual disease compared to 131 women (41.6%) who had PDS.

Of those assigned to NACT, 326/334 (98%) started chemotherapy and 295/334 (88%) went on to have IDS. In the PDS group, 315 (94.3%) had PDS and 88.4% started chemotherapy.

In Fagotti 2016, 57/74 women (77%) and 40/84 women (47.6%) had no macroscopic residual disease in the NACT and PDS arms, respectively; 16/74 (21.6%) and 38/84 (45.2%) had residual disease 0.1 cm to 1 cm in the NACT and PDS arms, respectively. Therefore, debulking to < 1 cm was achieved for 73/74 (98.6%) and 78/84 (92.8%) in the NACT and PDS arms, respectively; 1/74 (1.4%) and 6/84 (7.2%) had suboptimal debulking (residual disease > 1 cm) in the NACT and PDS arms, respectively (13 participants in the NACT arm did not undergo IDS). This is despite extensive pre-assessment and intraoperative exclusion (laparoscopic assessment), which differed significantly from the Kehoe 2015 and Vergote 2010 studies.

In Onda 2016, 83/150 women (55%) and 45/147 women (31%) had no macroscopic residual disease in the NACT and PDS arms, respectively; 24/150 (16%) and 47/147 (32%) had residual disease 0.1 cm to 1 cm in the NACT and PDS arms, respectively; and 23/150 (15%) and 55/147 (37%) had residual disease > 1 cm in the NACT and PDS arms, respectively. Overall, 107/150 women (71%) and 92/147 women (63%) had optimal debulking (defined as debulking to no residual disease > 1 cm) in the NACT and PDS arms, respectively. Higher optimal debulking rates than Kehoe 2015 and Vergote 2010 may be due to lower initial disease burden, since the entry criteria included all stage III disease, not just bulky stage IIIc, and 9 (6%) in the PDS and 10 (6.6%) in the NACT groups had no measurable disease (presumably by RECIST criteria (Eisenhauer 2009) but not stated) at outset.

Severe adverse effects (SAEs) (Analyses 1.6)

The trial of Fagotti 2016 reported major perioperative morbidity, initially when the trial had randomised 110 participants. Some level of granularity in adverse events was not given in the follow-up publication, so some analyses were based on the initial cohort (n = 110), whereas analyses included in the follow-up publication included all 171 women.

Some studies reported all SAEs during the study period (Kehoe 2015; Onda 2016; Vergote 2010), whereas some reported surgically-related SAEs only (Chekman 2015; Fagotti 2016). The following grade 3/4 (CTCAE 2017) SAEs were reported (Analysis 1.6):

Haemorrhage and blood transfusion requirements (Analyses 1.6.1 and 1.6.2)

Meta-analysis of three studies (Fagotti 2016; Kehoe 2015; Vergote 2010), assessing 1264 participants, found there may be little of no difference in risk of haemorrhage between NACT and PDS for initial treatment in advanced ovarian cancer (RR = 0.93, 95% CI 0.50 to 1.74; I^2 = 69%; low-certainty evidence).

In the Kehoe 2015 and Vergote 2010 studies, the need for blood transfusions and average blood loss were not reported in the published versions of the studies. However, Vergote 2010 provided unpublished data with respect to the number of women who received blood transfusions in the NACT and PDS groups. Meta-analysis of four trials (Chekman 2015; Fagotti 2016; Onda 2016; Vergote 2010), assessing 1085 participants, suggested NACT and IDS likely resulted in a slight reduction in needing a blood transfusion after surgery compared to PDS (RR 0.80, 95% CI 0.65 to 0.99; participants = 1085; I^2 = 50%; moderate-certainty evidence).

Venous thromboembolism (Analysis 1.6.3)

Meta-analysis of data from four studies (Fagotti 2016; Kehoe 2015; Onda 2016; Vergote 2010) suggested that there may be a reduction in the risk of venous thromboembolism in the NACT arm versus the PDS arm, although this was based on a low number of events (n = 27), so should be interpreted with caution (RR 0.28, 95% CI 0.09 to 0.90; participants = 1490; I^2 = 15%; low-certainty evidence).

Infection (Analysis 1.6.4)

Meta-analysis of data from four studies (Fagotti 2016; Kehoe 2015; Onda 2016; Vergote 2010) found women in the NACT arm probably had less risk of infection than in the PDS arm (RR 0.30; 95% CI 0.16 to 0.56; participants = 1490; I^2 = 0%, moderate-certainty evidence).

Gastrointestinal (GI) fistulae (Analysis 1.6.5)

Meta-analysis of data from four studies (Fagotti 2016; Kehoe 2015; Onda 2016; Vergote 2010), found that NACT may be associated with lower risk of severe gastrointestinal fistulae than PDS, although the overall event rate was very low (n = 17) (RR 0.30; 95% CI 0.09 to 0.97: 1490 participants; I^2= 0%; low-certainty evidence).

Other SAEs (Analyses 1.6.6 to 1.6.14 and 1.6.17)

Overall postoperative G3+ SAEs from two studies (Fagotti 2016; Onda 2016) found that the number of patients who had a G3+ SAE in the postoperative period was probably lower in the NACT group (RR 0.22, 95% CI 0.13 to 0.38; participants = 435; studies = 2; I^2 = 0%; moderate-certainty evidence) (see Analysis 1.6.18 and Figure 7).

Figure 7. In the PDS group 29 people out of 100 had G3+ post op serious adverse events (SAE) compared to 6 (95% CI 4 to 20) out of 100 for the NACT group. Green = no post op G3+ SAE with PDS/chemo; yellow = additional people who were better with NACT/IDS; red = people with G3+ SAEs with either NACT/PDS or PDS/chemo.

The proportion of remaining SAEs that were assessed was low. There was probably little or no difference between arms for risk of urinary/vaginal fistula, nausea, vomiting, diarrhoea, neutropenia, neurotoxicity, thrombocytopenia, anaemia, febrile neutropenia and renal toxicity (see analyses 1.6.6 to 1.6.14; 1.6.17; all low-certainty evidence). IDS may be associated with less risk of stoma formation, bowel resection, and postoperative grade 3+ events than PDS.

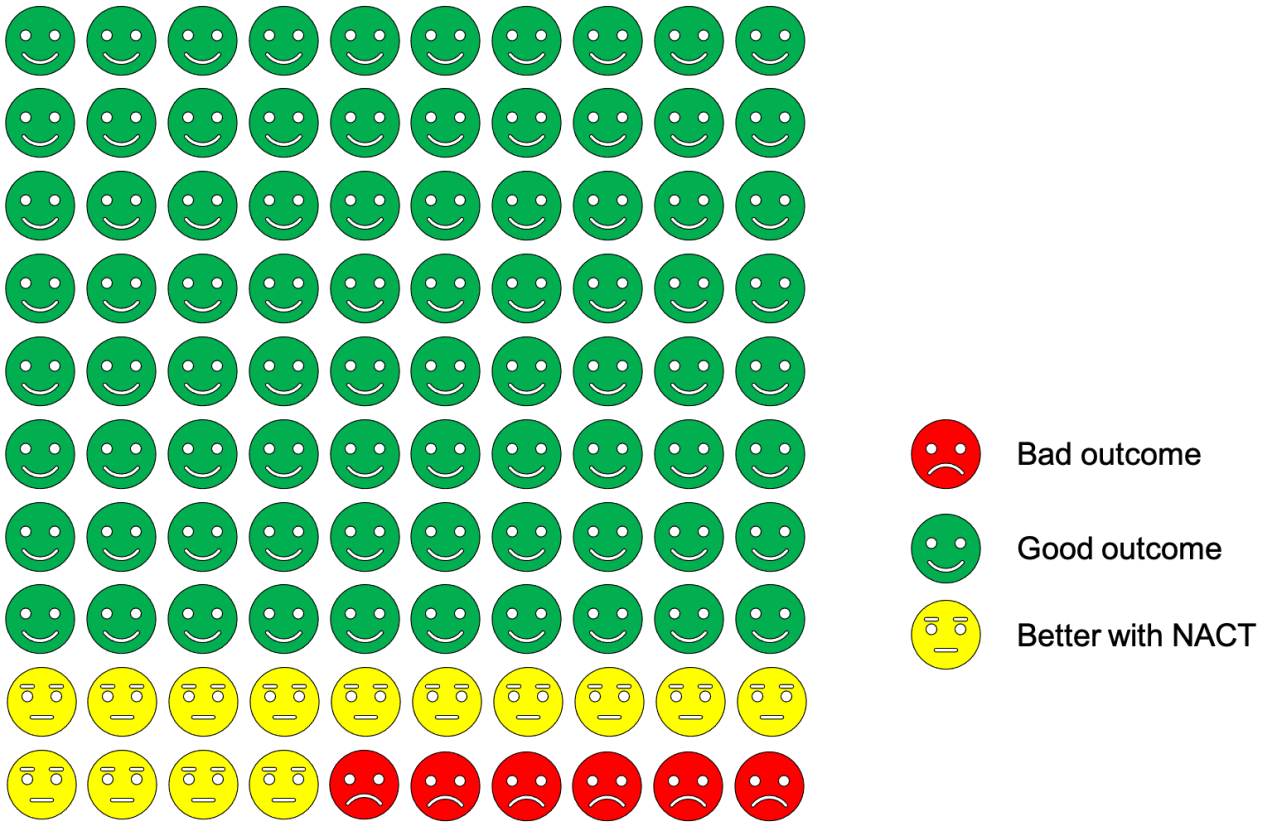
In the Chekman 2015 study, there were a total of 17 complications: 12/41 women in the PDS arm; 5/41 women in the NACT-IDS arm (intraoperative incidents). We were careful not to over interpret this result from a trial of low numbers in each arm, with issues regarding imprecision and unclear risk of bias.

The authors reported that eight re-operations (9.8%) were performed, mainly for abdominal and vascular complications; six (7.3%) in the PDS arm and two (2.4%) in the NACT-IDS arm.

Stoma formation (Analysis 1.6.15)

Women were less likely to require formation of a stoma (colostomy or ileostomy) in the NACT arm versus the PDS arm, although data were only presented in two of the studies (Fagotti 2016; Kehoe 2015) (RR 0.43, 95% CI 0.26 to 0.72; participants = 581; studies = 2; I^2 = 0%; moderate-certainty evidence) (Analysis 1.6.15 and Figure 8).

Figure 8. In the control group 20 people out of 100 had stoma formation following initial surgery compared to 6 (95% CI 2 to 15) out of 100 for the active treatment group. Green = no stoma with PDS/chemo; yellow = additional people who didn't require a stoma with NACT/IDS; red = people who required a stoma with either NACT/PDS or PDS/chemo.



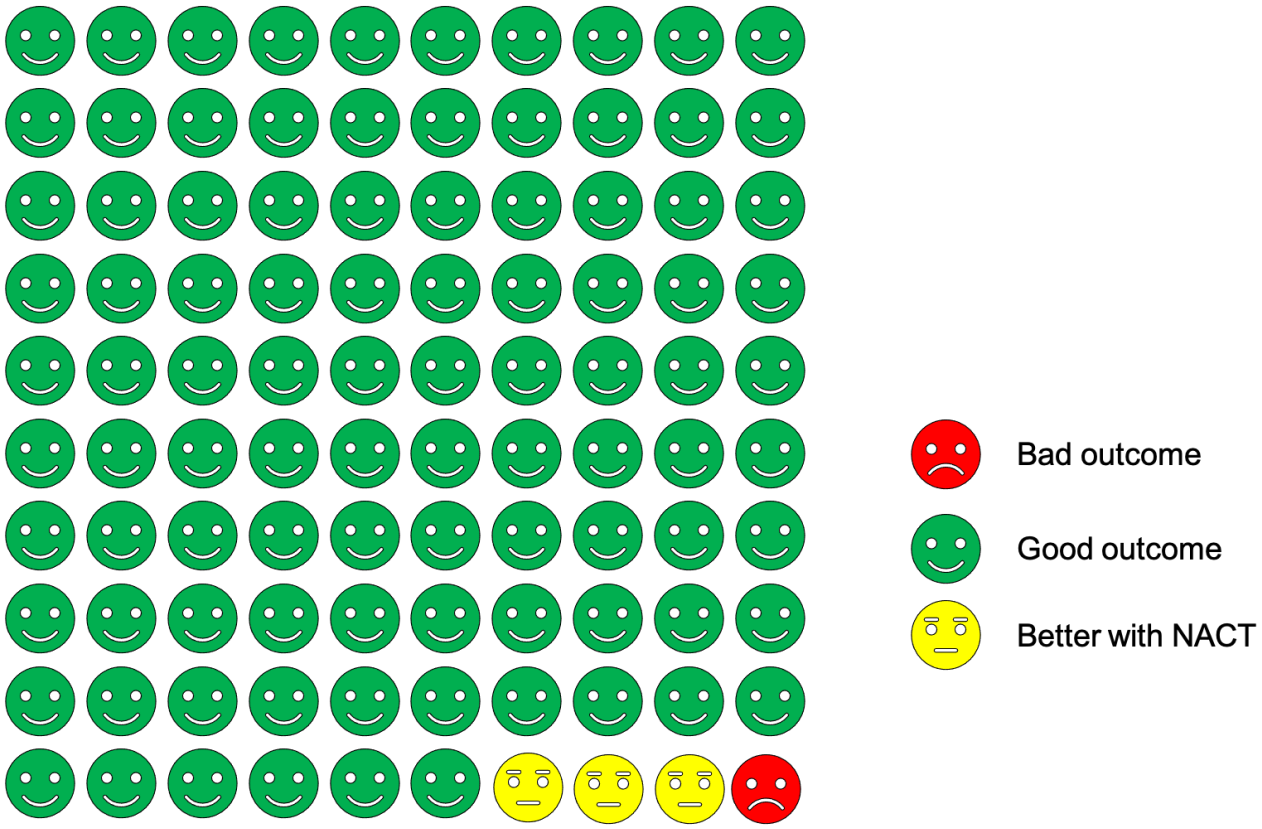
Bowel resection (Analysis 1.6.16)

Women were probably less likely to require a bowel resection (large and small bowel data combined) in the NACT arm versus the PDS arm from data in four studies (Fagotti 2016; Kehoe 2015; Onda 2016; Vergote 2010) (RR 0.49, 95% CI 0.30 to 0.79; participants = 1565; studies = 4; I^2 = 79%; moderate-certainty evidence) (Analysis 1.6.16).

Perioperative/postoperative mortality (Analysis 1.7)

Meta-analysis of five studies (Chekman 2015; Fagotti 2016; Kehoe 2015; Onda 2016; Vergote 2010), assessing the 1625 participants who had surgery, found women in the NACT arm had less risk of perioperative/postoperative mortality than in the PDS arm (Analysis 1.7; RR 0.16, 95% CI 0.06 to 0.46; participants = 1623; studies = 5; I^2 = 0%; high-certainty evidence). Three out of 787 (0.4%) women died within a month of surgery in the NACT arm compared to 26 out of 836 (3.1%) deaths in the PDS arm and, overall, 30/836 (3.6%) due to postoperative complications. There were an additional four deaths in Fagotti 2016 due to postoperative complications in women who survived more than 30 days after surgery, although these deaths were directly related to surgery. Overall, postoperative mortality was therefore 3.6% (30/836) in the PDS group versus 0.4% (3/787) in the NACT group (Analysis 1.7 and Figure 9).

Figure 9. In the PDS group 36 people out of 1000 died in the post-operative period compared to 6 (95% CI 2 to 17) out of 1000 for the NACT group. Green = alive at the end of the post-operative period with PDS/chemo; yellow = additional people who were alive with NACT/IDS; red = people who died in the post-operative period with either NACT/PDS or PDS/chemo.



In Chekman 2015, no deaths were recorded postoperatively (0 to 30 days), but one death was recorded after a second course of neoadjuvant chemotherapy (prior to surgery).

Chemotherapy-related toxicity (Analysis 1.8)

Chemotherapy-specific-related toxicity was not specifically reported in Vergote 2010 as all SAEs were reported together. However, median time to re-start chemotherapy after surgery was 18 days (range 5 to 55) and 19 days (range 0 to 84) in the NACT and PDS groups, respectively. In Fagotti 2016, the median time to start chemotherapy following surgery was lower in the NACT group (NACT = 27 days (range 16 to 37 days) versus PDS = 40 days (range 17 to 120 days); P < 0.0001)) for the initial 110 patient cohort.

Two trials (Kehoe 2015; Onda 2016), assessing 768 participants, found that there may be little or no difference in chemotherapy-related SAEs between arms, although we have low certainty in these results (Analysis 1.8; OR 0.88, 95% CI 0.57 to 1.36, I^2 = 54%; low-certainty evidence).

Quality of life (QoL) (Analyses 1.9 to 1.10)

Three studies (Kehoe 2015; Fagotti 2016; Vergote 2010), assessing 524 participants, reported on QoL at six months using the EORTC QLQ-C30 questionnaire. In two studies, individual symptoms were reported (Fagotti 2016; Vergote 2010). We did not interpret pooled results for individual symptoms due to heterogeneity in results and the summary effects are merely displayed in forest plots to demonstrate the heterogeneity. Results were either inconsistent or there did not appear to be any differences in QoL measures in individual domains between arms. The global health domain was the only domain to demonstrate a numerically significant difference between arms, but the magnitude of the difference was so small, it would be very unlikely to be clinically meaningful. Vergote 2010 and Kehoe 2015 also reported QoL at 12 months with similar results, but due to the high dropout rate, especially by 12 months, these results were of very low-certainty and should be interpreted with caution (Analysis 1.9; Analysis 1.10). Previously, the Kehoe 2015 results were reported separately, due to uncertainty in which QoL data were reported in the original paper. However, following clarification, we have been able to amalgamate these data. Further data from Kehoe 2015 for individual QoL parameters are awaited and it may be possible to combine further QoL data in future updates.

Duration of operation

Mean operating times in Chekman 2015 were 233 minutes (range 69 minutes to 360 minutes) and 273 minutes (range 144 minutes to 480 minutes) in the NACT and PDS groups, respectively. Mean operating times in the Fagotti 2016 study for IDS after NACT and PDS were 253.2 minutes (SD = 101.4) and 460.6 minutes (SD = 102.6), respectively.

In Vergote 2010, the median operating times were 180 minutes (range 30 minutes to 560 minutes) and 165 minutes (range 10 minutes to 720 minutes) in the IDS and PDS arms, respectively. Kehoe 2015 reported that the median operation time was 120 minutes in both groups (interquartiles ranges were 80 to 161 and 90 to 155 in the PDS and NACT arms, respectively; the overall range was 12 to 450 mins). Onda 2016 found that median operating time, when accounting for the main procedure only (not counting an additional debulking procedure in the PDS group) was 302 minutes in the NACT group and 240 minutes in the PDS group (P < 0.001). However, if the subsequent operative procedures were accounted for in both groups, median operating times were 270 minutes and 347 minutes in the NACT and PDS groups, respectively (P < 0.001). Due to disparities in the data collected, we are not able to combine these in a meta-analysis.

Length of stay following surgery

Fagotti 2016 reported mean length of hospital stay; in the NACT group, the mean was 6.7 days (SD = 3.9 days) and 14.8 days (SD = 11.3) in the PDS group (P < 0.001). In Kehoe 2015, length of stay was provided as follows: "fewer women were discharged from hospital within 14 days after surgery in the primary-surgery group compared with primary chemotherapy (198/249, 80% versus 197/211, 93%, P < 0·0001)". Data were not amenable to meta-analysis. These data were not available for Chekman 2015, Onda 2016 or Vergote 2010.

DISCUSSION

Summary of main results

We found five studies that met the inclusion criteria, including a total of 1774 randomised participants. One trial (Chekman 2015) was only available in abstract form (further details were provided by the trial author on request) and contributed to less than 5% of all participants included in the review. We found little or no difference in survival outcomes in women with stage IIIc/IV ovarian cancer who were treated with neoadjuvant chemotherapy (NACT) plus interval debulking surgery (IDS) compared with primary debulking surgery (PDS) plus chemotherapy. Surgically-related morbidity (grade 3/4) was probably higher in the PDS group (such as haemorrhagic, infective and thromboembolic adverse effects). NACT prior to surgery reduces postoperative deaths and the need for stoma formation by two-thirds and probably reduces the need for bowel resection by half. Quality of life (QoL) outcomes were poorly and incompletely reported and results were inconsistent in trials that reported this outcome. Choice of surgical treatment is likely to be dictated by clinical factors in and preferences of the patient, clinician training and surgeon preference.

Overall completeness and applicability of evidence

In a previous version of this review, the evidence for the non-inferiority of NACT versus PDS for advanced ovarian cancer was not widely applicable, as only participants with stage IIIc/IV ovarian tumours (extra-pelvic disease larger than 2 cm) were included in Vergote 2010, and the majority of participants had extensive disease (metastatic lesions larger than 10 cm were present in 61.6% of women)(Morrison 2012). In the subgroup of women with preoperative 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) (Vergote 2010 Supplementary appendix). Furthermore, when sub-grouped by FIGO stage, women with stage IV disease may have a survival advantage with NACT than with PDS although due to inconsistency between studies this should be interpreted with caution (HR 0.88, 95% CI 0.69 to 1.14; participants = 391; studies = 3)).

This update, with the addition of overall survival data, includes data from four studies with differing patient inclusion criteria, so the evidence for non-inferiority of NACT-IDS is more widely applicable.

Meta-analysis of four studies (Fagotti 2016; Kehoe 2015; Onda 2016; Vergote 2010), assessing 1692 participants, produced a hazard ratio of (HR 0.96, 95% CI 0.86 to 1.08), therefore there is high-certainty evidence for little or no difference in OS between NACT and PDS for initial treatment in advanced ovarian cancer, based on the relatively heterogeneous populations included in these studies.

Meta-analysis of four trials found moderate-certainty evidence for little or no difference in risk of disease progression between NACT and PDS for initial treatment in advanced ovarian cancer (HR 0.98, 95% CI 0.88 to 1.08; participants = 1692; studies = 4).

The QoL data analysis of variance, adjusted for baseline scores, showed that there may or may not be a difference in scores between NACT and PDS at six months (MD -0.29, 95% CI -2.77 to 2.20; participants = 524; studies = 3; I^2 = 81%)). However, we are very uncertain of these data and it is unlikely that there is a clinically meaningful difference. By 12 months we are even less certain of the data, due to high numbers of women dropping out, most likely due to disease progression.

The smaller studies of Onda 2016 (301 women) and Fagotti 2016 (171 women) published perioperative morbidity data initially. Updated survival data were published for both of these studies in 2020, including a larger cohort in Fagotti 2016 than in the initial cohort.

Heterogeneity of disease burden and treatments between studies

One of the criticisms of the Vergote 2010 and Kehoe 2015 studies has been that the macroscopic cytoreduction rates for both arms were lower than those reported in retrospective cohort studies. However, Vergote 2010 and Kehoe 2015 both included women with extensive disease: ~70% of women in each arm with metastatic deposits measuring > 5 cm, and a quarter of all participants had stage IV disease (Vergote 2010 specifically excluded stage IIIc disease based on para-aortic or pelvic lymph node metastases unless para-aortic lymph nodes larger than 2 cm). In Vergote 2010, 61% in the PDS arm had individual metastatic deposits larger than 10 cm (74% larger than 5 cm). Ten women in the PDS arm and 19 in the NAC/IDS arm were unable to receive either study treatment in Kehoe 2015 due to disease burden. This is similar to Onda 2016 where almost a third of women had stage IV disease. This is likely to represent the surgical equipoise at that time, so women with more bulky disease, thought to be less likely to be optimally debulked, were entered into the studies and women with disease thought amenable to surgery were not enrolled. This contrasts with Fagotti 2016 where much fewer women had stage IV disease (13 women (15.5%) women in the PDS arm versus eight women (9.2%) in the NACT/IDS arm). Additionally, in Fagotti 2016 women were only included, if they were deemed optimally debulkable (residual tumour < 1 cm) at laparoscopy, resulting in 130 of 240 women who underwent a staging laparoscopy being excluded from randomisation in the initial cohort of 110 patients (15 procedures

aborted due to too extensive disease for laparoscopy; 69 were excluded because of a PI score <8; 31 excluded due to a PI score > 12 or 31 who had presence of mesenteric retraction; and a further 15 found not to have epithelial ovarian/fallopian/peritoneal cancer). Women in Fagotti 2016 were also younger than those in the other three studies (PDS arm mean age 54.8 years (n = 84; SD = 9.7) versus 56.2 years (n = 87; SD = 10.7) in NACT arm). This study is therefore not representative of the many women with ovarian cancer, which limits its applicability when examined in isolation.

In the Japanese multi-centre Onda 2016 study, of 147 women who underwent PDS, optimal debulking was achieved in 37%. More than a third of women in the PDS arm underwent an additional attempt at cytoreductive surgery (additional debulking surgery (ADS)), despite maximal surgical effort at initial surgery, taking the total optimal debulking proportion (<1 cm residual disease) to 63% in the PDS arm (PDS + ADS after four cycles of chemotherapy). This is a significant amount of additional treatment in the PDS arm compared to the NACT/IDS arm and puts the study at high risk of performance bias, since these women received additional treatment compared to those in the NACT arm, which was selectively delivered, as the study participants and personnel were not blinded. A proportion of women in the Onda 2016 and Vergote 2010 studies underwent PDS and ADS (37% and 17%, respectively) (after four cycles of chemotherapy in Onda 2016 and six cycles in Vergote 2010). Kehoe 2015 also allowed for ADS after PDS, if incompletely debulked at PDS, but we have been unable to determine if any in the PDS arm underwent further ADS, and it would appear that none did. It would be expected that women in the PDS arm who underwent primary and ADS, to leave a lower volume of residual disease, should have superior outcomes to those women who had NACT-IDS, if surgical effort is the only determinant of survival; this does not seem to be the case from these RCT-level data.

The Fagotti 2016 trial was a mono-centric trial which only randomised women to the trial once they had undergone a staging laparoscopy that produced a predictive index score of disease burden of between ≥ 8 or ≤ 12, predictive of achieving optimal cytoreduction (Vizzielli 2014). If women were deemed as not able to have optimal cytoreduction, they were not eligible for randomisation. Not surprisingly, the macroscopic debulking rates achieved in the Fagotti 2016 study were higher than those of the other studies in the review; 90.9% of women in the PDS arm achieved optimal debulking to < 1 cm of residual disease (45.5% macroscopically debulked) compared with 90.4% in the NACT-IDS arm (57.7% macroscopically debulked). The improved median overall survival of up to 43 months in Fagotti 2016, in comparison with 27 months from the individual patient meta-analysis of the EORTC and CHORUS trial (Vergote 2018) represents differences in age, disease burden and additional chemotherapy agents (notably bevacizumab and Poly (ADP-ribose) polymerase (PARP) inhibitors). This is pertinent as the Vergote 2010 study, in further analyses (Van Meurs 2013) found that NACT particularly benefited women with stage IV disease with individual metastatic deposits of ≥ 4.5 cm, whereas PDS may be preferable for those with stage IIIc disease and individual metastatic deposits <4.5 cm. In women with either stage IIIc disease with larger metastatic deposits (≥4.5 cm) and those with stage IV disease and smaller volume metastatic disease (<4.5 cm) PDS and NACT were similarly effective. The more general applicability of the Fagotti 2016 trial is therefore compromised by selecting only those who are deemed as having the potential for optimal debulking rather than all-comers. Additionally, although complete debulking to no residual disease is associated with a survival advantage, given that, to date, there has been no RCT comparing PDS or NACT followed by IDS to chemotherapy alone, by not attempting any surgical treatment on the subset of women who had very bulky disease it is unclear if any differences in OS or PFS would have been apparent, if they had been included in the trial. Excluding women with a predictive index (PI) score of ≥12 therefore may have prevented those women who may have most benefited from NACT-IDS from inclusion in the study. It is therefore interesting that, despite differences in patient selection and subsequent treatment between the studies, findings were largely similar between the studies. This adds to the applicability of these findings.

Quality of the evidence

We consider the current evidence for primary outcomes of overall and progression-free survival to be of high to moderate-certainty. Further research may have an 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 and adverse events to be of high to low-certainty, downgraded due to risk of bias and a small number of events and further research may change these estimates. QoL outcomes provided very low-certainty evidence, mainly due to inconsistency, imprecision and substantial attrition.

Potential biases in the review process

To our knowledge there are no biases in the review process, other than a potential for bias due to the introduction of subgroup analyses (i.e. stage, age and residual disease) in the last update of the review that were not specified in the original protocol. At the stage this decision was made (first update), there was only one included study. The decision for subgroup analyses was therefore made prior to inclusion of the majority of studies in this version of the review. Specifically, the one author of previous versions of this review who was involved in a study included in this update had no role in screening, decisions about inclusion/exclusion, data extraction or analysis.

We still hope to include data from the Kumar 2009 trial. However, at the time of writing, the investigators had not published their final analyses, despite the trial being scheduled to be completed by 2012. We made the decision to discuss the interim data from this trial in Agreements and disagreements with other studies or reviews rather than as an included trial with incomplete outcomes to avoid potentially biasing the results. Once these data are published along with the results of the other ongoing trials (Mahner 2017; NCT04257786; NCT04515602; SUNNY), we plan to update the review.

Agreements and disagreements with other studies or reviews

Other studies

Investigators of the ongoing study Kumar 2009, have presented interim results (at the ACSO conferences in 2006 and 2007) despite the trial being scheduled for completion in 2012. Preliminary data from Kumar 2009 appear to corroborate the findings of the other included studies in this review. 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 versus NACT). Blood loss, perioperative mortality, postoperative 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 and again in January 2019) that this trial is now closed, that new analyses are being undertaken and that data will be presented in manuscript form soon. 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).

The study by Kumari 2020 was a prospective pilot RCT conducted in India (Jan 2012-Dec 2013) comparing early IDS after three cycles of NACT (control arm) with late IDS after six cycles of NACT (experimental arm). The study recruited 30 women with advanced ovarian epithelial cancer, the hypothesis being that late IDS would improve optimal cytoreduction rates. Optimal cytoreduction (defined as <1 cm deposits residual disease) was achieved more frequently in the late IDS arm (60%) compared to the early IDS arm (23%) (Odds ratio 10.5; P=0.01). Delivering six cycles of NACT before IDS increased the likelihood of achieving optimal cytoreduction, by a factor of 10, compared to early IDS. No other factor was associated with cytoreduction rate (CA125 / tumour size / age / performance status). However, women in the late IDS arm had a median of nine cycles of chemotherapy compared to a median of 6 cycles in the early IDS arm (P=0.0041), due to women in the late IDS arm having further chemotherapy following surgery.. Although at major risk of performance bias, this is a useful study, especially in the context of the COVID-19 pandemic when surgery has been delayed due to COVID-19 infection risk and limited access to operating theatres and ITU beds for major debulking procedures. It suggests there is still value in offering IDS to women who haven't been able to have surgery after 3 cycles.

Per-protocol pooled analysis of individual women data from two of the included studies

One study pooled longer-term survival data from women in the Kehoe 2015 and Vergote 2010 studies (Vergote 2018). We included this study as an additional reference to both of the studies from whom women were included. This was a pre-planned analysis prior to the launch of the Kehoe 2015 study. A total of 1220 women were included in the per-protocol pooled analysis (670 from Vergote 2010 and 550 from the Kehoe 2015), of whom 612 women received PDS and 608 NACT. Median follow-up was 7·6 years. When women from both studies were combined there was little or no difference in OS between the NACT and PDS groups (HR 0·97, 95% CI 0·86 to 1·09; P = 0·586). However, women with stage IV disease may have better OS and PFS outcomes with NACT versus PDS (OS HR 0·76, 95% CI 0·58 to 1·00; P = 0·048; PFS HR 0·77, 95% CI 0·59 to 1·00; P = 0·049). They concluded that when choosing between treatment strategies with women at diagnosis "one should account not only for the risk of perioperative morbidity and the possibility of debulking the women's disease to zero residual tumour, but also for FIGO stage and the extent of metastatic disease at presentation." They concluded that NACT, followed by IDS, should be standard of care in women with stage IV disease, with PDS reserved for "exceptional circumstances with easily resectable disease".

Systematic reviews

Systematic reviews of RCTs

A meta-analysis by Dai-yuan 2013 examining the role of IDS in ovarian cancer, combined the RCTs of Vergote 2010 and Rose 2004. However, the Rose 2004 study randomised women who had undergone PDS and three cycles of chemotherapy to undergo a further interval debulking surgery prior to completing three further cycles of chemotherapy or to complete three further cycles of chemotherapy without further IDS. Therefore, this meta-analysis did not compare the timing of chemotherapy in relation to surgery alone. There may also be some irregularities in the data extraction, as the authors state they were extracting data on atrial fibrillation duration, left ventricular size, ejection fraction and sinus rhythm maintenance without anti-arrhythmic drugs (which were not in the original study). The meta-analysis produced similar HRs to this review, despite using a fixed-effect model, as opposed to the random-effects model used in this review. HR for OS 0.98 (95% CI 0.85 to 1.14) and HR for PFS 1.03 (95% CI 0.91 to 1.16).

A systematic review by Yang 2017 included the same four studies (Fagotti 2016; Kehoe 2015; Onda 2016; Vergote 2010) as this review in their meta-analysis of serious adverse event and QoL data, but not survival data. They showed that the NACT group had lower risks of grade 3/4 infections (RR 0.30 95% CI 0.16 to 0.56), gastrointestinal (GI) fistulae (RR 0.24 95% CI 0.06 to 0.95) risk of any grade 3 or 4 event (RR 0.29 95% CI 0.11 to 0.78), and a lower rate of death within 28 days (RR 0.14 95% CI 0.04 to 0.49), although with a similar risk of blood transfusion (RR 0.60 95% CI 0.28 to 1.29). These findings are very similar to this review. Yang 2017 also found that the QoL data favoured the NACT group at the six months follow-up point. The likelihood of achieving a macroscopic debulk was higher in the NACT group (macroscopic debulk RR 1.95 95% CI 1.33-2.87; optimal debulk (< 1 cm) = RR 1.61 95% CI 1.05 to 2.47).

Systematic reviews of RCTs and non-randomised studies

A systematic review and meta-analysis by Xiao 2018 combined Vergote 2010 with nine cohort studies and two case-control studies. They calculated a median OS of 32 months with NACT and 37 months with PDS and a median PFS of 15 months with NACT and 15 months with PDS. Given the inclusion of observational studies in this review, there is likely to be critical risk of selection bias in the NACT group, as the NACT group contained older women with more co-morbidities, poorer performance status, higher CA125 at presentation and later FIGO stage, compared to the PDS group. This review also supported a higher optimal debulking rate achieved with NACT compared to PDS (despite more advanced disease in the NACT group) but, unsurprisingly given the imbalance between the groups, no survival benefit was conferred. The odds ratios produced for serious adverse events were in favour of NACT, although only major infection rates, wound complications and vascular events reached statistical significance.

A meta-analysis by Qin 2018 combined Kehoe 2015 and Vergote 2010 with 22 observational studies: 21 retrospective cohorts and one case-control study. The fixed-effect meta-analysis combining Kehoe 2015 and Vergote 2010 produced an HR for OS of 0.93 (95% CI 0.81 to 1.06) and an HR for PFS of 0.97 (95% CI 0.86 to 1.09), suggesting little or no difference between the two groups, similar to the findings of this review. Further, in keeping with the findings of this review, the risks of some serious adverse events (venous thromboembolism (VTE) , infection and GI events) were

lower in the NACT group. In addition, NACT was associated with a shorter stay in the intensive therapy unit (ITU) and overall shorter hospital stay compared to PDS. There was no difference found in risk of haemorrhage between the two groups. They included data from a trial by Melis 2016 , but this study has subsequently been withdrawn from publication calling into question its validity. As with our review and the reviews discussed below, the rates of optimal debulking were higher in the NACT group, but did not confer a survival advantage.

A meta-analysis by Zeng 2016 combined four RCTs, but like Daiyuan 2013 included different treatment strategies in the NACT/IDS arm: PDS versus NACT/IDS followed by completion chemotherapy (Kehoe 2015; Vergote 2010); PDS followed by chemotherapy with randomisation to either further cytoreductive surgery (ADS) (if progressive disease ruled out) and completion chemotherapy or completion chemotherapy alone (Rose 2004 and Van der Burg 1995). This meta-analysis produced HR for OS 0.94 (95% CI 0.81 to 1.08) and HR for PFS 0.89 (95% CI 0.77 to 1.03). As one would expect, there were high levels of heterogeneity between the studies included. This review also found that NACT favoured being able to achieve optimal cytoreduction (RR = 1.76 (95% CI 1.59 to 1.98)), but again did not confer a survival benefit.

Economic analyses

We did not specifically perform a search for articles examining the health economic effect of PDS versus NAC. However, our search found five studies which compared the approaches in a variety of settings. We will therefore discuss their results as a brief economic commentary and consider a formal economic analysis in future updates of this review.

Cost-effectiveness analyses based on non-randomised cohorts

Poonawalla 2015 identified a cohort of elderly women 65 years of age from the Surveillance, Epidemiology and End-results (SEER) Medicare-linked database in the USA from January 2000 to December 2009. These data are therefore not based on clinically equivalent groups in an RCT-setting, although propensity score was used to correct for differences in baseline characteristics. Costs of care from diagnosis to death or last Medicare claim were estimated, using the phase of care approach, and compared to years of survival to calculate the incremental cost-effectiveness-ratio (ICER). The authors calculated that the average life-time costs of NACT was $17,417 based on 2010 costs (estimated 2021 equivalent values of $21,007/€17,629/£15,109) more than PDS, and that the ICER was $174,173 (estimated 2021 equivalent values of $210,083/€176313/£151,101) due to the 0.1 incremental life-year gained from the NACT approach. Stratifying the women between high and low risk, the ICER for high-risk women was $42,988 per life-year saved (estimated 2021 equivalent values of $51,851/€43,516/£37,299), which met their threshold for cost-effectiveness. High-risk participants were those women known to have worse postoperative outcomes (those >75 years of age with stage 4 disease or those >75 years of age with stage 3 disease and co-morbidity score >/=1) and it was in this group that NACT was deemed cost-effective.

In another study, also from the SEER-Medicare database (1992 to 2009) Forde 2015 estimated the seven-month cost of care following PDS and NCACT for advanced ovarian cancer in women > 65 years of age. Of 4506 women, 82.4% received PDS and 17.6% NACT. Women with stage IV disease were more likely to have NACT. The authors found little or no difference in costs of care for women with stage IIIC disease between PDS and NACT. However, costs for those with stage IV disease were higher in those who had PDS (12% difference; $63,131 for PDS versus $55,302 for NACT; P < 0.0001. Costs were based on 2010 data and this difference of $7828 has an estimated 2021 values of $9441/€7925/£6791. Five-year OS in this non-randomised population was lower in the NACT group for both stage IIIC and IV (stage IIIC HR = 1.27, 95% CI 1.10 to 1.47; stage IV HR = 1.19, 95% CI 1.03 to 1.37).

Cost-effectiveness analyses modelled from RCT data

Rowland 2015 evaluated the cost implications of NACT versus PDS, limiting their analysis to those over 65 years of age. The authors modelled their analyses based on subgroup analyses, based on age, from Vergote 2010. They concluded that NACT was cost-saving compared to PDS in women over 65 years of age and that, assuming equal survival, NACT produced cost savings of $5616 based on 2010 USA Medicare reimbursement rates at that time (calculated as equivalent to $6773/€5685/£4871 in 2021).

A later cost-effectiveness study (Tran 2018) used data from all four studies included in our meta-analysis (Fagotti 2016; Kehoe 2015; Onda 2016; Vergote 2010) to model costs of NACT versus PDS, based on a hypothetical cohort of women aged 65 years with advanced epithelial ovarian cancer (EOC) of median baseline characteristics for women in the USA. They based costs on 2015 providers' fees for Medicare and Medicaid Services, taking into account both surgical and chemotherapy adverse events. They estimated that NACT costs $20,762 per woman compared with $27,796 for PDS, saving $7,034 per woman in the seven-month post-treatment time horizon (calculated as equivalent to $7805/€6549/£5613 in 2021). However, these data are affected by the relatively low macroscopic and optimal (< 1 cm residual disease) debulking rates in the RCTs used for the model.

The same team (Cole 2018) modelled costs of NACT and PDS based on the more aggressive surgical paradigm employed in Fagotti 2016. They based their model on a hypothetical annual cohort of 15,000 women in the USA with advanced ovarian cancer over a one-year time horizon based on US Medicare fee schedules and Hospital Cost and Utilization Project inflation adjusted to 2015. The authors based their calculations on the event rates in those randomised within Fagotti 2016 (not including those who underwent laparoscopy but were excluded from the study), thereby representing a cohort with less bulky disease than the other three studies (Kehoe 2015; Onda 2016; Vergote 2010). They found that NACT was associated with an estimated $142 million costs savings (calculated as equivalent to $157.6 million/€132 million/£113 million in 2021) based on the 15,000 women cohort. There were estimated to be 1098 fewer ovarian cancer related deaths, 1355 additional life-years and 1715 additional quality-adjusted life years (QALYs). NACT was associated with a predicted cost saving of $9452 per woman (calculated as equivalent to $10488/€8796/£7537 in 2021) and a 7.3% lower risk of postoperative death. These data may change now that OS data are available from Fagotti 2016, but have not been updated as yet.

Higher surgical complexity and higher optimal debulking rates are, as demonstrated, likely to widen the difference in costs, since those in the PDS arm require more complex surgery to achieve debulking, from the published RCT data. Re-calculating the costs and cost-effectiveness/QALY now that there are OS data

from Fagotti 2016 and the ongoing/unpublished studies, with higher macroscopic debulking rates and complexity, will be of great interest.

Other reviews

Many review articles and non-randomised cohort studies have been published on this subject, many representing single-institution cohorts and including criticisms of the studies included in this review. Many of these studies are at critical risk of selection bias, especially as many do not examine all patients within a population, including those not fit for surgery initially, and so are likely to over-estimate the benefits of upfront surgery (e.g. Mueller 2016). This emphasises the importance of to focusing on what is known from randomised data, where attempts have been made to limit these significant risks of bias. The reader is referred to the literature, since an in-depth narrative review of non-randomised studies is outside of the scope of this review.

Vergote 2010 performed post hoc multivariate analyses on their data. Achievement of macroscopic debulking 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 a review by Du Bois 2009 and other non-randomised studies.

Vergote 2011b went on to review the results of their Vergote 2010 study, discussing their results in context with other studies (including Rose 2004 and Van der Burg 1995) and their implications for practice. They recommended selection criteria for utilising NACT in stage IIIc/IV disease. These are the Leuven selection criteria for women when considering 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 include ~50% of women with stage IIIc and IV disease in an otherwise unselected population. While agreeing that surgical skills are important, the authors stressed that radicality of surgery should be tailored to the general condition and extent of disease of the women, in order to decrease postoperative morbidity and mortality.

A non-systematic review/opinion piece by Schorge 2014 (interestingly entitled "Primary debulking surgery for advanced ovarian cancer: are you a believer or a dissenter?") argued that the decision about when to operate involves finely balancing an appropriately aggressive surgical technique to achieve macroscopic debulking whilst trying to avoid unnecessary morbidity. They state that data show that women benefit from a single maximal debulking effort, but the timing of that effort remains controversial. As the greatest survival benefit is associated with no macroscopic residual disease after surgery, the ability to assess preoperatively which women are most likely to by effectively cytoreduced, by triaging to either PDS or NACT-IDS, involves many complex factors. These factors include the woman's existing co-morbidities, her current physical condition, the surgical team, preoperative imaging and discussion and decision making between the multi-disciplinary team (MDT) and the woman.

The authors conclude that women who appear to benefit the most from PDS are those with stage IIIA or IIIB disease (excluded from the largest studies of Kehoe 2015 and Vergote 2010), those with stage IIIC and a Fagotti laparoscopic predicative index (PI) score of < 8 (Fagotti 2006; Fagotti 2013; Vizzielli 2014), or those with stage IIIC with promising MDT imaging review at an 'expert' centre routinely able to incorporate ultra-radical procedures. In contrast those women who appear to benefit the most from NACT-IDS are women with stage IIIC disease that is too extensive to be optimally debulked, based on imaging and/or laparoscopic scoring, women with stage IV disease, women with a performance status too poor to undergo an attempt at PDS or women without access to an experienced ovarian cancer surgical team, or elderly or morbidly obese women when ultra-radical procedures appear necessary.

A recent study (Havrilesky 2019) investigated patient preferences for attributes of PDS versus NACT for treatment of newly diagnosed ovarian cancer using a survey, educational video and discrete choice experiment activities. Overall the 101 participants preferred better clinical outcomes, less extensive surgery, lower surgical mortality risks, lower risks of readmission and longer PFS and OS. OS ranked the most important factor for consideration, followed by complications requiring readmission, PFS, surgical mortality, extent of surgery and lastly treatment order. Participants would tolerate higher risks of operative morbidity and mortality to gain more substantial survival outcomes (6 months). Conversely, participants were also willing to accept a reduction in survival outcomes (a 11-month reduction in PFS(95% CI 5 to 19 months) and a 7-month reduction in OS (95% CI 2 to 12 months)) to achieve a reduction in risk of surgical mortality. Limitations of this study were that 95% of participants had already received chemotherapy, a third were currently receiving chemotherapy and a third of all participants had recurrent disease. As the participants were not treatment naïve their previous experiences may have impacted on their perception of and tolerance for treatment risks versus survival advantages gained.

A review by Sato 2014 argues that there may be a difference in the assessment of the degree of macroscopic debulking achieved following PDS or NACT-IDS. As NACT-IDS is associated with tissue fibrosis and adhesions induced by chemotherapy, interpretation of tumour spread within the peritoneal cavity may be compromised. Incomplete tumour resection after NACT-IDS may occur, if perioperative evaluation of tumour spread is incorrect and therefore incomplete resection of potentially resectable areas may occur. The authors argue that microscopically carcinomatous areas have a benign appearance more often after NACT than at primary surgery. The authors highlighted that at present the optimal number of chemotherapy cycles in the NACT-IDS setting is unknown.

Based on the currently available data there has been a shift to offering NACT in some treatment settings. A retrospective national cohort study by Wright 2014 reviewed US SEER data from 1991 to 2007 for women with stage II-IV ovarian cancer. Using regression

analysis to adjust for effects of confounding variables on outcome and propensity score analysis to estimate the probability that a woman would undergo a given intervention, they performed a stratified analysis on women who lived longer than six months and underwent both surgery and chemotherapy in 'high volume' centres. This was defined as a hospital referral region that had more than 25 women attend for cancer-directed therapy, either surgery or chemotherapy over the 16-year period. In the initial observational analysis of 5345 (55.8%) women underwent PDS and 2238 (23.8%) underwent NACT, the remainder had no treatment.

The percentage of women undergoing NACT-IDS increased from 19.7% in 1991 to 31.8% in 2007, with a concomitant decrease in PDS from 63.2% in 1991 to 49.5% in 2007. Women most likely to receive NACT-IDS were older, recently diagnosed (i.e. in the 2000s not 1990s), have serous histology, live in metropolitan areas, have stage III or IV disease and have a Charlson co-morbidity score of 1. The substantial imbalance between treatment groups suggests strong selection bias in the cohort and there were strong associations between area of residence in the USA and primary treatment received. An instrumental variable analysis was performed to assess for geographic variation in treatment pattern (the difference in the expected rates of NACT use and the observed rates of NACT use). Once this instrumental variable analysis was performed, the primary treatment chosen had minimal effect on cancer-specific survival (HR 0.94, 95% CI 0.58 to 1.52) or OS (HR 1.04, % CI 0.67 to 1.60). When the observational cohort and propensity-scored cohort survival data were calculated this favoured PDS (HR 1.27 (95% CI 1.19 to 1.35) and HR 1.24 (95% CI 1.1.5 to 1.34), respectively). The authors concluded that in the subset of women who have both surgery and chemotherapy (regardless of total cycles completed), there is no evidence of a difference in survival regardless of timing of surgery. The median OS in the propensity-scored cohort was 27.2 months in the PDS group and 21 months in the NACT-IDS group, not hugely dissimilar to Vergote 2010 data of 30 months in the NACT-IDS group and 29 months in the PDS group, emphasising the applicability of the RCT data included in this review. The authors acknowledge that excluding women who survived less than six months from the analysis may have biased survival estimates.

A retrospective cohort Rauh-Hain 2017 of women less than 70 years of age without co-morbidities from the National Cancer Database in the USA found 22,962 women had been treated for stage III or IV ovarian cancer between 2003 to 2011. Of these, 3126 women had undergone NACT, with or without subsequent IDS. Using propensity scoring, the authors matched each woman in the NACT group with a woman in the PDS group, controlling for age, year at diagnosis, race, ethnicity, treating facility type, insurance status, stage, histological subtype and grade. The authors compared OS in 2935 matched pairs from the retrospective cohort. Once matched they calculated an OS HR of 1.18 (95% CI 1.11 to 1.26), an 18% higher hazard of death (all-cause mortality) in the NACT group. Although the authors compared the matched pairs on an intention-to-treat basis (women who underwent PDS but never received chemotherapy and women who underwent NACT but never underwent IDS were included) 26% of the NACT group never received surgery implying that either they were not fit enough to undergo surgery or their disease progressed on chemotherapy. As with any observational cohort data there is selection bias in the NACT cohort, as we do not know why treatment decision were made. Prior to the propensity scoring, the NACT group were known to be significantly older and less likely to have stage III disease in comparison with the PDS group. They noted that on sensitivity analysis, "lower survival in women who received NACT could be explained by a higher prevalence of limited performance status in women undergoing NACT". Propensity scoring attempts to reduce selection bias in observational studies, but there may well be other unidentified confounding variables that are present in the NACT group to account for the lower survival figures.

A Korean retrospective (2006 to 2014) cohort review of 435 consecutive women operated on in one centre looked at morbidity and survival differences after a paradigm shift in practice in 2010 to utilise more NACT-IDS (Lee 2018). The authors split the cohort into two groups. Group 1 were women operated on between 2006 to 2010. In this group 181 women (83.3%) underwent PDS and 35 women underwent NACT-IDS (16.2%). Group 2 consisted of women who were operated on between 2011 to 2014 during which time 112 women (51.1%) underwent PDS and 107 (48.9%) underwent NACT-IDS. The paradigm shift involved women being treated with NACT-IDS if they fulfilled one of three considerations: (1) pulmonary or liver parenchymal metastases visible on preoperative imaging; (2) medically inoperable due to co-morbidities; (3) optimal cytoreduction was deemed infeasible due to high tumour burden, as defined by a Fagotti PI score of > 8 at diagnostic laparoscopy. This is in contrast to the Fagotti 2016 study, which included women if the PI score was between 8 and 12. The two groups differed substantially in their baseline characteristics. Group 2 contained significantly more women with stage IV disease, ASA score 2, 3 and 4, higher median CA 125 levels and underwent > six cycles of chemotherapy. Intra-peritoneal chemotherapy was utilised in 13% of group 1 women but none of the women in group 2. The progression-free survival in group 2 compared to group 1 was HR 1.01 (95% CI 0.75 to 1.37) and overall survival HR 0.93 (95% CI 0.63 to 1.36) with no differences in survival despite the increased use of NACT in group 2. The shift to increased use of NACT was also associated with increased rates of achieving a macroscopic debulk (G1 = 10.2%; G2 = 21.5%) without increasing perioperative morbidity and mortality. The rates of performing more complex surgical procedures also increased in group 2 (G1 = 35.6%; G2 = 57.5%) with no change in perioperative morbidity between the two groups. The authors conclude that the use of NACT did not improve the survival rate, however, there were no survival differences between the groups after increased use of NACT, despite the women in group 2 having more stage IV disease, more co-morbidities and more extensive surgery than those women in group 1.

Melamed 2018 conducted a quasi-experimental fuzzy regression discontinuity design (Fuzzy RDD) and cross-sectional analysis comparing five regions in the USA. Two regions (New England and East South Central - 95 hospitals) had rapidly increased their use of NACT in 2011 to 2012 by 27.3% and 23.3%, respectively. These regions were compared to three control regions (South Atlantic, West North Central and East North Central - 378 hospitals) where rates of NACT use in 2011 to 2012 only increased by 2%. They compared survival outcomes, censored at three years after diagnosis, for 6034 women; 1156 women in the increased NACT regions and 4878 women in the control regions. The natural experiment compared the different regions and a cross-sectional analysis compared the year and percentage of NACT use on survival. In 2013, two out of the three control regions increased their use of NACT, which allowed for further comparison between control regions. All-cause mortality in the increased NACT regions decreased HR 0.81(95% CI 0.71 to 0.94) compared to the control

regions, which saw no change in all cause mortality (HR 1.02, 95% CI 0.93 to 1.12). Death rates within 30- and 90-days of surgery also decreased in the regions that had increased NACT (30-day mortality from 3.1% to 1.8% and 90-day mortality from 7.0% to 4.0%), which also differed from the control regions (30-day mortality from 1.9% to 2.2%; and 90-day mortality from 5.0% to 4.3%). The two control regions that went on to increase their use of NACT in 2013 also saw a reduction in mortality hazard compared to the control region that did not increase the use of NACT. The authors concluded that survival increased in the regions with increased use of NACT because NACT decreased surgical morbidity and mortality and that this reduction is greater in clinical practice than that seen in RCTs. They postulated whether PDS might be more extensive in the USA than in countries that have been involved in RCTs comparing PDS and NACT, which might explain the increased survival benefits in their cohort. The authors acknowledged that survival benefits may attenuate after three years, the time point at which their data were censored, compared to RCT data, which censored follow-up at five years. They concluded that not all women will benefit from NACT and that the survival benefit seen has been from increased adoption of NACT, occurring selectively in those women with stage IV disease and older women. They also highlight that the regions that increased their use of NACT had higher baseline perioperative mortality than control regions and speculated whether, in those regions with better than average surgical outcomes, increased use of NACT might not achieve the same increase in survival benefits.

AUTHORS' CONCLUSIONS

Implications for practice

It is of note that the role of NACT versus PDS remains an area of controversy in the gynaecological oncology community, despite four well-conducted studies, with differing inclusion criteria, demonstrating little or no difference in survival outcomes and reduced severe adverse events in those who had NACT. It is an area which often suffers from a distinct lack of equipoise. This is most often directed as criticism of the results of the included studies, largely based on concerns regarding low rates of optional/ macroscopic debulking achieved in Kehoe 2015 and Vergote 2010, especially. Further studies have been set up to specifically address some of these concerns, although it should be noted that the Fagotti 2016 study achieved excellent debulking rates, although with the exclusion of higher risk women, both in terms of age and disease status. This limits the applicability of the Fagotti 2016 data on its own to the wider population of women with advanced ovarian cancer, but strengthens the outcomes and applicability within the context of the meta-analysis.

Current evidence is that a combination of chemotherapy and debulking surgery with maximal tolerable effort, is standard treatment for women with advanced ovarian cancer. The order of these treatment modalities appears to have little or no difference on survival outcomes for the overall population. These data support the role of PDS as treatment for advanced (stage IIIc/ IV) ovarian cancer where achieving a macroscopic debulk can be reasonably expected. NACT may be a reasonable (or preferred) alternative for women with stage IV disease, poor performance status or co-morbidities. Compared to PDS, NACT may increase the rate of macroscopic cytoreduction, but this does not appear to translate into an increase in OS. e know from another RCT that removal of microscopic lymph node disease does not improve survival (Harter 2019). The authors of Fagotti 2016 in their discussion noted that those with macroscopically debulked disease and those with residual disease <1 cm at PDS "have superimposable median progression-free survival". These data suggest that small volume, chemotherapy-sensitive disease deposits are effectively treated by neoadjuvant chemotherapy.

The existing quality of evidence is of high to moderate certainty for survival outcomes and high to low certainty for adverse events and very-low certainty for quality of life (QoL) outcomes. One important outcome for women to consider is that, from these data, NACT reduces the risk by around two-thirds of needing a stoma following the operation (one stoma saved for every seven women who have NACT compared to PDS; number needed to treat for an additional beneficial outcome' (NNTB) = 6.89), which may or may not be reversible later, depending on indication and subsequent response to treatment. NACT also reduces the risk of dying after surgery (3 fewer postoperative death for every 100 women having NACT compared to PDS; NNTB = 30.3); these outcomes were of high certainty.

The Leuven selection criteria (Vergote 2011b; Vergote 2016) may offer a reasonable guide to women selection for PDS versus NACT, although it would be important to validate these criteria in a clinical trial setting.

As far as we are aware, there is, to date, no study that compares NACT/ interval debulking surgery (IDS) with NACT alone, although this review did not specifically search for studies in this area. These data are therefore limited to those patients in whom the intention was to perform IDS after NACT at the outset; we have not examined the role of IDS versus no IDS. However, those with disease refractory to chemotherapy have a very poor prognosis and QoL should be the primary concern in this situation, as they are unlikely to benefit from major surgery. The other patient cohort not addressed by these studies are those who may not have been fit enough to be considered surgical candidates at the outset, but whose performance status may be sufficiently improved by chemotherapy to be considered for IDS.

Interestingly, it would appear that some have misinterpreted retrospective data, which show an association between survival and degree of surgical debulking, as evidence that surgery is not indicated, if a macroscopic debulk is not thought achievable. This has not been tested in an RCT setting and cannot be extrapolated from the available data. A recent non-randomised study (NRS), comparing centres with a different surgical ethos, demonstrates that those who have chemotherapy alone, with no attempt at debulking surgery, do poorly (Hall 2019). A recent audit of ovarian cancer care in England demonstrated significant differences in rates of treatment for ovarian cancer between regions, including rates of surgery and combination of surgery and chemotherapy (http://www.ncin.org.uk/cancer_type_and_topic_specific_work/cancer_type_specific_work/gynaecological_cancer/gynaecological_cancer_hub/ovarian_cancer_audit_feasibility_pilot_outputs).

Importantly, data from the studies included in this review do not support or refute an ultra-radical approach to surgery, as patients in both arms had maximal surgical effort.

Cost-benefit analyses based on models derived from RCT data, suggest that a NACT strategy offers improved cost-effectiveness over a one-year time horizon following initial treatment, although these data will require updating now that OS data are available from all of the included studies in this review.

Implications for research

There are currently four ongoing studies (Mahner 2017; NCT04257786; NCT04515602; SUNNY) and one unpublished RCT (Kumar 2009). Mahner 2017 aims to address the role of ultra-radical primary debulking surgery (to achieve higher rates of macroscopic resection) versus NACT/IDS. The results of these studies will hopefully address questions raised by studies with lower optimal and macroscopic debulking rates.

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. These were poorly and/or incompletely reported across included studies in this review. Data on rates of stoma formation should also be provided, since women worry about this prior to surgery and it is an important outcome for them.

This review does not address the role of NACT/IDS versus chemotherapy only, without IDS (NACT by definition is followed by other treatment). It can be extrapolated from other studies (e.g. Rose 2004; Van der Burg 1995), that NACT/IDS compared to chemotherapy alone is very likely to improve OS in first-line treatment. A Cochrane Review (Tangjitgamol 2010) demonstrated improved survival for women who had IDS following PDS, but only where there was no previous maximal debulking attempt by a gynaecological oncologist. In addition, results from the studies included in this review show a strong association between achievement of optimal debulking and an improved prognosis. However, studies of secondary debulking surgery in a recurrent disease setting have not been so clear cut and demonstrate improved survival outcomes only in women when macroscopic debulking can be achieved, in one study (Du Bois 2017; Du Bois 2020), but not in another (Coleman 2018). An RCT would be needed to address the value of adding IDS to first-line chemotherapy treatment versus chemotherapy alone, but is very unlikely to be thought to be ethical, as non-randomised data strongly support debulking surgery in a primary setting in women who are fit enough to be considered for major surgery (e.g. Hall 2019).

The Leuven selection criteria (Vergote 2011b; Vergote 2016) or similar triage tools to determine which women would be better served by PDS or NACT as first treatment for advanced ovarian cancer need to be validated in a clinical trial setting and prognostic selection criteria examined in a prognostic methods review.

An interesting article from one of our excluded studies (Wenzel 2017), examined the role of a women decision-making tool to help women come to an individual decision regarding intraperitoneal chemotherapy in ovarian cancer. A similar tool to aid shared decision-making for timing of primary surgery in advanced ovarian cancer would be extremely valuable.

As yet there has never been a randomised study to address the role of ultra-radical surgery in ovarian cancer. Data used to support this approach are based on retrospective review of data, often highly selected and at critical risk of bias. It would not be acceptable in a chemotherapy study to demonstrate survival curves divided retrospectively into groups based on initial response to treatment, yet this routinely happens in surgical studies. Furthermore, the argument for well-conducted prospective randomised trials to confirm or refute doctrine in ovarian cancer debulking is supported by the results of the recent LIONS study (Harter 2019). This was an area where a large number of non-randomised studies, including retrospective series, population studies, and re-analysis of prospective trials, reported an improved survival with systematic lymphadenectomy, as discussed in Eisenhauer 2019, which is similar to the evidence used to support ultra-radical surgery. Harter 2019 performed a well-conducted RCT that compared systematic removal of intra-abdominal lymph nodes with removal of clinically enlarged nodes only. Women were required to have had otherwise macroscopic debulking achieved and were randomised once this had been achieved, during surgery, to systematic lymphadenectomy or debulking of enlarged nodes. They demonstrated no survival benefit from the additional surgery (hazard ratio (HR) for death 1.06; 95% confidence interval (CI), 0.83 to 1.34; P = 0.65), and those who had systematic lymphadenectomy had clinically meaningful increases in serious postoperative complications, including repeat laparotomy (12.4% versus. 6.5%; P = 0.01) and higher death rates within 60 days of surgery (3.1% versus. 0.9%; P = 0.049). This study adds weight to the need for well-balanced RCTs to examine the role of surgery. It would be important to include details of all women not included and/or operated on within the study, so that we can compare outcomes at a population level, ascertain how selective the inclusion criteria are for involvement in the study, and how applicable their findings might be to the general population of women with advanced ovarian cancer. Interestingly, data from a cohort study where ultra-radical surgery was introduced at a population level, did not demonstrate improved outcomes (Falconer 2020). The shift to an ultra-radical surgical approach led to an reduction in the proportion of women who had surgery as part of their treatment (10% fewer), presumably because more women were not thought fit enough for an ultra-radical approach. The lead author, Dr. Salehi, Director of ovarian cancer surgery at Karolinska University Hospital, in Stockholm, Sweden, in a podcast discussing the paper (https://soundcloud.com/bmjpodcasts/salehi-outcomes-of-ultra-radical-surgery-in-ovarian-cancerwav) emphasised the need for studies on survival outcomes of ovarian cancer surgery to publish the outcomes including those who have and do not have debulking surgery within a defined population, since otherwise there is a significant risk of over-estimating the benefits of ultra-radical surgery by selecting out those who do less well. Other questions that remain in first-line treatment of advanced ovarian cancer include optimal treatment options in more elderly women, since few women over 70 years of age were included in any of the studies included in this review. This population is ill-served by clinical trials generally and, with an increasingly elderly population in many countries, this is an ever-expanding cohort of women for who we have little evidence to support recommendations for treatment.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Chekman 2015

Study characteristics	
Methods	Randomised trial, conducted in Algeria between 1 June 2008 and 31 April 2014 Single-centre study; single surgeon operated on all women in both groups.
Participants	90 women with FIGO stage IIIc ovarian carcinoma enrolled and underwent surgery. 82 women randomised, 41 to PDS and 41 to IDS The diagnosis of stage IIIC ovarian carcinoma was confirmed by laparoscopy (78 cases) or laparotomy (3 cases) A thoraco-abdomino-pelvic scan and tumour markers CA-125 and CA-19.9
Interventions	Primary complete cytoreduction surgery followed by chemotherapy (G1) or NACT chemotherapy followed by debulking surgery then further chemotherapy (G2) Chemotherapy regimen used was carboplatin ([AUC] 5) + paclitaxel 175 mg/m^2, every 3 weeks 44% of women in the IDS arm had 6 cycles of chemotherapy prior to debulking surgery, 10% had 4 cycles and 15% had 3 cycles. In the PDS arm, 78% of women had 6 cycles of chemotherapy after their surgery.
Outcomes	Rate of debulking to residual disease to nodules <1 cm or complete resection, OS, recurrence-free survival (RFS), morbidity and rate of lumboaortic lymphadenectomy
Notes	The trial was in abstract form only but Professor Chekman kindly provided us with the following information on request: The mean operating time was 254.2 min with (range 69 min to 480 min) PDS (G1); mean operating time 273 min; (range 144 min to 480 min) IDS (G2); mean operating time 233 min; (range 69 min to 360 min)

Chekman 2015 *(Continued)*

Average blood loss:

24 women (29%) were transfused; 13 women (16%) were transfused 1 unit; 9 women (11%) were transfused 2 units; 2 women (2.4%), were transfused 3 units

PDS group: 15 women underwent blood transfusion (18%) versus IDS (G2): 9 women underwent blood transfusion (11%).

There were no postoperative deaths (0 to 30 days)

1 death recorded after the second cycle of NACT

They performed 8 re-operations (9.8%) mainly for abdominal and vascular complications: PDS group (G1) six (7.3%); and IDS group (G2) two (2.4%)

Macroscopic resection was achieved in 30 women: 16 in PDS group (G1); and 14 in IDS group *(G2).*

There were 36 recurrences:

20 women in the PDS group (G1); and 16 women in the IDS group (G2)

Another frequently recurring recurrence was abdominal-pelvic lymph node recurrence with 19.4% of women with evidence of abdomino-pelvic nodal relapse in the total population. This was similar in both groups. The other recurrences were localised, in order of frequency, in the hepatic (n = 6), pulmonary (n = 2), cerebral (n = 1) and inguinal (n = 2) levels (it should be noted that one or more sites may be affected by tumour recurrence).

Isolated biological recurrences (increase in CA-125 without associated radiological evidence) were not recorded.

In this trial, 22% of women had recurred before the first year, 38% between the first and second year, 25% between the second and third year and 13.8% beyond the third year. Thus, most recurrences (86%) were recorded during the first three years and 15% after the third year (time of occurrence of recurrence (P = 0.49)).

There were 24 deaths:

15 in the PDS group (G1); and 9 in the IDS group (G2)

Of the 12 remaining women who had a recurrence and remained alive, 5 were in the PDS group (G1) and 7 were in the IDS group (G2).

The mean PFS was 13.15 months (95% CI 9.19 to 17.10).

In the PDS group (G1), mean PFS was 27.92 months [range 7 to 64] and in the IDS group (G2) mean PFS was 24.72 months [range 11 to 52].

Surgical management of recurrence occurred in 19.4% of cases.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	The randomisation was performed in the operating room by random draw by someone other than the surgeon, once verification of inclusion criteria and resectability under laparoscopy or laparotomy had been confirmed. Histological confirmation of carcinomatosis of ovarian origin was by extemporaneous examination.
Allocation concealment (selection bias)	Unclear risk	Information lacking about the concealment process

Chekman 2015 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study and so some outcomes at high risk of bias
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study and no details of independent blinded assessment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Minimal data provided regarding outcomes; only percentages provided for OS and PFS, no raw numbers, no confidence intervals or statistical calculations provided. Morbidity rate provided but unclear as to what specific morbidities this rate referred to
Selective reporting (reporting bias)	Unclear risk	No information regarding why lumboaortic lymphadenectomy chosen as an outcome. No information regarding what constituted morbidity data
Other bias	Unclear risk	Insufficient information to permit judgement

Fagotti 2016

Study characteristics	
Methods	Single institution (Italy) randomised phase III clinical trial, superiority trial (SCORPION) enrolled 280 women
Participants	Women aged 18 to 75 years with FIGO stage IIIc or IV ovarian, fallopian tube, or primary peritoneal cancer and histological confirmation of diagnosis. Histological sample obtained through staging laparoscopy and high tumour load calculated through laparoscopic predictive index (PI). PI between 8 and 12 without evidence of mesenteric retraction became inclusion criteria to go onto randomisation into the trial arms (110 randomised initially and presented in 2016 reference; additional 61 patients in 2020 update with OS data; total 171 participants).
Interventions	PDS + systemic adjuvant chemotherapy (arm A, standard) or to NACT + ITS (arm B, experimental)
Outcomes	Co-primary outcome measures were PFS and perioperative outcomes (early and late postoperative complications). Secondary outcomes were OS and QoL. 171 patients were randomly assigned to primary debulking surgery (PDS) (n = 84) versus neoadjuvant chemotherapy (NACT) (n = 87). **Mean age (SD);** PDS = 54.8 (9.7); NACT = 56.2 (10.7) **ECOG performance status:** PS = 0: PDS = 40 (47.6%); NACT = 39 (44.8%) PS = 1: PDS = 35 (41.7%); NACT = 41 (47.1%) PS = 2: PDS = 9 (10.7%); NACT = 7 (8%) **FIGO Stage:** Stage IIIc: PDS = 71 = (84.5%); NACT = 79 (90.8%) Stage IV: PDS = 13 (15.5%); NACT = 8 (9.2%) **Median follow-up:** 59 months (95% CI 53 to 64 months)

Fagotti 2016 *(Continued)*

Median overall survival:

PDS = 41 months for patients; NACT = 43 months (HR 1.12, 95% CI 0.76 to 1.65; P = 0.56)

Median PFS:

PDS = 15 months; NACT = 14 months (HR 1.05, 95% CI 0.77 to 1.44; P = 0.73)

Median number of chemotherapy cycles = 6 in both groups; range 0 to 6 cycles in PDS arm and 3 to 6 in NACT arm

Women in the NACT arm received a median number of four cycles prior to IDS.

3 women in the PDS arm progressed and did not receive chemotherapy. Chemotherapy schedule was as follows:

- 3-weekly carboplatin-paclitaxel: 31 (60.8%) PDS arm versus 29 (55.8%) NACT arm (P = 0.691);

- 3-weekly carboplatin-paclitaxel-bevacizumab: 14 (27.4%) PDS arm versus 20 (38.5%) NACT arm (P = 0.296);

- weekly carboplatin-paclitaxel: 5 (9.8%) PDS arm versus 3 (5.7%) NACT arm (P = 0.444);

- weekly carboplatin: 1 (1.9%) PDS arm versus 0 (0%) NACT arm (P = 0.310).

Median duration of treatment (randomisation to completion): 38 weeks for PDS (range 17 to 45 weeks) and 28 weeks for NACT arm (range 16 to 34 weeks). This was largely due to increased time to start/restart chemotherapy after surgery: median time after PDS was 40 days (range 17 to 120 days) versus 27 days after IDS (range 16 to 37 days) (P = 0.001).

Operative time (mins), mean (SD): PDS = 460.6 mins (102.6); NACT = 253.2 mins (101.4); P < 0.0001

Surgical complexity score (SCS): (P < 0.0001)

SCS 1: PDS = 0 (0%); NACT = 43 (58.1%)

SCS 2: PDS = 9 (10.7%); NACT = 20 (27.0%)

SCS 3: PDS = 75 (89.3%); NACT = 11 (14.9%)

Size of residual disease (P = 0.001)

No macroscopic disease: PDS = 40 (47.6%); NACT = 57 (77.0%)

0.1-1 cm: PDS = 38 (45.2%); NACT = 16 (21.6%)

> 1 cm: PDS = 6 (7.1%); NACT = 1 (1.4%)

Patients with postoperative major complications (G3+ SAEs)

Early (≤ 30 days): PDS = 39 (46.4%); NACT = 7 (9.5%); P < 0.0001

Late (1-6 months): PDS = (11.9%); NACT = 1 (1.4%); P = 0.009

Notes	Trial registered on ClinicalTrials.gov (No. NCT01461850) We are very grateful to Professor Fagotti for providing additional information for this study. We understand that further information will be published.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A centrally performed, computer-generated list for block randomisation (1:1 ratio) was used. Women randomly (max allowable percentage deviation =

Fagotti 2016 *(Continued)*

		10%) allocated to PDS + systemic adjuvant chemotherapy (arm A, standard) or to NACT + IDS (arm B, experimental)
Allocation concealment (selection bias)	Unclear risk	Randomisation was done centrally by an independent DMC (CUSH-CTC), however there was no mention of whether the sequence was protected prior to assignment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind participants or personnel to interventions in the trial. It was unclear what impact this would have in terms of bias, although it did carry a high risk.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study and no indication of independent blinded assessment
Incomplete outcome data (attrition bias) All outcomes	High risk	Substantial missing data for QoL outcomes. Unable to provide chemotherapy SAE data due to missing data. Postop SAEs more fully presented for initial 110 cohort. Additional unpublished data provided by author
Selective reporting (reporting bias)	Unclear risk	Data for OS and PFS for entire cohort provided in subsequent publication and unpublished data from author for entire cohort. SASs during chemotherapy not reported and only partial QoL outcomes reported due to missing data (see above)
Other bias	Unclear risk	The authors stated that the types of surgery performed on women in each arm of the study were significantly different. In women in the PDS arm, upper abdominal surgical procedures were performed in all women compared to 42.3% of women in the IDS arm. This is likely due to the beneficial effect of chemotherapy reducing the volume of disease but as the study was not blinded, there is potential for high risk of bias. Median duration of entire treatment from randomisation to completion of medical treatment was also longer in the PDS arm (38 weeks versus 28 weeks). This was due to a statistically significant difference in time to start post-surgery chemotherapy (median time post-PDS 40 days, median time post-IDS 27 days). This was likely due to the greater extent of surgery required for those with higher volume disease in the PDS group, but due to lack of blinding risk of bias was unclear. No conflict of interest declared

Kehoe 2015

Study characteristics	
Methods	Multicentre international RCT non-inferiority trial (CHORUS)
Participants	552 women with stage IIIc/IV EOC enrolled in the UK and New Zealand
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 Median follow-up of surviving women = 4.4 years (IQR 3.5–6.1) Surgery scheduled after 3 cycles of chemotherapy in NACT group

Kehoe 2015 *(Continued)*

Chemotherapy details:

Single-agent carboplatin: NACT = 63 (23%); PDS = 66 (24%);

Carboplatin paclitaxel: NACT = 210 (77%); PDS = 207 (75%);

Carboplatin plus other chemotherapy agent: NACT = 1 (< 1%); PDS = 3 (1%).

Dose modification required: NACT = 100 (39%); PDS = 87 (38%)

PDS group: 251 (91%) of 276 women started treatment as allocated; 212 (77%) had adjuvant chemotherapy.

- 15 had primary chemotherapy:
  - 11 unfit for surgery;
  - 3 clinician's choice;
  - 1 because of women's choice.
- Of the 15 who had primary chemotherapy:
  - 4 had surgery after chemotherapy (2 after four cycles);
    - 3 had more chemotherapy after surgery (2 had two cycles);
    - 1 did not have more chemotherapy after surgery.
- 11 did not have surgery after chemotherapy (7 had six cycles):
  - 5 unfit;
  - 3 disease progression;
  - 2 had a complete response to chemotherapy;
  - 1 through woman's choice.
- 10 did not have surgery or chemotherapy:
  - 3 died before treatment;
  - 3 unfit;
  - 2 withdrew from trial;
  - 1 disease progression;
  - 1 no malignancy.
- 10 did not have surgery or chemotherapy:
  - 3 died before treatment;
  - 3 unfit;
  - 2 withdrew from trial;
  - 1 disease progression;
  - 1 no malignancy.

NACT group: 253 (92%) of 274 women started treatment as allocated and 217 (79%) had IDS.

Median duration of treatment was 22 weeks in both groups (NACT interquartile range (IQR) 19 to 24 weeks; PDS IQR 17 to 24 weeks).

- 2 had primary surgery:
  - 1 unfit for primary chemotherapy, but then had six cycles after surgery;
  - 1 had benign disease.
- 19 did not have chemotherapy or surgery:
  - 6 ineligible malignancy;
  - 5 died before treatment;
  - 3 no malignancy;
  - 2 deemed inoperable;
  - 3 withdrew from the trial.
- 16 did not have more chemotherapy after surgery:
  - 6 died;
  - 3 did not have ovarian cancer;
  - 3 had surgery after the full six cycles of chemotherapy;

Kehoe 2015 *(Continued)*

- 3 because of women's choice;
- 1 progressive disease.

Notes	www.ctu.mrc.ac.uk/plugins/StudyDisplay/protocols/CHORUS protocol Version 2.0 - 05 June 2008.pdf Additional age and survival details: < 50 years: OS 22.8 months (18.5 to 34.4); PFS 13.2 months (9.9 to 17.1) 50 to 70 years: OS 24.1 (20.6 to 28.4); PFS 11.4 (10.5 to 12.5) > 70 years: OS 20.8 (14.7 to 25.8); PFS 10.4 (8.8 to 12.0) We are very grateful to Professor Kehoe and his team for providing additional information for this study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random assignment centrally at the Medical Research Council Clinical Trials Unit by telephone using a minimisation method with a random element. Women stratified according to randomising centre, largest radiological tumour size, clinical FIGO stage, and prespecified chemotherapy regimen with equal probability of assignment to each treatment arm 2 women who had been randomised were subsequently excluded. One woman had been randomised by mistake as an administrative error and one woman was found not to have the capacity to consent and was therefore ineligible for the trial.
Allocation concealment (selection bias)	Low risk	Central randomisation by the Medical Research Council Clinical Trials Unit by telephone
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded, therefore high risk for some outcomes assessed by investigators involved with patient care (e.g. optimal debulking)
Blinding of outcome assessment (detection bias) All outcomes	High risk	No report of blinded central assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	All women accounted for and analysed by ITT analysis
Selective reporting (reporting bias)	Unclear risk	All pertinent outcomes appeared to have been reported in some capacity. Prespecified outcomes as per clinicaltrials.gov protocol for OS; PFS and QoL - see outcomes section in methods and clinical trials.gov website. Only global QoL outcomes reported at baseline, 6 months and 12 months
Other bias	Unclear risk	64 centres: surgery performed by specialist gynaecological oncologists; further 23 registered centres: only non-surgical management provided. Supplementary data in table 7 showed that hysterectomy/bilateral salpingo-oophorectomy (BSO) and omentectomy performed in varying proportions. Unclear what effect this might have on outcomes

Onda 2016

Study characteristics	
Methods	Randomised phase III non-inferiority study (JCOG0602) conducted in 34 institutions in Japan
Participants	301 women aged 20 to 75 years enrolled with stage III or IV ovarian, tubal and peritoneal cancers diagnosed by clinical findings, imaging studies (CT, MRI and CXR) and cytology of ascites, pleural effusions or tumour centesis
Interventions	PDS followed by 8 cycles of chemotherapy +/- additional IDS if not completely debulked prior to commencing chemotherapy compared to 4 cycles of NACT followed by IDS and a further 4 cycles of chemotherapy
Outcomes	Primary outcomes of OS and PFS Planned follow-up initially 5 years, extended to 6 years Secondary outcomes of adverse events, frequency and duration of surgery, amount of blood loss and frequency of blood, plasma and albumin transfusions, postoperative mortality within 30 days of surgery **Median age** (range): PDS = 62 (25-86); NACT = 63 (33-81) **Stage:** PDS: stage 3 = 257 (77%); stage 4 = 77 (23%); other = 2 (0.6%); NACT: stage 3 = 253 (76%); stage 4 = 81 (24%) **Performance status (PS):** PS 0-1: PDS = 130 (87.2%); NACT = 131 (86.2%) PS 2-3: PDS = 19 (12.8%); NACT = 21 (13.8%) **Median cycles of chemotherapy:** NACT = 8 (IQR 7 to 8); PDS = 8 (IQR 6 to 8) **Chemotherapy schedule:** Carboplatin (AUC6) and paclitaxel 175 mg/m^2 given 3-weekly for a total of 8 cycles with IDS scheduled after 4 cycles **Overall survival:** HR for death with NACT compared with PDS was 1.052 (90.8% CI, 0.835 to 1.326; P = 0.24 for non-inferiority calculated using the Cox proportional hazard model stratified by FIGO stage, PS and age) **Progression-free survival:** HR for progression with NACT compared with PDS was 0.96 (95% CI, 0.75 to 1.23 calculated by the Cox proportional hazard model stratified by the FIGO stage, PS and age) **Optimal debulking at first surgical effort (0 cm & < 1 cm):** PDS = 55/147 (37%); NACT = 107/130 (82%) **Postoperative G3+ events after initial surgical effort:** PDS = 15.0% (n = 22/147); NACT = 4.6% (n = 6/130) **Operation time:** PDS = 341 min; NACT = 273 min; P < 0.001 **Postoperative any G3+ SAEs:** PDS = 15.6%; NACT = 4.6%; P = 0.003 **Chemotherapy-related non-haematological G3-4 SAEs:**

Onda 2016 *(Continued)*

	First 4 cycles chemotherapy: PDS = 28/138 (20·3%); NACT = 27 (18·0%); P = 0.65 Second 4 cycles chemotherapy: PDS = 11 (8·8%); NACT = 15 (11·9%); P = 0·54 **Completion of treatment:** PDS = 99 (66.4%); NACT = 103 (67.8%); P = 0.90
Notes	49 women randomised to primary debulking arm underwent additional interval debulking surgery. We are very grateful to Professor Onda for providing additional data for this meta-analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The JCOG Data Centre randomly assigned treatment to each women via a minimisation method with equal probability of assignment to each treatment arm. Balancing factors were institution, stage (III versus IV), performance status (0 to 1 versus 2 to 3) and age (< 60 versus > 60).
Allocation concealment (selection bias)	Low risk	The JCOG Data Centre randomly assigned treatment to each women via a minimisation method with equal probability of assignment to each treatment arm.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Women and treating physicians were not masked to assigned treatment.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Individuals assessing outcomes and analysing data were not masked to assigned treatment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	OS and PFS analysed using appropriate statistical methods. All women accounted for and similar numbers completed treatment in each arm
Selective reporting (reporting bias)	Low risk	Study recognised that QoL may contribute to measures of treatment invasiveness, but scope was on survival outcomes. Study protocol published alongside paper as supplementary information
Other bias	High risk	Fourteen women (one in PDS and 13 in NACT) underwent some type of surgery (off-protocol treatment). These off-protocol surgeries were not included as PDS or IDS in the analysis. Appeared to be significantly more in NACT group No ITT analysis carried out

Vergote 2010

Study characteristics

Methods	EORTC-GCG 55971 Multicentre non-inferiority RCT; 59 institutions in Belgium, Canada, the UK, Sweden, the Netherlands, Italy, Norway, Spain, Austria, Portugal, Ireland and Argentina Recruitment period: 1998 to 2006 Median follow-up: 56.4 months

Vergote 2010 *(Continued)*

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
	
	Median follow-up = 4.7 years
	
	Chemotherapy details:
	
	Platinum-taxane: NACT = 283(87.9%); PDS = 243 (78.4%)
	
	Platinum only: NACT = 20 (6.2%); PDS = 25 (8.1%)
	
	Other: NACT = 19 (5.9%); PDS 21 (6.8%)
	
	No chemotherapy: NACT = 0 (0%); PDS = 21 (6.8%)
	
	Median time to re-start chemotherapy after surgery in days (range):
	
	NACT = 18 days (5 to 55) versus PDS 19 days (0 to 84)
	
	• 336 were assigned to PDS
	• 315 received assigned intervention
	• 21 did not receive assigned intervention
	  ◦ 8 (38%) were withdrawn by physician
	  ◦ 3 (14%) declined to participate
	  ◦ 3 (14%) had different histologic diagnosis
	  ◦ 1 (5%) died
	  ◦ 2 (10%) had unresectable tumour
	  ◦ 3 (14%) had logistic or administrative problem
	  ◦ 1 (5%) had unknown reason
	• 315 (94%) underwent primary debulking
	  ◦ 297 (88%) started chemotherapy
	  ◦ 57 (17%) underwent interval debulking
	  ◦ 11 (3%) underwent second-look procedure
	• 334 were assigned to NACT
	• 326 received assigned intervention
	  ◦ 8 did not receive assigned intervention
	  ◦ 3 (38%) were withdrawn by physician
	  ◦ 2 (25%) declined to participate
	  ◦ 1 (13%) had different histologic diagnosis
	  ◦ 1 (13%) died
	  ◦ 1 (13%) had logistic or administrative problem
	  ◦ 2 (1%) underwent primary debulking
	• 326 (98%) started NACT

Vergote 2010 *(Continued)*

- 295 (88%) underwent interval debulking
- 6 (2%) underwent second-look procedure

Notes

Baseline characteristics were similar: stage IIIc (75.7% versus 76.5%) or stage IV (22.9% versus 24.3%); mean age 63 years (NACT) versus 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% versus 74.5%) suggesting NACT-related tumour shrinkage. Optimal debulking (80.6% versus 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 versus 29 months (NACT versus PDS) and median PFS was 12 months for both groups.

Intervention effects on OS differed significantly between participating countries.

A per-protocol analysis of those who underwent surgery (322/334 in NACT arm and 310/336 in PDS arm) was performed. However, 295 women in the NACT group underwent IDS and 315 women underwent PDS. Data from the published supplementary data differed from those in Figure 2 of the published paper. These data were from the supplementary data, although we noted that the percentages are calculated from the 295 and 315 denominators of women who actually had NACT/IDS and PDS, respectively, rather than the per-protocol analysis, as the table suggested. After debulking surgery, 7 women assigned to NACT and 11 women assigned to PDS were subsequently found on final histology not to have EOC.

QoL data reported in separate publication (Greimel and et al. 2013 see additional reference under Vergote 2010 **)**

Only 404 women included in QoL analysis. QoL was limited to data from institutions with the best compliance. Over 50% baseline compliance rate and 35% at follow-up chosen as pragmatic cut-off

Women in the QoL study subset differed from the entire population.

Only institutions with good QoL compliance were included in the QoL substudy. The institutions with good QoL compliance differed from those studies excluded from the QoL analysis and compared to institutions with poor QoL compliance had:

- better OS (median 32.30 versus 23.29 months; P = 0.0006);
- PFS (median 12.35 versus 9.92 months; P = 0.0002);
- 39.9% optimal debulking surgery compared to 19.9% in excluded institutions (P = 0.0011);
- more women with biopsy-proven EOC (90.3% versus 79.3%; P = 0.0050);
- more women with larger tumours (P = 0.0034);
- laparoscopy used more frequently (40.3% versus 21.4%) and FNA cytology used less frequently (36.1% versus 56.0%) for biopsy in the selected centres (P = 0.0002);
- fewer women with unknown tumour grade (35.6% versus 48.5%; P = 0.0009);
- No differences were found in terms of age, WHO performance status and FIGO stage between institutions.

Quote: "No differences between the treatment arms in the QoL functioning or symptoms scales, except for pain and dyspnoea. At baseline women treated with PDS had significantly higher pain scores (P = 0.046; PDS mean 36.7; NACT mean 29.9) and significantly lower dyspnoea scores (P = 0.049; PDS mean 22.9; NACT mean 27.9) compared to women treated with NACT. However, the difference was below 10 points indicating no clinically relevant difference."

We are very grateful to Professor Vergote for providing additional information for this study.

Risk of bias

Vergote 2010 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation done centrally by computer-generated randomisation, but detail of methods lacking in published data. Minimisation used to stratify for institution, biopsy method, tumour stage and largest preoperative tumour size. QoL outcomes were based on a selected number of institutions selected for their QoL data compliance.
Allocation concealment (selection bias)	Unclear risk	Central allocation but detail of methods lacking and data from 48 women from Argentina were excluded after randomisation owing to "potential authorisation irregularities"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded, therefore high risk for some outcomes assessed by investigators involved with patient care (e.g. optimal debulking)
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study and no mention of central independent blinded assessment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	3/336 versus 5/334 lost to follow-up but substantial proportion were missing for QoL outcome; overall outcomes were complete.
Selective reporting (reporting bias)	Unclear risk	All prespecified outcomes reported. Analysis by ITT and per-protocol However, QoL outcome was based on a selected number of institutions with better QoL compliance. While the trial authors offered justification for their approach, several differences were found when comparing the outcomes of the 404 selected women (of which, only 212 were assessed in QoL domains) to the overall populations of 670 women. Women from the selected institutions had significantly better OS and PFS when compared to women treated in institutions which were excluded because of poor compliance rates.
Other bias	Unclear risk	48 post-randomisation exclusions from the Argentinian centre owing to quote: "authorisation irregularities" were indicated erroneously as pre-randomisation exclusions on the study-flow diagram. The investigators stated that "The results of the study were similar whether the 48 patients....were included or excluded".

BSO: bilateral salpingo oophorectomy
CEA: carcinoembryonic antigen
CT: computer tomography
EOC: epithelial ovarian cancer
FIGO: Federation of International Gynaecologists and Obstetricians
FNA: fine needle aspiration; HR: hazard ratio; IDS: interval debulking surgery; ITT: intention to treat; IQR: interquartile range; MRI: magnetic resonance imaging; NACT: neoadjuvant chemotherapy; OS: overall survival; PDS: primary debulking surgery; PFS: progression-free survival; QoL: quality of life; RCT: randomised controlled trial; 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

Study	Reason for exclusion
Baekelandt 2003	Review article
Bertelsen 1990	RCT of chemotherapy (cisplatin versus 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
Chan 2017	Wrong intervention, participants randomised to either weekly with 3-weekly paclitaxel. No surgical randomisation
Chi 2012	Wrong study design, retrospective review, no randomisation
Cole 2018	Wrong study design; economic analysis comparing treatment strategies but no randomisation
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
Cowan 2017	Editorial article, not an RCT
Da Costa 2014	Wrong study design, retrospective cohort.
Dai-yuan 2013	Wrong study design, meta-analysis
Daniele 2017	Wrong Intervention. Evalution of adding Bevacizumab to NACT prior to IDS. Not an RCT
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
ESGO 2013	Wrong study design, conference proceedings. No studies identified that had not already been found.
Evdokimova 1982	RCT of NACT then surgery versus 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
Fagö-Olsen 2014	Wrong study design, prospective cohort
Fagotti 2018	Commentary in response to per protocol joint analysis of Kehoe 2015 and Vergote 2010 studies

Study	Reason for exclusion
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
Forde 2015	Wrong study design, cost analysis
Fujiwara 2013	Wrong study design, review article
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)
Grosso 2013	Wrong intervention, no randomisation
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 perioperative 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
Iranian Society Reproductive Medicine Conference	Wrong study design, conference proceedings no RCTs identified
Jacob 1991	Retrospective case-control series
Kayikcioglu 2000	Retrospective series of 189 women. No randomisation
Kayikcioglu 2001	Retrospective series of 205 women. No randomisation
Kehoe 2011	Wrong study design, recruitment to CHORUS trial poster
Kuhn 2001	Prospective NRS of 31 women treated with NACT vs 32 women with conventional treatment
Kumar 2015	Wrong study design, review article.
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
Lee 2018	Wrong study design - non RCT - experience from a single cancer centre

Study	Reason for exclusion
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
Liu 2015	Wrong study design, retrospective cohort study
Liu 2017	Trial comparing intra-peritoneal chemotherapy timing rather than timing of surgery in relation to chemotherapy administration.
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 versus intraperitoneal NACT (NCIC CTG OV.21 protocol)
Mahner 2006	Conference presentation of Polcher 2009
Mahner 2014	Review article
Makar 2016	Review article
Malzoni 1993	Case report
Mazzeo 2003	Retrospective case series of 45 women
Melamed 2018	Wrong study design: quasi-experimental fuzzy regression discontinuity design and cross-sectional analysis.
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
Nick 2015	Wrong study design, case series
Oe 2011	Not an RCT but methods not clear. More details requested from authors
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

Study	Reason for exclusion
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, perioperative morbidity and mortality. Concluded that 2 NACT cycles is a reasonable option. Any residual disease associated with survival rates
Poonawalla 2015	Non RCT - cost-effectiveness study comparing NACT and PDS in elderly patients
Prescott 2016	Wrong study design: retrospective study on effect of blood transfusion in Vergote 2010 study
Qin 2018	Systematic review of RCTS and observational studies
Querleu 2013	Wrong study design, letter
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
Rauh-Hain 2017	Wrong study design; population level comparison of OS outcomes of NACT versus PDS
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 versus 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
Rowland 2013	Wrong study design, cost analysis (abstract)
Rowland 2015	Wrong study design, cost analysis (paper)
Rutten 2012	Wrong intervention, randomisation to laparoscopy or not prior to PDS
Salzer 1990	Prospective non-randomised cohort study of different chemotherapy regimens and IDS
Sato 2014	Wrong study design, review
Sayyah-Melli 2013	Wrong study design, prospective cohort
Schorge 2014	Wrong study design, review
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)

Study	Reason for exclusion
Surwit 1999	Retrospective case series of 39 women receiving NACT prior to surgery
Taskin 2013	Wrong study design, not randomised, retrospective cohort study.
Taylor 2015	Wrong study design, retrospective case series.
Tran 2018	Wrong study design: cost-effectiveness study comparing different treatment approaches
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
Van der Burg 1995	RCT of IDS following suboptimal primary surgery (319 women)
Van Meurs 2013	Wrong study design, biomarker analysis
Varma 1990	Abstract of the later full Trial by Redman 1994, comparing secondary debulking surgery or chemotherapy after all women had initially undergone primary debulking surgery
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
Vergote 2018	Pooled analysis of individual patient data from the EORTC 55971(Vergote 2010) and Kehoe 2015 trials. Data already included in review.
Vergote 2019	Pooled analysis of individual patient data from the EORTC 55971(Vergote 2010) and Kehoe 2015 trials. Data already included in review.
Vrscaj 2002	Retrospective case-control study of 75 women with advanced ovarian cancer
Wenzel 2017	Wrong Intervention. RCT trialling a patient decision making tool around IV or IP chemotherapy versus standard care. No surgical randomisation.
Wright 2013	Wrong study design, retrospective study
Wu 2012	Wrong study design, retrospective study
Xiao 2018	Systematic review and meta-analysis
Yang 2017	Meta-analysis of perioperative outcomes
Zamagni 2014	Wrong study design, comparison of 3 versus 6 cycles of chemotherapy
Zeng 2016	Wrong study design, systematic review of surgery in primary treatment of 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 studies awaiting classification *[ordered by study ID]*

Jiang 2018

Methods	To investigate the role and significance of neoadjuvant chemotherapy in advanced ovarian cancer.
Participants	128 patients clinically diagnosed with stage IIC-IV advanced epithelial ovarian cancer (EOC)
Interventions	Neoadjuvant chemotherapy (NACT) combined with interval cytoreductive surgery (ICS) group (n=66) and primary cytoreductive surgery (PCS) group (n=62). Chemotherapy in the PCS group was administered after cytoreductive surgery.
Outcomes	Progression-free survival (PFS) and overall survival (OS) Secondary outcomes include operative time, bleeding, optimal debulking surgery, rate of clinical remission. Longer operating time in PDS group (mean 275.94mins +/- 70.84) versus NACT (mean 215.65mins +/- 68.48) P < 0.05. Higher blood loss in PDS group (mean 794.94mls +/- 250.16) versus NACT (mean 467.84mls +/-220.14) P < 0.05. Lower optimal debulking rate in PDS group (38.7%) versus NACT (60.6%) P < 0.05. Mean follow up time 61.3 months. 28 deaths in NACT group (42.4%) and 32 deaths in PDS group (51.6%) not significantly different. Mean PFS NACT 18.5 months versus 17.9 PDS not significantly different. Mean OS NACT 47.5 months versus 46.3 months PDS not significantly different.
Notes	Study describes itself as a retrospective cross sectional study although women were 'randomised' into NACT or PCS groups. Author contacted for clarification of study design and further data.

EOC: epithelial ovarian cancer; ICS: interval cytoreductive surgery; IDS: interval debulking surgery; NACT: neoadjuvant chemotherapy; NCIC CTG: NCIC Clinical Trial Group; NRS: non-randomised study; NS: not significant; OS: overall survival; PCS: primary cytoreductive surgery; PDS: primary debulking surgery; PFS; Progression-free survival; RCT: randomised controlled trial

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

Kumar 2009

Study name	Kumar
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	

Kumar 2009 *(Continued)*

Contact information	lalitaiims@yahoo.com
Notes	Clinical Trials Register: NCT00715286 Interim results presented at 2007 ASCO meeting: 113/139 women evaluable, 20% optimally debulked in PDS group versus 85% in the NACT group. NACT group also experienced less blood loss (P = 0.01), shorter hospital stay (P = 0.04), less postoperative infection (2 cases versus 7 cases; P = 0.06) and less operative mortality (1 deaths versus 5 deaths; P = 0.08). Median OS was 29 months in PDS group versus 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 versus 600 mL; P < 0.0001), reduced postoperative infections (1.54% versus 14.5%; P < 0.025), reduced operating time (75.4 minutes versus 89.2 minutes; P < 0.001) and shorter hospital stay (7.6 days versus 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 versus NACT) was 0.94; 95% CI 0.56 to 1.56. HR for PFS (PDS versus 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. The authors stated that complete results will be published soon.

Mahner 2017

Study name	Role of neoadjuvant chemotherapy in advanced ovarian cancer: TRUST-trial of radical upfront surgical therapy in advanced ovarian cancer (ENGOT ov33 / AGO-OVAR OP7)
Methods	Multi-centre international randomised controlled trial comparing primary debulking surgery (maximally debulked - complete gross resection) followed by 6 cycles of chemotherapy (control arm) with 3 cycles of neoadjuvant chemotherapy followed by interval debulking surgery (maximally debulked - complete gross resection) and another 3 cycles of chemotherapy (experimental arm). There are 3 parts to the trial the first 2 parts were conducted in Germany alone. The 3rd part is the multi-centre international trial including centres in the UK (1), USA (1), France (3), Germany (8), Italy (3), Denmark (1), Austria (1) and Sweden (2). All are actively recruiting at present except Austria. The trial aims to recruit 686 participants
Participants	Suspected or histologically-confirmed, newly diagnosed invasive epithelial ovarian cancer FIGO stage IIIB-IV (IV only if resectable metastasis) Females aged ≥ 18 years Women who have given their written informed consent Good performance status (ECOG 0/1) Good ASA score (1/2) Preoperative CA 125/CEA ratio ≥ 25 (if CA-125 is elevated)* If < 25 and/or biopsy with non-serous, non-endometrioid histology, esophago-gastro-duodenoscopy (EGD) and colonoscopy mandatory to exclude gastrointestinal primary cancer Assessment of an experienced surgeon, that is based on all available information, the women can undergo the procedure and the tumour can potentially be completely resected Adequate bone marrow function: Absolute neutrophil count (ANC) ≥ 1.5 x 109/L. This ANC cannot have been induced or supported by granulocyte colony stimulating factors. Platelet count ≥ 100 x 109/L. Renal function: Serum-Creatinine ≤ 1.5 x institutional upper limit normal (ULN). Hepatic function: Bilirubin ≤ 1.5 x ULN.

Mahner 2017 *(Continued)*

	SGOT ≤ 3 x ULN Alkaline phosphatase ≤ 2.5 x ULN. Neurologic function: Neuropathy (sensory and motor) less than or equal to CTCAE Grade 1
Interventions	Primary debulking surgery followed by 6 cycles of chemotherapy (control arm) or 3 cycles of neoadjuvant chemotherapy followed by interval debulking surgery and a further 3 cycles of chemotherapy (experimental arm)
Outcomes	Primary outcome measure is OS (Women will be followed up for a minimum of 5 years after registration/randomisation or until death) Secondary outcome measures are: Progression-free survival (PFS) (Women will be followed up for a minimum of 5 years after registration/randomisation or until death) Progression-free survival time is calculated from the date of randomisation until the date of first progressive disease or death, whichever occurs first or date of last contact (censored observation). Progressive disease is defined as clinical or imaging-detected tumour progression or death in cases without prior documented tumour progression. Progression-free survival 2 (PFS2) (Women will be followed up for a minimum of 5 years after registration/randomisation or until death) PFS2 time is calculated from the date of randomisation until the date of second progressive disease or death, whichever occurs first or date of last contact (censored observation). Time to first subsequent anticancer therapy or death (TFST) (Time Frame: Women will be followed up for a minimum of 5 years after registration/randomisation or until death) Time to first subsequent anticancer therapy is calculated from the date of randomisation until the starting date of the first subsequent anticancer therapy or death, whichever occurs first or date of last contact (censored observation). Maintenance treatments following a cytostatic treatment are not considered separate treatment lines. Time to second subsequent anticancer therapy or death (TSST) (Time frame: Women will be followed up for a minimum of 5 years after registration/randomisation or until death) Time to second subsequent anticancer therapy is calculated from the date of randomisation until the starting date of the second subsequent anticancer therapy or death, whichever occurs first or date of last contact (censored observation). Maintenance treatments following a cytostatic treatment are not considered separate treatment lines. QoL (Time frame: women will be followed up for a minimum of 5 years after registration/randomisation or until death) QoL as measured by EORTC QLQ-C30 (Version 3), EORTC QLQ-OV28, EQ-5D-3L Documentation of surgical complications (Time frame: women will be followed up for 1 year after surgery or until death) Assessment of safety: documentation of surgical complications 28 days after surgery and 1 year after surgery.
Starting date	Recruitment commenced in July 2016 and is expected to close in April 2023.
Contact information	office-wiesbaden@ago-ovar.de
Notes	

NCT04257786

Study name	NCT04257786
Methods	Randomised open label study
Participants	80 participants. Females aged 18 years to 80 years with advanced epithelial ovarian cancer. Stage 2D or more ; Performance status (PS) according to Eastern Cooperative Oncology Group (ECOG) ≤ 2 No contra-indication to bevacizumab.
Interventions	Primary surgery then chemotherapy versus Neoadjuvant chemotherapy (NACT) followed by surgery
Outcomes	Primary outcome: Percentage of patient where complete resection of the tumour can be achieved
Starting date	1/3/2020
Contact information	Ali Hussien Ali Sayed, Specialist, Assiut University, Egypt
Notes	

NCT04515602

Study name	FOCUS (NCT04515602)
Methods	Randomised phase III open label multicenter study
Participants	410 female participants with pathologically confirmed stage IIIC and IV epithelial ovarian cancer, fallopian tube cancer or primary peritoneal carcinoma; **Part 1** • Females aged ≥ 18 years and cPCI score ≤ 8; • Performance status (ECOG 0-2); • Good ASA (1/2); • Adequate bone marrow, renal and hepatic function to receive chemotherapy and subsequent surgery. **Part 2** • Females aged ≥ 18 years, and < 70 years with cPCI score ≥ 10; • For FIGO IVB patients, abdominal lesions should be confined to one lobe of liver parenchyma metastasis or splenic metastasis. All extra-abdominal metastases should be resectable, such as inguinal lymph nodes, solitary supraclavicular, retrocrural or paracardial nodes; • Good performance status (ECOG 0-1);

NCT04515602 *(Continued)*

	• Good ASA score (1/2); • Adequate bone marrow, renal and hepatic function to receive chemotherapy and subsequent surgery
Interventions	**Part 1, Arm I** **(low/medium tumour burden)** **PDS:** Primary debulking surgery with a maximum cytoreduction, then followed by 6 cycles of Paclitaxel 175mg/m^2 or Docetaxel 60-75 mg/m^2 plus Carboplatin AUC (area under the curve) 5. For patients with gBRCA/sBRCA mutation and CR/PR after first-line chemotherapy, maintenance therapy of PARP inhibitors. **Part 1 Arm II (low/medium tumour burden)** **NACT:** 3 cycles of Paclitaxel 175mg/m^2 or Docetaxel 60-75 mg/m^2 plus Carboplatin AUC (area under the curve) 5, Interval debulking surgery with a maximal cytoreduction of complete gross resection, then followed by another 3 cycles of chemotherapy. For patients with gBRCA/sBRCA mutation and CR/PR after first-line chemotherapy, maintenance therapy of PARP inhibitors. **Part 2 Arm I (high tumour burden)** **PDS:** Primary debulking surgery with a maximum cytoreduction, then followed by 6 cycles of Paclitaxel 175mg/m^2 or Docetaxel 60-75 mg/m^2 plus Carboplatin AUC (area under the curve) 5. For patients with gBRCA/sBRCA mutation and CR/PR after first-line chemotherapy, maintenance therapy of PARP inhibitors. **Part 2 Arm II (high tumour burden)** **NACT:** 3 cycles of Paclitaxel 175mg/m^2 or Docetaxel 60-75 mg/m^2 plus Carboplatin AUC (area under the curve) 5, Interval debulking surgery with a maximal cytoreduction of complete gross resection, then followed by another 3 cycles of chemotherapy. For patients with gBRCA/sBRCA mutation and CR/PR after first-line chemotherapy, maintenance therapy of PARP inhibitors.
Outcomes	**Primary:** • Overall survival **Secondary:** • Progression-free survival; • Postoperative complications evaluated at 30-day, 60-day, 90-day after upfront cytoreductive surgery or interval debulking surgery; • Quality of life (Qol) as measured by QOQ-C30; • Quality of life (Qol) as measured by FACT-O; • The overall survival time minus the total treatment time of surgery and chemotherapy after randomisation, regardless of the targeted therapy; • Time to first subsequent anticancer therapy; • Time to secondary subsequent anticancer therapy; • Progression-free survival 2.

NCT04515602 *(Continued)*

Starting date	estimated start date January 2021
Contact information	Lina Shen (shen.lina@zs-hospital.sh.cn); Tingyu Luan (luan.yuting@zs-hospital.sh.cn)
Notes	**Sponsors and Collaborators:** Shanghai Gynecologic Oncology Group, Obstetrics & Gynecology Hospital of Fudan University, Xinhua Hospital, Shanghai Jiao Tong University School of Medicine Shanghai First Maternity and Infant Hospital Estimated completion date January 2028.

SUNNY

Study name	Study of upfront surgery versus neoadjuvant chemotherapy in patients with advanced ovarian cancer (SUNNY) in China and Korea
Methods	To compare the efficacy and safety in women with FIGO (2014) stage IIIC or IV epithelial ovarian cancer, fallopian tube cancer, or peritoneal carcinoma treated with neoadjuvant chemotherapy followed by interval debulking surgery versus upfront surgery. A randomised phase III multi-centre study
Participants	A total of 456 women will be accrued for this study within 5 years. Inclusion criteria • Age ≥ 18 years. • Pathologic confirmed stage IIIC and IV epithelial ovarian cancer, fallopian tube cancer or primary peritoneal carcinoma (diagnosis by biopsy or fine needle aspiration*). Laparoscopic biopsy with pictures is recommended. * If fine needle aspiration showing an adenocarcinoma, women should satisfy the following conditions: a. the patient has a pelvic mass, and b. omental cake or other metastasis larger than 2 cm in the upper abdomen, or pathologic confirmed extra-abdominal metastasis, and c. serum CA-125/CEA ratio>25. If serum CA-125/CEA ratio<25 or malignancies of other origins, such as breasts and digestive tract, are suspected from symptoms, physical examinations or imaging diagnosis, endoscopy or ultrasonography should be done to exclusive metastasis ovarian cancer. • ECOG performance status of 0 to 2 • ASA score of 1 to 2 • Adequate bone marrow, liver and renal function to receive chemotherapy and subsequently to undergo surgery • White blood cells >3,000/μL, absolute neutrophil count ≥1,500/μL, platelets ≥100,000/μL, haemoglobin ≥9 g/dL • Serum creatinine <1.25 x upper limit of normal (ULN) or creatinine clearance ≥60 mL/min according to Cockroft-Gault formula or to local lab measurement • Serum bilirubin <1.25 x ULN, AST(SGOT) and ALT(SGPT) < 2.5 x ULN • Comply with the study protocol and follow-up • Written informed consent Exclusion Criteria • Women with non-epithelial tumours as well as borderline tumours • Mucinous ovarian cancer • Low-grade ovarian cancer • Synchronous or metachronous (within 5 years) malignancy other than carcinoma in situ

SUNNY *(Continued)*	• Any other concurrent medical conditions contraindicating surgery or chemotherapy that could compromise the adherence to the protocol • Other conditions, such as religious, psychological and other factors, that could interfere with provision of informed consent, compliance to study procedures, or follow-up
Interventions	Women will receive upfront maximal cytoreductive surgery followed by at least 6 cycles of adjuvant chemotherapy or 3 cycles of neoadjuvant chemotherapy followed by interval debulking surgery, and then at least 3 cycles of adjuvant chemotherapy. Women are followed every 3 months within the first 5 years, and then every 6 months.
Outcomes	Primary outcome measure • OS Secondary outcome measures • PFS • Postoperative complications - the surgical complications will be evaluated at 30-day after upfront cytoreductive surgery or interval debulking surgery • QoL assessments using QOQ-C30 questionnaire
Starting date	December 2015
Contact information	Rong Jiang, MD - jiang.rong@zs-hospital.sh.cn Yuting Luan, RN - yutingluan@163.com
Notes	Estimated study completion date December 2022

ALT: alanine aminotransferase; ASCO: American Society of Clinical Oncology; ASA; American Society of Anesthesiology; AST: aspartate aminotransferase; AUC: area under the curve; BRCA: Breast cancer susceptibility protein (g = germline; s = somatic); CI: confidence interval; cPCI: clinical peritoneal cancer index; 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; PR: partial regression; RCT: randomised controlled trial; ULN: upper limit of normal.

DATA AND ANALYSES

Comparison 1. NACT vs PDS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Overall survival	4	1692	Hazard Ratio (IV, Random, 95% CI)	0.96 [0.86, 1.08]
1.2 Overall survival by age	3	1391	Hazard Ratio (IV, Random, 95% CI)	0.94 [0.83, 1.06]
1.2.1 Age < 50 years	2	129	Hazard Ratio (IV, Random, 95% CI)	1.12 [0.64, 1.96]
1.2.2 Age <60 years	1	157	Hazard Ratio (IV, Random, 95% CI)	0.71 [0.50, 1.01]
1.2.3 Age 50-60 years	1	57	Hazard Ratio (IV, Random, 95% CI)	1.17 [0.59, 2.29]
1.2.4 Age 50-70 years	1	439	Hazard Ratio (IV, Random, 95% CI)	0.96 [0.77, 1.19]
1.2.5 Age 60-70 years	2	271	Hazard Ratio (IV, Random, 95% CI)	0.93 [0.71, 1.22]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2.6 Age > 70 years	3	338	Hazard Ratio (IV, Random, 95% CI)	0.99 [0.78, 1.25]
1.3 Overall survival by residual disease	2	1173	Hazard Ratio (IV, Random, 95% CI)	0.93 [0.79, 1.11]
1.3.1 Residual disease up to 0.5cm	2	334	Hazard Ratio (IV, Random, 95% CI)	1.12 [0.58, 2.13]
1.3.2 0.5cm > Residual disease ≤ 1cm	2	399	Hazard Ratio (IV, Random, 95% CI)	0.86 [0.69, 1.08]
1.3.3 Residual tumour > 1 cm	1	172	Hazard Ratio (IV, Random, 95% CI)	0.89 [0.64, 1.24]
1.3.4 Residual disease 1-2cm	1	218	Hazard Ratio (IV, Random, 95% CI)	0.82 [0.61, 1.10]
1.3.5 Residual disease >2cm	1	50	Hazard Ratio (IV, Random, 95% CI)	1.08 [0.59, 1.99]
1.4 Overall survival by stage	3	1519	Hazard Ratio (IV, Random, 95% CI)	0.95 [0.84, 1.08]
1.4.1 Stage 3	3	1128	Hazard Ratio (IV, Random, 95% CI)	0.98 [0.85, 1.14]
1.4.2 Stage 4	3	391	Hazard Ratio (IV, Random, 95% CI)	0.88 [0.69, 1.14]
1.5 Progression-free survival	4	1692	Hazard Ratio (IV, Random, 95% CI)	0.98 [0.88, 1.08]
1.6 Surgically-related severe adverse effects (grade 3+)	5		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.6.1 Haemorrhage	3	1264	Risk Ratio (IV, Random, 95% CI)	0.93 [0.50, 1.74]
1.6.2 Need for blood transfusion	4	1085	Risk Ratio (IV, Random, 95% CI)	0.80 [0.65, 0.99]
1.6.3 Venous thromboembolism	4	1490	Risk Ratio (IV, Random, 95% CI)	0.28 [0.09, 0.90]
1.6.4 Infection	4	1490	Risk Ratio (IV, Random, 95% CI)	0.30 [0.16, 0.56]
1.6.5 Gastrointestinal fistula	4	1541	Risk Ratio (IV, Random, 95% CI)	0.30 [0.09, 0.97]
1.6.6 Urinary/vaginal fistula	2	1106	Risk Ratio (IV, Random, 95% CI)	1.06 [0.15, 7.49]
1.6.7 Nausea	2	577	Risk Ratio (IV, Random, 95% CI)	0.42 [0.02, 8.23]
1.6.8 Vomiting	2	577	Risk Ratio (IV, Random, 95% CI)	0.41 [0.03, 6.03]
1.6.9 Diarrhoea	1	474	Risk Ratio (IV, Random, 95% CI)	0.58 [0.11, 3.15]

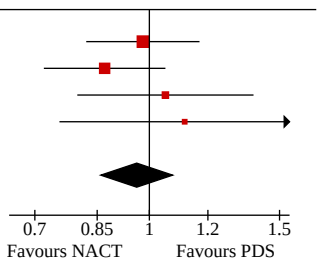
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.6.10 Neutropenia	1	103	Risk Ratio (IV, Random, 95% CI)	1.15 [0.48, 2.74]
1.6.11 Neutrotoxicity	1	103	Risk Ratio (IV, Random, 95% CI)	1.02 [0.15, 6.97]
1.6.12 Thrombocytopenia	1	103	Risk Ratio (IV, Random, 95% CI)	5.10 [0.25, 103.61]
1.6.13 Febrile neutropenia	1	103	Risk Ratio (IV, Random, 95% CI)	3.06 [0.13, 73.36]
1.6.14 Renal toxicity	1	103	Risk Ratio (IV, Random, 95% CI)	Not estimable
1.6.15 Stoma formation	2	632	Risk Ratio (IV, Random, 95% CI)	0.29 [0.12, 0.74]
1.6.16 Bowel resection	4	1565	Risk Ratio (IV, Random, 95% CI)	0.49 [0.30, 0.79]
1.6.17 Splenectomy	3	1067	Risk Ratio (IV, Random, 95% CI)	0.31 [0.08, 1.12]
1.6.18 Post- operative G3+ events	2	435	Risk Ratio (IV, Random, 95% CI)	0.22 [0.13, 0.38]
1.7 Postoperative mortality	5	1623	Risk Ratio (IV, Random, 95% CI)	0.16 [0.06, 0.46]
1.8 Chemotherapy-related SAEs (G3+)	2	768	Odds Ratio (IV, Random, 95% CI)	0.88 [0.57, 1.36]
1.9 EORTC QLQ-C30 QoL at 6 months	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.9.1 Global health	3	524	Mean Difference (IV, Random, 95% CI)	-0.29 [-2.77, 2.20]
1.9.2 Fatigue	2	307	Mean Difference (IV, Random, 95% CI)	-0.55 [-6.02, 4.93]
1.9.3 Nausea	2	307	Mean Difference (IV, Random, 95% CI)	2.12 [-0.36, 4.61]
1.9.4 Pain	2	307	Mean Difference (IV, Random, 95% CI)	0.35 [-7.41, 8.12]
1.9.5 Constipation	2	307	Mean Difference (IV, Random, 95% CI)	-2.17 [-7.24, 2.89]
1.9.6 Insomnia	2	307	Mean Difference (IV, Random, 95% CI)	0.30 [-0.86, 1.47]
1.9.7 Apetite loss	2	307	Mean Difference (IV, Random, 95% CI)	0.47 [-0.31, 1.24]
1.9.8 Dyspneoa	2	307	Mean Difference (IV, Random, 95% CI)	2.47 [-3.42, 8.36]
1.9.9 Diarrhoea	2	307	Mean Difference (IV, Random, 95% CI)	-0.77 [-12.69, 11.15]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.9.10 Financial difficulties	2	307	Mean Difference (IV, Random, 95% CI)	2.46 [-5.33, 10.25]
1.10 EORTC QLQ-C30 QoL at 12 months	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.10.1 Global health	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.10.2 Fatigue	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.10.3 Nausea	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.10.4 Pain	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.10.5 Dyspneoa	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.10.6 Insomnia	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.10.7 Apetite loss	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.10.8 Constipation	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.10.9 Diarrhoea	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.10.10 Financial difficulties	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

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

Study or Subgroup	log[Hazard Ratio]	SE	Favours NACT Total	PDS Total	Weight	Hazard Ratio IV, Random, 95% CI
Vergote 2010 (1)	-0.0202	0.09	334	336	40.2%	0.98 [0.82 , 1.17]
Kehoe 2015	-0.1393	0.0966	274	276	34.9%	0.87 [0.72 , 1.05]
Onda 2016	0.05	0.14	152	149	16.6%	1.05 [0.80 , 1.38]
Fagotti 2016	0.11	0.199	87	84	8.2%	1.12 [0.76 , 1.65]
Total (95% CI)			**847**	**845**	**100.0%**	**0.96 [0.86 , 1.08]**

Heterogeneity: Tau² = 0.00; Chi² = 2.09, df = 3 (P = 0.55); I² = 0%
Test for overall effect: Z = 0.69 (P = 0.49)
Test for subgroup differences: Not applicable

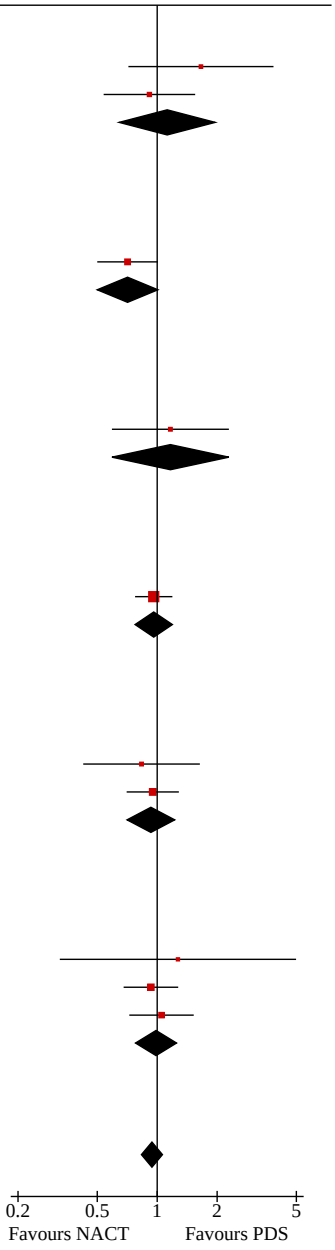


Footnotes

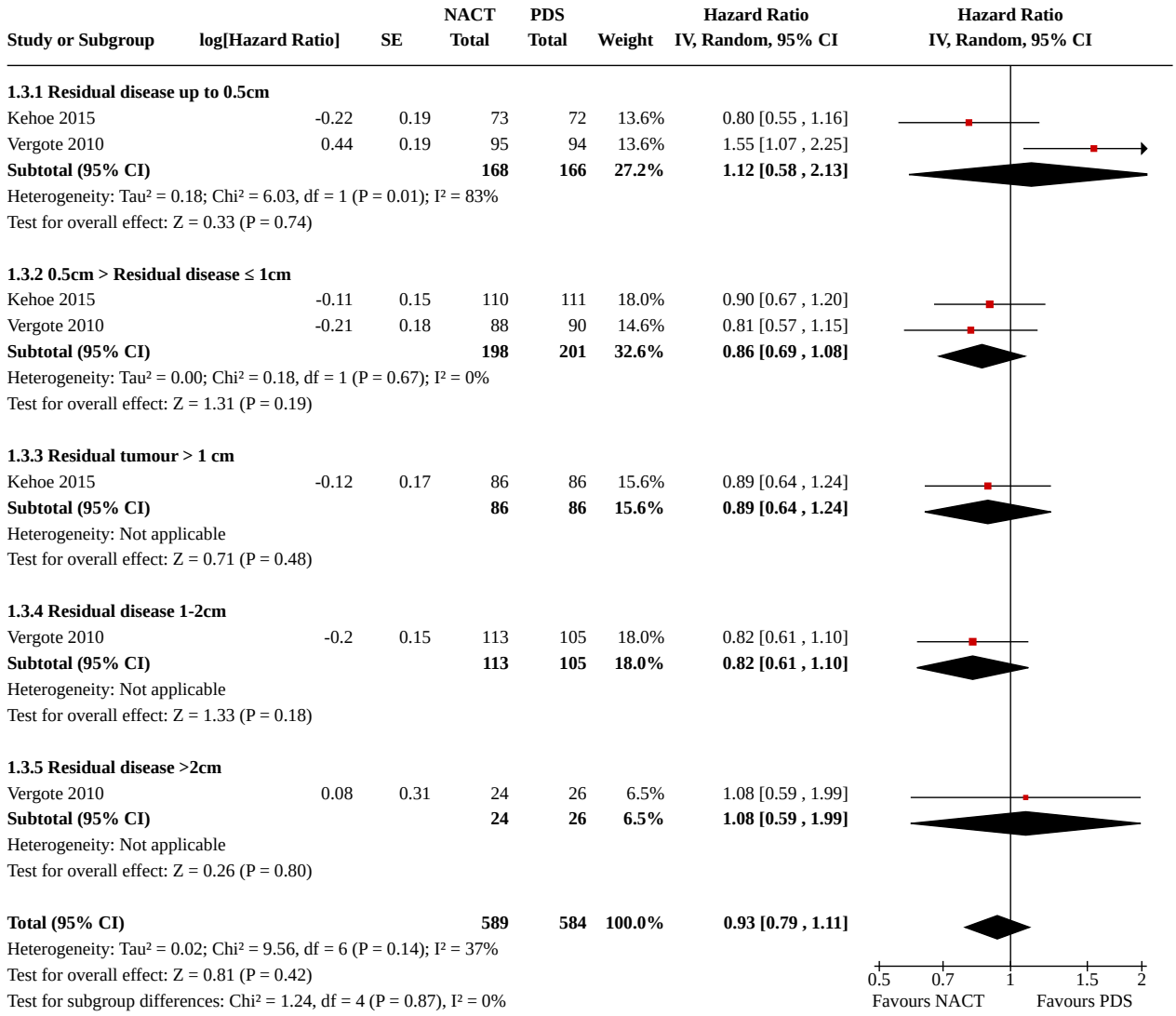
(1) We have applied 95% CIs (investigators reported 90% CIs).

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

Study or Subgroup	log[Hazard Ratio]	SE	NACT Total	PDS Total	Weight	Hazard Ratio IV, Random, 95% CI
1.2.1 Age < 50 years						
Fagotti 2016	0.506	0.428	23	22	2.1%	1.66 [0.72 , 3.84]
Vergote 2010	-0.09	0.27	47	37	5.3%	0.91 [0.54 , 1.55]
Subtotal (95% CI)			**70**	**59**	**7.4%**	**1.12 [0.64 , 1.96]**
Heterogeneity: Tau² = 0.05; Chi² = 1.39, df = 1 (P = 0.24); I² = 28%						
Test for overall effect: Z = 0.41 (P = 0.68)						
1.2.2 Age <60 years						
Kehoe 2015	-0.3425	0.1789	75	82	12.0%	0.71 [0.50 , 1.01]
Subtotal (95% CI)			**75**	**82**	**12.0%**	**0.71 [0.50 , 1.01]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.91 (P = 0.06)						
1.2.3 Age 50-60 years						
Fagotti 2016	0.1528	0.345	23	34	3.2%	1.17 [0.59 , 2.29]
Subtotal (95% CI)			**23**	**34**	**3.2%**	**1.17 [0.59 , 2.29]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.44 (P = 0.66)						
1.2.4 Age 50-70 years						
Vergote 2010	-0.04	0.11	210	229	31.7%	0.96 [0.77 , 1.19]
Subtotal (95% CI)			**210**	**229**	**31.7%**	**0.96 [0.77 , 1.19]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.36 (P = 0.72)						
1.2.5 Age 60-70 years						
Fagotti 2016	-0.181	0.344	33	23	3.2%	0.83 [0.43 , 1.64]
Kehoe 2015	-0.0513	0.154	116	99	16.2%	0.95 [0.70 , 1.28]
Subtotal (95% CI)			**149**	**122**	**19.4%**	**0.93 [0.71 , 1.22]**
Heterogeneity: Tau² = 0.00; Chi² = 0.12, df = 1 (P = 0.73); I² = 0%						
Test for overall effect: Z = 0.52 (P = 0.60)						
1.2.6 Age > 70 years						
Fagotti 2016	0.24	0.697	8	5	0.8%	1.27 [0.32 , 4.98]
Kehoe 2015	-0.0726	0.161	83	95	14.8%	0.93 [0.68 , 1.28]
Vergote 2010	0.05	0.19	77	70	10.6%	1.05 [0.72 , 1.53]
Subtotal (95% CI)			**168**	**170**	**26.2%**	**0.99 [0.78 , 1.25]**
Heterogeneity: Tau² = 0.00; Chi² = 0.38, df = 2 (P = 0.83); I² = 0%						
Test for overall effect: Z = 0.11 (P = 0.91)						
Total (95% CI)			**695**	**696**	**100.0%**	**0.94 [0.83 , 1.06]**
Heterogeneity: Tau² = 0.00; Chi² = 5.32, df = 9 (P = 0.81); I² = 0%						
Test for overall effect: Z = 0.98 (P = 0.33)						
Test for subgroup differences: Chi² = 3.45, df = 5 (P = 0.63), I² = 0%						

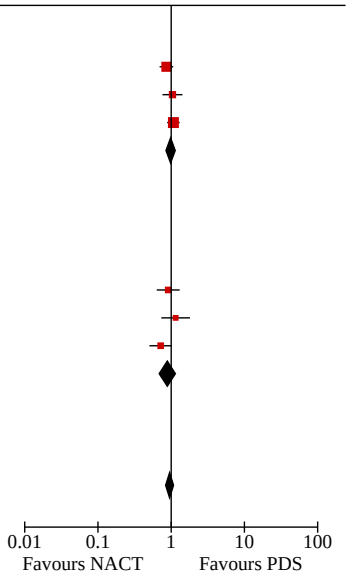


Analysis 1.3. Comparison 1: NACT vs PDS, Outcome 3: Overall survival by residual disease



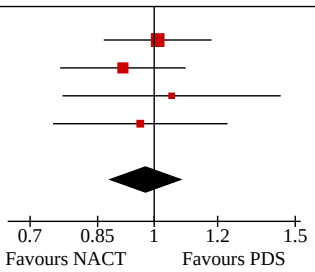
Analysis 1.4. Comparison 1: NACT vs PDS, Outcome 4: Overall survival by stage

Study or Subgroup	log[Hazard Ratio]	SE	NACT Total	PDS Total	Weight	Hazard Ratio IV, Random, 95% CI
1.4.1 Stage 3						
Kehoe 2015	-0.150823	0.109	206	206	26.5%	0.86 [0.69 , 1.06]
Onda 2016	0.04	0.16	105	100	13.9%	1.04 [0.76 , 1.42]
Vergote 2010	0.07	0.1	253	258	30.3%	1.07 [0.88 , 1.30]
Subtotal (95% CI)			**564**	**564**	**70.7%**	**0.98 [0.85 , 1.14]**
Heterogeneity: Tau² = 0.00; Chi² = 2.39, df = 2 (P = 0.30); I² = 16%						
Test for overall effect: Z = 0.25 (P = 0.80)						
1.4.2 Stage 4						
Kehoe 2015	-0.094311	0.1836	68	70	10.9%	0.91 [0.63 , 1.30]
Onda 2016	0.14	0.23	47	49	7.2%	1.15 [0.73 , 1.81]
Vergote 2010	-0.33	0.18	81	76	11.3%	0.72 [0.51 , 1.02]
Subtotal (95% CI)			**196**	**195**	**29.3%**	**0.88 [0.69 , 1.14]**
Heterogeneity: Tau² = 0.01; Chi² = 2.65, df = 2 (P = 0.27); I² = 25%						
Test for overall effect: Z = 0.94 (P = 0.35)						
Total (95% CI)			**760**	**759**	**100.0%**	**0.95 [0.84 , 1.08]**
Heterogeneity: Tau² = 0.00; Chi² = 5.77, df = 5 (P = 0.33); I² = 13%						
Test for overall effect: Z = 0.80 (P = 0.42)						
Test for subgroup differences: Chi² = 0.48, df = 1 (P = 0.49), I² = 0%						



Analysis 1.5. Comparison 1: NACT vs PDS, Outcome 5: Progression-free survival

Study or Subgroup	log[Hazard Ratio]	SE	NACT Total	PDS Total	Weight	Hazard Ratio IV, Random, 95% CI
Vergote 2010 (1)	0.01	0.079	334	336	42.3%	1.01 [0.87 , 1.18]
Kehoe 2015 (2)	-0.09	0.092	274	276	31.2%	0.91 [0.76 , 1.09]
Fagotti 2016	0.05	0.16	87	84	10.3%	1.05 [0.77 , 1.44]
Onda 2016	-0.04	0.128	152	149	16.1%	0.96 [0.75 , 1.23]
Total (95% CI)			**847**	**845**	**100.0%**	**0.98 [0.88 , 1.08]**
Heterogeneity: Tau² = 0.00; Chi² = 0.93, df = 3 (P = 0.82); I² = 0%						
Test for overall effect: Z = 0.49 (P = 0.62)						
Test for subgroup differences: Not applicable						



Footnotes

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

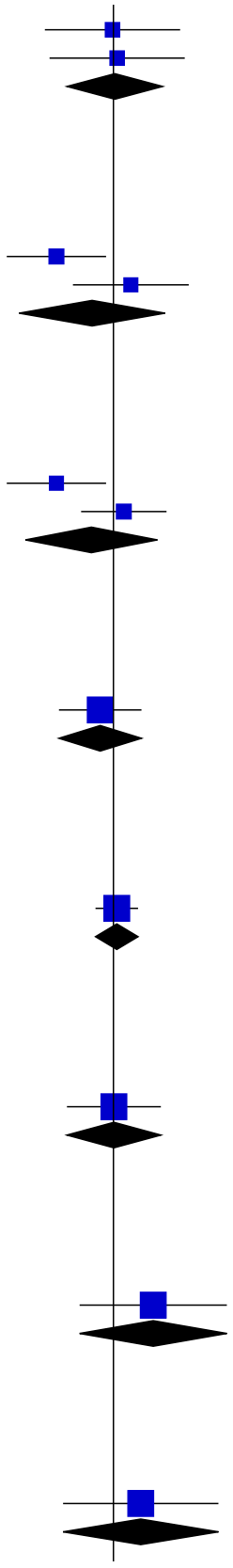
(2) 0.09

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

Study or Subgroup	NACT Events	NACT Total	PDS Events	PDS Total	Weight	Risk Ratio IV, Random, 95% CI
1.6.1 Haemorrhage						
Vergote 2010 (1)	12	322	23	310	31.0%	0.50 [0.25 , 0.99]
Kehoe 2015	14	219	8	255	25.6%	2.04 [0.87 , 4.77]
Fagotti 2016 (2)	34	74	42	84	43.4%	0.92 [0.66 , 1.27]
Subtotal (95% CI)		**615**		**649**	**100.0%**	**0.93 [0.50 , 1.74]**
Total events:	60		73			
Heterogeneity: Tau² = 0.20; Chi² = 6.39, df = 2 (P = 0.04); I² = 69%						
Test for overall effect: Z = 0.21 (P = 0.83)						
1.6.2 Need for blood transfusion						
Vergote 2010	155	289	181	310	47.0%	0.92 [0.80 , 1.06]
Chekman 2015	9	41	15	41	7.9%	0.60 [0.30 , 1.21]
Fagotti 2016	5	52	15	55	4.7%	0.35 [0.14 , 0.90]
Onda 2016	79	150	98	147	40.4%	0.79 [0.65 , 0.96]
Subtotal (95% CI)		**532**		**553**	**100.0%**	**0.80 [0.65 , 0.99]**
Total events:	248		309			
Heterogeneity: Tau² = 0.02; Chi² = 6.03, df = 3 (P = 0.11); I² = 50%						
Test for overall effect: Z = 2.07 (P = 0.04)						
1.6.3 Venous thromboembolism						
Vergote 2010	0	322	8	310	15.0%	0.06 [0.00 , 0.98]
Kehoe 2015	0	219	5	255	14.6%	0.11 [0.01 , 1.90]
Fagotti 2016	0	52	3	55	14.1%	0.15 [0.01 , 2.85]
Onda 2016	4	130	7	147	56.3%	0.65 [0.19 , 2.16]
Subtotal (95% CI)		**723**		**767**	**100.0%**	**0.28 [0.09 , 0.90]**
Total events:	4		23			
Heterogeneity: Tau² = 0.25; Chi² = 3.53, df = 3 (P = 0.32); I² = 15%						
Test for overall effect: Z = 2.14 (P = 0.03)						
1.6.4 Infection						
Vergote 2010	5	322	25	310	43.8%	0.19 [0.07 , 0.50]
Kehoe 2015	6	219	16	255	46.4%	0.44 [0.17 , 1.10]
Fagotti 2016	0	52	4	55	4.7%	0.12 [0.01 , 2.13]
Onda 2016	1	130	1	147	5.2%	1.13 [0.07 , 17.90]
Subtotal (95% CI)		**723**		**767**	**100.0%**	**0.30 [0.16 , 0.56]**
Total events:	12		46			
Heterogeneity: Tau² = 0.00; Chi² = 2.77, df = 3 (P = 0.43); I² = 0%						
Test for overall effect: Z = 3.75 (P = 0.0002)						
1.6.5 Gastrointestinal fistula						
Vergote 2010	1	322	3	310	27.9%	0.32 [0.03 , 3.07]
Kehoe 2015	1	219	2	255	24.8%	0.58 [0.05 , 6.38]
Onda 2016	0	130	5	147	17.1%	0.10 [0.01 , 1.84]
Fagotti 2016 (3)	1	74	4	84	30.2%	0.28 [0.03 , 2.48]
Subtotal (95% CI)		**745**		**796**	**100.0%**	**0.30 [0.09 , 0.97]**
Total events:	3		14			
Heterogeneity: Tau² = 0.00; Chi² = 0.83, df = 3 (P = 0.84); I² = 0%						
Test for overall effect: Z = 2.01 (P = 0.04)						
1.6.6 Urinary/vaginal fistula						
Vergote 2010	1	322	1	310	50.0%	0.96 [0.06 , 15.32]
Kehoe 2015	1	219	1	255	50.0%	1.16 [0.07 , 18.51]

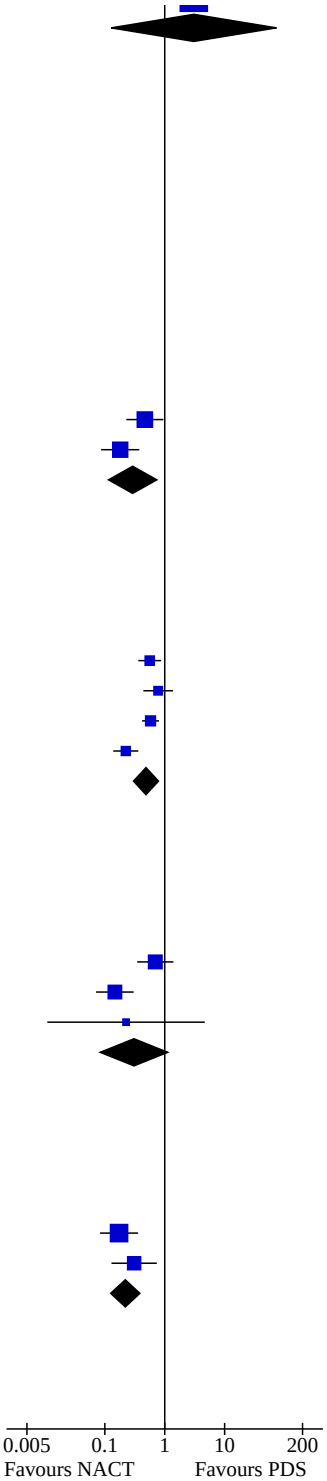
Analysis 1.6. (Continued)

Vergote 2010	1	322	1	310	50.0%	0.96 [0.06 , 15.32]
Kehoe 2015	1	219	1	255	50.0%	1.16 [0.07 , 18.51]
Subtotal (95% CI)		**541**		**565**	**100.0%**	**1.06 [0.15 , 7.49]**
Total events:	2		2			
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.92); I² = 0%						
Test for overall effect: Z = 0.06 (P = 0.95)						
1.6.7 Nausea						
Kehoe 2015	1	219	12	255	52.1%	0.10 [0.01 , 0.74]
Fagotti 2016	2	51	1	52	47.9%	2.04 [0.19 , 21.80]
Subtotal (95% CI)		**270**		**307**	**100.0%**	**0.42 [0.02 , 8.23]**
Total events:	3		13			
Heterogeneity: Tau² = 3.37; Chi² = 3.66, df = 1 (P = 0.06); I² = 73%						
Test for overall effect: Z = 0.57 (P = 0.57)						
1.6.8 Vomiting						
Kehoe 2015	1	219	12	255	48.2%	0.10 [0.01 , 0.74]
Fagotti 2016	3	51	2	52	51.8%	1.53 [0.27 , 8.77]
Subtotal (95% CI)		**270**		**307**	**100.0%**	**0.41 [0.03 , 6.03]**
Total events:	4		14			
Heterogeneity: Tau² = 2.87; Chi² = 4.07, df = 1 (P = 0.04); I² = 75%						
Test for overall effect: Z = 0.66 (P = 0.51)						
1.6.9 Diarrhoea						
Kehoe 2015	2	219	4	255	100.0%	0.58 [0.11 , 3.15]
Subtotal (95% CI)		**219**		**255**	**100.0%**	**0.58 [0.11 , 3.15]**
Total events:	2		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.63 (P = 0.53)						
1.6.10 Neutropenia						
Fagotti 2016	9	51	8	52	100.0%	1.15 [0.48 , 2.74]
Subtotal (95% CI)		**51**		**52**	**100.0%**	**1.15 [0.48 , 2.74]**
Total events:	9		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.31 (P = 0.76)						
1.6.11 Neutrotoxicity						
Fagotti 2016	2	51	2	52	100.0%	1.02 [0.15 , 6.97]
Subtotal (95% CI)		**51**		**52**	**100.0%**	**1.02 [0.15 , 6.97]**
Total events:	2		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.02 (P = 0.98)						
1.6.12 Thrombocytopenia						
Fagotti 2016	2	51	0	52	100.0%	5.10 [0.25 , 103.61]
Subtotal (95% CI)		**51**		**52**	**100.0%**	**5.10 [0.25 , 103.61]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.06 (P = 0.29)						
1.6.13 Febrile neutropenia						
Fagotti 2016	1	51	0	52	100.0%	3.06 [0.13 , 73.36]
Subtotal (95% CI)		**51**		**52**	**100.0%**	**3.06 [0.13 , 73.36]**
Total events:	1		0			



Analysis 1.6. (Continued)

Subtotal (95% CI)		**51**		**52**	**100.0%**	**3.06 [0.13 , 73.36]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
1.6.14 Renal toxicity						
Fagotti 2016	0	51	0	52		Not estimable
Subtotal (95% CI)		**51**		**52**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.6.15 Stoma formation						
Kehoe 2015	10	219	25	255	50.5%	0.47 [0.23 , 0.95]
Fagotti 2016	7	74	44	84	49.5%	0.18 [0.09 , 0.38]
Subtotal (95% CI)		**293**		**339**	**100.0%**	**0.29 [0.12 , 0.74]**
Total events:	17		69			
Heterogeneity: Tau² = 0.31; Chi² = 3.30, df = 1 (P = 0.07); I² = 70%						
Test for overall effect: Z = 2.60 (P = 0.009)						
1.6.16 Bowel resection						
Vergote 2010	28	322	48	310	25.4%	0.56 [0.36 , 0.87]
Kehoe 2015	18	219	27	255	22.2%	0.78 [0.44 , 1.37]
Onda 2016	39	152	66	149	28.1%	0.58 [0.42 , 0.80]
Fagotti 2016 (4)	14	74	71	84	24.4%	0.22 [0.14 , 0.36]
Subtotal (95% CI)		**767**		**798**	**100.0%**	**0.49 [0.30 , 0.79]**
Total events:	99		212			
Heterogeneity: Tau² = 0.19; Chi² = 14.10, df = 3 (P = 0.003); I² = 79%						
Test for overall effect: Z = 2.94 (P = 0.003)						
1.6.17 Splenectomy						
Vergote 2010	13	322	18	310	43.5%	0.70 [0.35 , 1.39]
Fagotti 2016	7	74	54	84	43.1%	0.15 [0.07 , 0.30]
Onda 2016	0	130	2	147	13.4%	0.23 [0.01 , 4.66]
Subtotal (95% CI)		**526**		**541**	**100.0%**	**0.31 [0.08 , 1.12]**
Total events:	20		74			
Heterogeneity: Tau² = 0.88; Chi² = 9.26, df = 2 (P = 0.010); I² = 78%						
Test for overall effect: Z = 1.79 (P = 0.07)						
1.6.18 Post- operative G3+ events						
Fagotti 2016 (5)	7	74	46	84	58.7%	0.17 [0.08 , 0.36]
Onda 2016	6	130	22	147	41.3%	0.31 [0.13 , 0.74]
Subtotal (95% CI)		**204**		**231**	**100.0%**	**0.22 [0.13 , 0.38]**
Total events:	13		68			
Heterogeneity: Tau² = 0.00; Chi² = 1.00, df = 1 (P = 0.32); I² = 0%						
Test for overall effect: Z = 5.31 (P < 0.00001)						



Footnotes

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

(2) Estimated Blood Loss >750 ml for those who had surgery

(3) three pancreatic fistulae and one biliary fistula

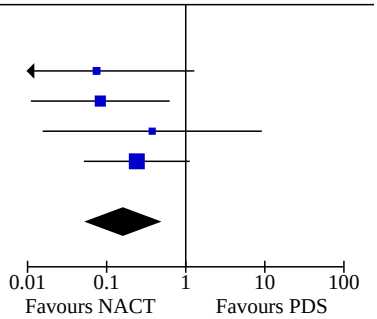
(4) Single bowel resection (NACT = 10 versus PDS = 52); multiple bowel resections (NACT= 4 versus PDS =19)

(5) within 30 days of surgery. Further post-op SAE > 30 days (NACT =1; PDS = 13)

Analysis 1.7. Comparison 1: NACT vs PDS, Outcome 7: Postoperative mortality

Study or Subgroup	NACT Events	NACT Total	PDS Events	PDS Total	Weight	Risk Ratio IV, Random, 95% CI
Chekman 2015	0	41	0	40		Not estimable
Fagotti 2016 (1)	0	75	7	84	13.9%	0.07 [0.00 , 1.28]
Kehoe 2015 (2)	1	219	14	255	27.6%	0.08 [0.01 , 0.63]
Onda 2016 (3)	0	130	1	147	11.1%	0.38 [0.02 , 9.16]
Vergote 2010 (2)	2	322	8	310	47.4%	0.24 [0.05 , 1.12]
Total (95% CI)		**787**		**836**	**100.0%**	**0.16 [0.06 , 0.46]**
Total events:	3		30			

Heterogeneity: Tau² = 0.00; Chi² = 1.22, df = 3 (P = 0.75); I² = 0%
Test for overall effect: Z = 3.38 (P = 0.0007)
Test for subgroup differences: Not applicable



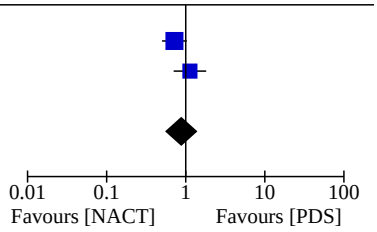
Footnotes

(1) Fagotti 2016 includes 3 post-op deaths within 30 days and a further 4 late post-op deaths, over 30 days, due to post-op complications.
(2) deaths within 28 days of surgery
(3) Defined as 'treatment-related deaths related to surgery' within 4 weeks of surgery

Analysis 1.8. Comparison 1: NACT vs PDS, Outcome 8: Chemotherapy-related SAEs (G3+)

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio IV, Random, 95% CI
Kehoe 2015	102	254	110	228	56.0%	0.72 [0.50 , 1.03]
Onda 2016 (1)	62	149	53	137	44.0%	1.13 [0.70 , 1.81]
Total (95% CI)		**403**		**365**	**100.0%**	**0.88 [0.57 , 1.36]**
Total events:	164		163			

Heterogeneity: Tau² = 0.06; Chi² = 2.20, df = 1 (P = 0.14); I² = 54%
Test for overall effect: Z = 0.58 (P = 0.56)
Test for subgroup differences: Not applicable

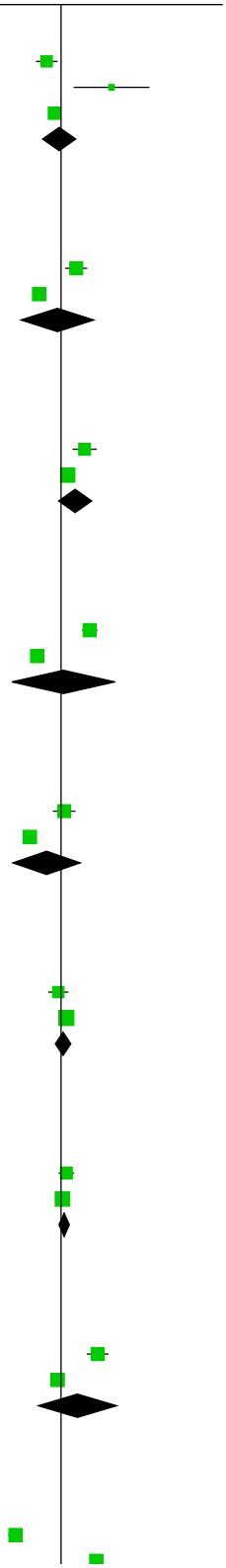


Footnotes

(1) Combination of SAEs during cycles 1-4 and 5-8 (All SAEs excluding bone marrow suppression)

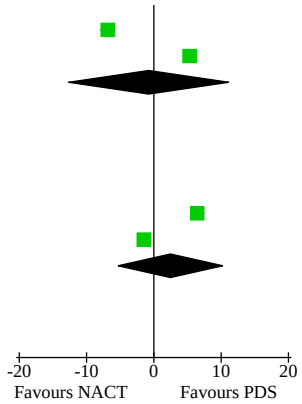
Analysis 1.9. Comparison 1: NACT vs PDS, Outcome 9: EORTC QLQ-C30 QoL at 6 months

Study or Subgroup	NACT Mean	NACT SD	NACT Total	PDS Mean	PDS SD	PDS Total	Weight	Mean Difference IV, Random, 95% CI
1.9.1 Global health								
Fagotti 2016	59.14	4.08	49	61.28	3.98	46	40.2%	-2.14 [-3.76 , -0.52]
Kehoe 2015	69.1	18.71	114	61.5	23.63	103	13.6%	7.60 [1.89 , 13.31]
Vergote 2010 (1)	72.1	2.8	99	73.1	3	113	46.2%	-1.00 [-1.78 , -0.22]
Subtotal (95% CI)			**262**			**262**	**100.0%**	**-0.29 [-2.77 , 2.20]**
Heterogeneity: Tau² = 3.33; Chi² = 10.56, df = 2 (P = 0.005); I² = 81%								
Test for overall effect: Z = 0.22 (P = 0.82)								
1.9.2 Fatigue								
Fagotti 2016	34.33	4.5	49	32.04	3.74	46	49.3%	2.29 [0.63 , 3.95]
Vergote 2010	25.7	3.5	99	29	3.8	113	50.7%	-3.30 [-4.28 , -2.32]
Subtotal (95% CI)			**148**			**159**	**100.0%**	**-0.55 [-6.02 , 4.93]**
Heterogeneity: Tau² = 15.14; Chi² = 32.25, df = 1 (P < 0.00001); I² = 97%								
Test for overall effect: Z = 0.20 (P = 0.84)								
1.9.3 Nausea								
Fagotti 2016	34.37	4.72	49	30.82	4.34	46	44.1%	3.55 [1.73 , 5.37]
Vergote 2010	4.2	2.2	99	3.2	2.3	113	55.9%	1.00 [0.39 , 1.61]
Subtotal (95% CI)			**148**			**159**	**100.0%**	**2.12 [-0.36 , 4.61]**
Heterogeneity: Tau² = 2.77; Chi² = 6.77, df = 1 (P = 0.009); I² = 85%								
Test for overall effect: Z = 1.68 (P = 0.09)								
1.9.4 Pain								
Fagotti 2016	14.86	3.37	49	10.54	2.25	46	49.9%	4.32 [3.17 , 5.47]
Vergote 2010	15.4	3.6	99	19	3.8	113	50.1%	-3.60 [-4.60 , -2.60]
Subtotal (95% CI)			**148**			**159**	**100.0%**	**0.35 [-7.41 , 8.12]**
Heterogeneity: Tau² = 31.06; Chi² = 104.45, df = 1 (P < 0.00001); I² = 99%								
Test for overall effect: Z = 0.09 (P = 0.93)								
1.9.5 Constipation								
Fagotti 2016	41.43	4.42	49	40.96	4.05	46	48.8%	0.47 [-1.23 , 2.17]
Vergote 2010	13.2	2.6	99	17.9	2.8	113	51.2%	-4.70 [-5.43 , -3.97]
Subtotal (95% CI)			**148**			**159**	**100.0%**	**-2.17 [-7.24 , 2.89]**
Heterogeneity: Tau² = 12.92; Chi² = 29.93, df = 1 (P < 0.00001); I² = 97%								
Test for overall effect: Z = 0.84 (P = 0.40)								
1.9.6 Insomnia								
Fagotti 2016	17.49	3.74	49	17.9	3.8	46	40.9%	-0.41 [-1.93 , 1.11]
Vergote 2010	27.2	4.1	99	26.4	4.3	113	59.1%	0.80 [-0.33 , 1.93]
Subtotal (95% CI)			**148**			**159**	**100.0%**	**0.30 [-0.86 , 1.47]**
Heterogeneity: Tau² = 0.27; Chi² = 1.57, df = 1 (P = 0.21); I² = 36%								
Test for overall effect: Z = 0.51 (P = 0.61)								
1.9.7 Apetite loss								
Fagotti 2016	24.61	3.32	49	23.8	2.49	46	43.8%	0.81 [-0.37 , 1.99]
Vergote 2010	9.5	3.7	99	9.3	4	113	56.2%	0.20 [-0.84 , 1.24]
Subtotal (95% CI)			**148**			**159**	**100.0%**	**0.47 [-0.31 , 1.24]**
Heterogeneity: Tau² = 0.00; Chi² = 0.58, df = 1 (P = 0.45); I² = 0%								
Test for overall effect: Z = 1.18 (P = 0.24)								
1.9.8 Dyspneoa								
Fagotti 2016	20.73	4.33	49	15.22	3.8	46	49.4%	5.51 [3.87 , 7.15]
Vergote 2010	16.3	3.7	99	16.8	3.9	113	50.6%	-0.50 [-1.52 , 0.52]
Subtotal (95% CI)			**148**			**159**	**100.0%**	**2.47 [-3.42 , 8.36]**
Heterogeneity: Tau² = 17.58; Chi² = 37.26, df = 1 (P < 0.00001); I² = 97%								
Test for overall effect: Z = 0.82 (P = 0.41)								
1.9.9 Diarrhoea								
Fagotti 2016	7.12	1.91	49	13.98	3.3	46	49.9%	-6.86 [-7.95 , -5.77]
Vergote 2010	9.4	1.9	99	4.1	2	113	50.1%	5.30 [4.77 , 5.83]



Analysis 1.9. (Continued)

Fagotti 2016	7.12	1.91	49	13.98	3.3	46	49.9%	-6.86 [-7.95 , -5.77]
Vergote 2010	9.4	1.9	99	4.1	2	113	50.1%	5.30 [4.77 , 5.83]
Subtotal (95% CI)			**148**			**159**	**100.0%**	**-0.77 [-12.69 , 11.15]**
Heterogeneity: Tau² = 73.74; Chi² = 386.02, df = 1 (P < 0.00001); I² = 100%								
Test for overall effect: Z = 0.13 (P = 0.90)								
1.9.10 Financial difficulties								
Fagotti 2016	39.47	2.56	49	33.02	2.66	46	49.8%	6.45 [5.40 , 7.50]
Vergote 2010	10.2	1.9	99	11.7	2	113	50.2%	-1.50 [-2.03 , -0.97]
Subtotal (95% CI)			**148**			**159**	**100.0%**	**2.46 [-5.33 , 10.25]**
Heterogeneity: Tau² = 31.42; Chi² = 175.84, df = 1 (P < 0.00001); I² = 99%								
Test for overall effect: Z = 0.62 (P = 0.54)								
Test for subgroup differences: Chi² = 4.05, df = 9 (P = 0.91), I² = 0%								

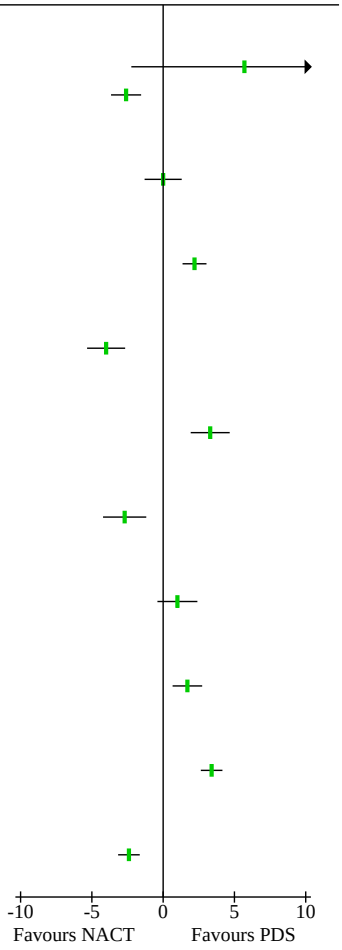


Footnotes

(1) Kehoe 2015 data now combined, as authors confirm Global QoL scores were on same EORTC QLQ-C30 scale as Vergote 2010 and Fagotti 2016 studies

Analysis 1.10. Comparison 1: NACT vs PDS, Outcome 10: EORTC QLQ-C30 QoL at 12 months

	NACT			PDS			Mean Difference	Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**IV, Random, 95% CI**	**IV, Random, 95% CI**
1.10.1 Global health								
Kehoe 2015	67.5	22.38	69	61.8	24.16	64	5.70 [-2.23 , 13.63]	
Vergote 2010	67.8	3.1	64	70.4	3.3	78	-2.60 [-3.66 , -1.54]	
1.10.2 Fatigue								
Vergote 2010	29.1	3.8	64	29.1	4.1	78	0.00 [-1.30 , 1.30]	
1.10.3 Nausea								
Vergote 2010	5.6	2.4	64	3.4	2.7	78	2.20 [1.36 , 3.04]	
1.10.4 Pain								
Vergote 2010	15.1	3.9	64	19.1	4.2	78	-4.00 [-5.33 , -2.67]	
1.10.5 Dyspneoa								
Vergote 2010	18.9	4	64	15.6	4.3	78	3.30 [1.93 , 4.67]	
1.10.6 Insomnia								
Vergote 2010	22.1	4.4	64	24.8	4.8	78	-2.70 [-4.22 , -1.18]	
1.10.7 Apetite loss								
Vergote 2010	10.6	4.1	64	9.6	4.4	78	1.00 [-0.40 , 2.40]	
1.10.8 Constipation								
Vergote 2010	14.2	3	64	12.5	3.3	78	1.70 [0.66 , 2.74]	
1.10.9 Diarrhoea								
Vergote 2010	8.1	2.2	64	4.7	2.4	78	3.40 [2.64 , 4.16]	
1.10.10 Financial difficulties								
Vergote 2010	10	2.2	64	12.4	2.4	78	-2.40 [-3.16 , -1.64]	



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 as all included studies used 2009 classification not 2018

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 date:

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.

MEDLINE Sept 2006 to date:

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

#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 or <80% assessed at endpoint for at least the primary outcomes);
- 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
7 April 2021	New citation required but conclusions have not changed	Review updated but conclusions not changed
7 April 2021	New search has been performed	New search to 9 October 2020 and data added from studies included in previous version

HISTORY

Protocol first published: Issue 3, 2005
Review first published: Issue 4, 2007

Date	Event	Description
1 February 2021	Amended	Correction to survival data for Kehoe 2015
1 February 2021	New citation required but conclusions have not changed	New citation required but conclusions have not changed. Correction to survival data for Kehoe 2015
29 May 2019	New search has been performed	Search updated 11 February 2019.
28 May 2019	New citation required but conclusions have not changed	Updated with inclusion of four new studies. Three ongoing unpublished studies identified.
27 March 2014	Amended	Contact details updated.

Date	Event	Description
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 #a; Kumar #a; Onda #a).
21 June 2012	New citation required and conclusions have changed	One new trial (Vergote 2010) included. Conclusions changed.

CONTRIBUTIONS OF AUTHORS

- Sarah Coleridge: co-review author, sifted original search results, assessed papers, evaluated included papers, extracted data and co-wrote this review update.
- Andrew Bryant: assisted with data extraction, data analysis and writing of the final version of the review update.
- Sean Kehoe: original idea for review and approved final versions of the protocol, original review and previous updates.
- Jo Morrison: co-review author, wrote protocol, sifted search results, assessed papers, evaluated included papers, extracted data, contributed to analysis and co-wrote the review and its updates.

DECLARATIONS OF INTEREST

Sarah Coleridge: no conflict of interest
Andrew Bryant: no conflict of interest
Sean Kehoe: principle investigator of included study, therefore excluded from title screening, data extraction and all analyses/GRADE decisions
Jo Morrison: no conflict of interest

SOURCES OF SUPPORT

Internal sources

- New Source of support, UK

  The review update was performed without formal internal support.

External sources

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

  A previous up-date of the 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. This most recent updates has been performed without specific funding. No external support was received for this update.

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 and reporting the risk of bias of included studies has changed from the protocol.

We apply GRADE approach and have added a 'Summary of findings' table, which was not part of Cochrane methodology at the time the original protocol was published.

Although these were not in the original protocol, these were included in the previous update of this review and applied again to this latest update, so were pre-specified prior to this update.

On advice of a reviewer we have added bowel resection and stoma formation to the outcome measures and included these in the Summary of findings 1, as these are important outcomes for women and can have life-long effects. In this update we have also included post-operative death as a specific outcome in the Summary of findings 1, which although it is a grade 5 SAE of surgical morbidity, which was therefore one of the specified outcomes for collection, was not separately reported in previous versions of the review.

INDEX TERMS

Medical Subject Headings (MeSH)

Antineoplastic Agents [*therapeutic use]; Bias; *Carcinoma, Ovarian Epithelial [drug therapy] [mortality] [pathology] [surgery]; Chemotherapy, Adjuvant [methods] [mortality]; Cytoreduction Surgical Procedures [adverse effects] [*methods] [mortality]; Neoadjuvant Therapy [*methods]; *Ovarian Neoplasms [drug therapy] [mortality] [pathology] [surgery]; Postoperative Complications [epidemiology] [etiology]; Preoperative Care; Progression-Free Survival; Randomized Controlled Trials as Topic; Treatment Outcome

MeSH check words

Female; Humans