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Ultra-radical (extensive) surgery versus standard surgery for the primary cytoreduction of advanced epithelial ovarian cancer (Review)

Hiu S, Bryant A, Gajjar K, Kunonga PT, Naik R

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[Intervention Review]

Ultra-radical (extensive) surgery versus standard surgery for the primary cytoreduction of advanced epithelial ovarian cancer

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ABSTRACT

Background

Ovarian cancer is the seventh most common cancer among women and the leading cause of death in women with gynaecological malignancies. Opinions differ regarding the role of ultra-radical (extensive) cytoreductive surgery in ovarian cancer treatment.

Objectives

To evaluate the effectiveness and morbidity associated with ultra-radical/extensive surgery in the management of advanced-stage epithelial ovarian cancer.

Search methods

We searched CENTRAL (2021, Issue 11), MEDLINE Ovid and Embase Ovid up to November 2021. We also searched registers of clinical trials, abstracts of scientific meetings, reference lists of included studies and contacted experts in the field.

Selection criteria

Randomised controlled trials (RCTs) or non-randomised studies (NRS), analysed using multivariate methods, that compared ultra-radical/extensive and standard surgery in women with advanced primary epithelial ovarian cancer.

Data collection and analysis

Two review authors independently assessed whether potentially relevant studies met the inclusion criteria, abstracted data and assessed the risk of bias. We identified three NRS and conducted meta-analyses where possible.

Main results

We identified three retrospective observational studies for inclusion in the review. Two studies included women exclusively undergoing upfront primary debulking surgery (PDS) and the other study including both PDS and interval debulking surgical (IDS) procedures. All studies were at critical risk of bias due to retrospective and non-randomised study designs.

Meta-analysis of two studies, assessing 397 participants, found that women who underwent radical procedures, as part of PDS, may have a lower risk of mortality compared to women who underwent standard surgery (adjusted HR 0.60, 95% CI 0.43 to 0.82; I^2 = 0%; very low-certainty evidence), but the evidence is very uncertain. The results were robust to a sensitivity analysis including women with more-

extensive disease (carcinomatosis) (adjusted HR 0.61, 95% CI 0.44 to 0.85; I^2 = 0%; n = 283, very low-certainty evidence), but the evidence is very uncertain.

One study reported a comparison of radical versus standard surgical procedures associated with both PDS and IDS procedures, but a multivariate analysis was only undertaken for disease-free survival (DFS) and therefore the certainty of the evidence was not assessable for overall survival (OS) and remains very low. The lack of reporting of OS meant the study was at high risk of bias for selective reporting of outcomes.

One study, 203 participants, found that women who underwent radical procedures as part of PDS may have a lower risk of disease progression or death compared to women who underwent standard surgery (adjusted HR 0.62, 95% CI 0.42 to 0.92; very low-certainty evidence), but the evidence is very uncertain. The results were robust to a sensitivity analysis in one study including women with carcinomatosis (adjusted HR 0.52, 95% CI 0.33 to 0.82; n = 139; very low-certainty evidence), but the evidence is very uncertain.

A combined analysis in one study found that women who underwent radical procedures (using both PDS and IDS) may have an increased chance of disease progression or death than those who received standard surgery (adjusted HR 1.60, 95% CI 1.11 to 2.31; I^2 = 0%; n = 527; very low-certainty evidence), but the evidence is very uncertain. In absolute and unadjusted terms, the DFS was 19.3 months in the standard surgery group, 15.8 in the PDS group and 15.9 months in the IDS group.

All studies were at critical risk of bias and we only identified very low-certainty evidence for all outcomes reported in the review. Perioperative mortality, adverse events and quality of life (QoL) outcomes were either not reported or inadequately reported in the included studies. Two studies reported perioperative mortality (death within 30 days of surgery), but they did not use any statistical adjustment. In total, there were only four deaths within 30 days of surgery in both studies. All were observed in the standard surgery group, but we did not report a risk ratio (RR) to avoid potentially misleading results with so few deaths and very low-certainty evidence. Similarly, one study reported postoperative morbidity, but the authors did not use any statistical adjustment. Postoperative morbidity occurred more commonly in women who received ultra-radical surgery compared to standard surgery, but the certainty of the evidence was very low.

Authors' conclusions

We found only very low-certainty evidence comparing ultra-radical surgery and standard surgery in women with advanced ovarian cancer. The evidence was limited to retrospective, NRSs and so is at critical risk of bias. The results may suggest that ultra-radical surgery could result in improved OS, but results are based on very few women who were chosen to undergo each intervention, rather than a randomised study and intention-to-treat analysis, and so the evidence is very uncertain. Results for progression/DFS were inconsistent and evidence was sparse. QoL and morbidity was incompletely or not reported in the three included studies.

A separate prognostic review assessing residual disease as a prognostic factor in this area has been addressed elsewhere, which demonstrates the prognostic effect of macroscopic debulking to no macroscopic residual disease.

In order to aid existing guidelines, the role of ultra-radical surgery in the management of advanced-stage ovarian cancer could be addressed through the conduct of a sufficiently powered, RCT comparing ultra-radical and standard surgery, or well-designed NRSs, if this is not possible.

PLAIN LANGUAGE SUMMARY

Ultra-radical (extensive) surgery versus standard surgery to remove tumours in women with advanced ovarian cancer

Review question

What are the benefits and harms of ultra-radical (extensive) versus standard surgery in the management of ovarian cancer?

Background

The ovaries are small glands found on either side of the womb that produce and store eggs, and make hormones that control the menstrual cycle (periods). Ovarian cancer is the most common cause of death in women with a cancer of the reproductive system. Opinions differ about whether women with advanced ovarian cancer have better outcomes if they have 'ultra-radical' surgery, which is much more extensive than standard surgery, to remove tumours. Standard surgery in an advanced disease setting still has an element of radicality and comprises as a minimum many of the surgical procedures involved in more radical surgery. Ultra-radical (extensive) surgery is an extension of standard surgery and may include at least one additional extensive surgical procedure.

Review methods

We searched the scientific literature for studies comparing ultra-radical and standard surgery for women with advanced ovarian cancer. We looked for randomised controlled trials, which are regarded as the best type of study, and for non-randomised studies that were analysed using methods that allow for differences between the groups of women receiving different types of surgery.

Key results

We identified three non-randomised studies. The evidence is very limited and uncertain for all results since women were chosen to undergo each type of treatment, rather than randomly allocated, so there is a very high (critical) risk of bias in these types of studies.

In two studies (397 women), women who had radical surgery to remove the tumour may have 18% to 57% less chance of death compared to women who had standard surgery. The results were similar for women with more-extensive disease. There were very few deaths within 30 days of surgery. There may be less chance of disease progression with radical surgery.

One study compared radical versus standard surgery associated with both upfront primary (tumour removed before starting chemotherapy) and interval debulking (tumour removed between chemotherapy sessions) surgery on death, but the comparison was not fair and there was high risk of bias for reporting of outcomes.

One study (203 women) found that women who had radical procedures as part of upfront primary debulking surgery may have 8% to 58% less chance of disease progression or death compared to women who had standard surgery. The results were similar when including only the 139 women with more-extensive disease (where risk was 18% to 67% lower).

One analysis (527 women) merging radical surgery groups in one study found that women who underwent ultra-radical procedures (using both upfront primary and interval debulking surgical procedures) may be associated with 11% to 60% increased chance of disease progression or death than those who received standard surgery.

All studies were at very high (critical) risk of bias and we were very unsure about the evidence. We included relatively few women due to our stringent inclusion criteria. Studies either did not report or inadequately reported death, side effects or quality of life.

Main conclusions and certainty in the evidence

Although some of these results may suggest that survival may be better in women receiving upfront primary ultra-radical surgery rather than standard surgery, extreme caution is required with interpretation, as the studies were not well designed or analysed, and thus the effects could even be in the opposite direction.

We are unable to reach any definite conclusions about the relative benefits and harms of the two types of surgery. Better designed, large studies are needed.

Summary of findings 1. Ultra-radical (extensive) surgery compared to standard surgery in women with stage IIIc or IV ovarian cancer

Ultra-radical (extensive) surgery compared to standard (radical) surgery in women with stage IIIc or IV ovarian cancer

Patient or population: women with stage IIIc or IV ovarian cancer
Setting: –
Intervention: ultra-radical (extensive) surgery
Comparison: standard surgery

Outcomes	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	What does this mean?	Comments
Survival (overall and disease- specific) Follow-up: median 43–49 months Overall survival was listed as the desired primary outcome in the protocol and we note the potential issues of reporting disease-specific survival.	**HR 0.60** (0.43 to 0.82)	397 (2 studies)	⊕⊖⊖⊖ **Very low**[a,b,c]	Survival may be prolonged in woman who received ultra-radical surgery compared to standard surgery but the evidence was limited and very uncertain. More studies are needed.	We could not present illustrative absolute effects because a representative control group risk could not be ascertained from the studies. The HR estimates were adjusted for in multivariable analyses and this cannot be done in absolute terms so we made no attempt as numbers were likely to mislead. 1 study reported 5-year disease-specific survival rather than categorising deaths by any cause. We made an assumption that most women with advanced-stage disease would die of the disease rather than other comorbidities. The results were robust to a sensitivity analysis that included 2 studies assessing 283 women with more-extensive disease (carcinomatosis) (adjusted HR 0.61, 95% CI 0.44 to 0.85; I^2 = 0%; very low-certainty evidence).
Progression-free survival Follow-up: median 43	**HR 0.62** (0.42 to 0.92)	203 (1 observational study)	⊕⊖⊖⊖ **Very low**[a,b,c]	Disease progression may be delayed in woman who received ultra-radical surgery compared to standard surgery but the evidence was limited and very uncertain. More studies are needed.	Participants received upfront debulking surgery. The results were robust to a sensitivity analysis assessing a subset of 139 women with carcinomatosis (adjusted HR 0.52, 95% CI 0.33 to 0.82; very low-certainty evidence).

Disease-free survival Follow-up: median 49 months	**HR 1.60** (1.11 to 2.31)	527 (2 analyses from 1 observational study)	⊕⊖⊖⊖ **Very low**[a,b,c]	Disease may relapse earlier in woman who received ultra-radical surgery compared to standard surgery but the evidence was limited and very uncertain. More studies are needed.	Participants received upfront and interval debulking surgical procedures.
Rate of optimal cytoreduction	Although a secondary outcome, 'Optimal cytoreduction' was not reported in any multivariate analyses in any of the studies. We did not present any unadjusted results for this as it is likely that 'optimal cytoreduction' will be higher in ultraradical surgery and would not be a fair comparison.				
Recurrence rate	Not reported				
(Loco)regional control	Not reported				
Adverse event: **perioperative mortality** Follow-up: median 43–49 months	In total there were only 4 deaths within 30 days of surgery in both studies and none in the ultra-radical group. We did not report a RR as to not provide potentially misleading results with so few deaths.	397 (2 observational studies)	⊕⊖⊖⊖ **Very low**[a,b,c]	In total there were only 4 deaths within 30 days of surgery in both studies and none in the ultra-radical group. However, the evidence is limited and very uncertain and more studies are needed.	None of the studies reporting this serious adverse event used any statistical adjustment. Upfront debulking surgery In 1 study, there were 0 reported cases of perioperative mortality within 30 days in the ultra-radical surgery group versus 3 women died in the standard surgical group. In another study, perioperative death within 30 days occurred in 0/119 (0%) in the surgery group versus 1/84 (1.2%) in the standard group.
Adverse event: **serious postoperative morbidity** Follow-up: median 43	**RR 3.24** (1.84 to 5.68)	203 (1 observational study)	⊕⊖⊖⊖ **Very low**[a,b,c]	Significant postoperative morbidity occurred in 32/84 (38.1%) women in the in ultra-radical group versus 14/119 (11.8%) women in the standard surgery group. However, the evidence is limited and very uncertain and more studies are needed.	This study did not use any statistical adjustment for this adverse event. Women received upfront debulking surgery.
Quality of Life	Not reported				

CI: confidence interval; **HR:** hazard ratio; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

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

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[a]Downgraded one level for sparse data.
[b]Downgraded one level for high risk of bias concerns.
[c]Downgraded one level as outcomes were incompletely or inadequately (or both) reported.

BACKGROUND

Description of the condition

Ovarian cancer is the seventh most common cancer among women and the leading cause of death in women with gynaecological malignancies. Globally, there are over 200,000 new cases per year, with approximately 6.1 new cases per 100,000 women per year. A woman's cumulative risk of developing ovarian cancer by the age of 75 years is 0.7%: 0.5% in low-income countries and 1.0% in low- to middle-income countries (GLOBOCAN 2018). It is less common in women under the age of 40 years, and the incidence increases with age. In Europe, approximately 38% of women with ovarian cancer are alive five years after diagnosis (EUROCARE 2015), largely because the early stages of the disease often present with very few, if any, specific symptoms so most women present with advanced-stage disease (Bast 2020; Kirby 2020; Kurman 2008; Lancet 2007; Siegel 2020; Visintin 2008; Webb 2017). Symptoms include: abdominal distension, bloating, indigestion, urinary frequency, urinary urgency, early satiety, weight loss, reduced appetite, abdominal and pelvic pain, and, less commonly, vaginal bleeding (Rani 2018).

Cancers of the ovary are classified according to their cells of origin. Most ovarian cancers originate from the surface (epithelial) cells of the ovary/fallopian tubes and are termed epithelial tumours, although some cancers can also arise from the substance of the ovary, called stromal tumours, or from embryological differentiation (sex cord and germ cell tumours) (American Cancer Society 2020; CRUK 2018; Kurman 2014). The staging of ovarian cancer is based on the International Federation of Gynaecology and Obstetrics (FIGO) classification system (Berek 2018; PDQ Adult Treatment Editorial Board 2021; Prat 2014)). FIGO staging depends on the findings at the time of surgery. Stages I and II constitute early-stage disease, where stage I is limited to the ovaries and stage II tumours extend to the pelvis. Stages III and IV constitute advanced disease. In stage III, the tumour extends outside the pelvis, or involves lymph nodes within the pelvis, and stage IV is where the tumour has spread to distant sites such as the liver, lungs and lymph nodes in the neck (Berek 2018).

Description of the intervention

Treatment for women with epithelial ovarian cancer (EOC) is a combination of surgery and platinum- and taxane-based chemotherapy. Prognosis depends not only on the stage and histological type of the tumour, but also how much disease is left behind (residual disease) following surgery. Studies have shown that residual disease after initial surgery is a strong independent prognostic factor for survival, with improvements in both overall and progression-free survival (PFS) being greatest in women with no visible disease, also known as no macroscopic residual disease (NMRD) or minimal (less than 1 cm, currently termed near-optimal cytoreduction) visible residual disease at the end of surgery (Bryant 2021). Women who undergo more-extensive surgery may be more likely to have tumour deposits of 2 cm or less at the end of surgery (Bristow 2002; Crawford 2005; Horowitz 2015). Survival for women who have residual tumour deposits of more than 2 cm or up to 2 cm at the end of the surgery appears to be similar, further suggesting that optimal cytoreduction is associated with improved survival rates (Bristow 2002; Bryant 2021). However, the extent of surgical resection required to achieve optimal cytoreduction remains controversial. There appears to be a universally diverse practice with huge variations in achieving the NMRD rate of between 22% and 98% (Bryant 2021).

Although there is a lack of evidence demonstrating a benefit from performing a hysterectomy at the time of debulking surgery, this is accepted practice as it aids the diagnosis of a primary tumour site, for example, serous papillary cancers and carcinosarcomas may originate from both the uterus and ovaries. It also helps in excluding synchronous primary uterine tumours. While systematic lymphadenectomy of non-bulky nodes has been shown to worsen outcomes (Harter 2019), removing the uterus and cervix, both tubes and ovaries, the omentum and enlarged lymph nodes is part of standard surgery (Aletti 2006a; Norell 2020; PDQ Adult Treatment Editorial Board 2021; Todo 2003; Vergote 2016).

There has been a shift in recent years in some centres to attempts at achieving complete cytoreduction with use of more-extensive and radical procedures in performing cytoreductive surgery (Phillips 2019). To achieve NMRD, surgeons often have to perform radical and ultra-radical procedures with associated significant postoperative morbidity and mortality. There were Grade 3 and 4 complications in 19% of women after debulking surgery for advanced ovarian cancer (Benedetti Panici 2015). In one meta-analysis, there were no important differences in the quality of life (QoL) of women in three randomised controlled trials (RCTs) comparing primary surgery with improvements over baseline at six and 12 months. However, there was insufficient evidence on QoL outcomes of women undergoing extensive or ultra-radical surgery compared with those undergoing less-extensive surgery (Kumar 2019). However, the results of the SOCQER-2 (Surgery in Ovarian Cancer – Quality of Life Evaluation Research – 2) cohort study showed the global QoL of women undergoing low-, intermediate- and high-complex surgery (based on a surgical complexity score) improved at 12 months after surgery and was no worse in women undergoing extensive surgery (Sundar 2021). This is an interesting result, as, if there are no significant differences in QoL and general morbidity after more-extensive surgery, then centres may be more inclined to perform more-aggressive surgery more often. Postoperative mortality within 28 days following debulking surgery for ovarian cancer was reported in 2.5% of cases who underwent primary debulking surgery in the EORTC (European Organisation for Research and Treatment of Cancer) 55971 and 6% of cases in CHORUS (Chemotherapy Or Upfront Surgery) trials (Kehoe 2015; Vergote 2010).

Women with widespread disease, which involves the upper abdomen, affecting the diaphragm, liver, spleen and omentum, or widespread disease affecting the bowel, will need much more radical surgery in order to achieve NMRD or optimal cytoreduction. The complexity of the procedures required to achieve these outcomes undoubtedly increases. Radical surgery including bowel resection, splenectomy, liver resection and diaphragmatic stripping has been described in the literature as treatment for advanced ovarian cancer with low complication rates (Bristow 2003; Eisenkop 2001; Jaeger 2001; Merideth 2003; Montz 1989; Norell 2020; Pomel 2004; Vergote 2016). NICE (National Institute for Health and Care Excellence) has previously published guidance on ultra-radical (extensive) surgery for advanced ovarian cancer (NICE 2013). Standard surgery in an advanced disease setting still has an element of radicality and comprises as a minimum, total hysterectomy, bilateral adnexectomy with excision of the pelvic peritoneum, total omentectomy including the

supracolic omentum, removal of bulky pelvic and lumbo-aortic nodes, simple peritonectomies, localised colonic resection, or a combination of these. Procedures such as appendicectomy may have previously been considered part of standard surgery, but evidence now suggests that this could be unnecessary and may cause harm. Ultra-radical (extensive) surgery is an extension of standard surgery including at least one of the following: stripping of the peritoneum over the diaphragm, extensive stripping of the peritoneum, multiple resections of the bowel (excluding localised colonic resection), liver resection, partial gastrectomy, cholecystectomy and splenectomy (with or without resection of the tail of the pancreas) (NICE 2013).

How the intervention might work

It has been proposed that multiple factors, including tumour biology, determine the manner of disease progression, which in turn influences the likelihood of surgical cytoreduction (Colombo 2019; Eisenkop 2001; Hoskins 1992; Markman 2007). Supporters of less-radical surgery argue that the initial extent of advanced disease reflects the aggressiveness of the tumour, and ultimately dictates treatment success. Therefore, when radical surgery becomes necessary to achieve optimal cytoreduction, it may not improve survival, despite leaving minimal residual disease (Colombo 2019; Covens 2000). Furthermore, the role of surgery has been questioned because patients who undergo surgery to achieve NMRD often represent women who may be younger and fitter, and have relatively small preoperative tumour loads and, therefore, less biologically aggressive tumours, and that differences in tumour biology account for the survival benefits that are reported to be from surgery (Eisenkop 1998; Hoskins 1992; Norell 2020; Vergote 2016). Perhaps of greater concern is the patient morbidity that is incurred during such radical procedures, both in the perioperative and postoperative periods (Chen 1985; Sundar 2021; van Dam 1996; Venesmaa 1992).

Ultra-radical surgery is associated with a prolonged operating time and exposure to anaesthesia. This may increase the risk of hypothermia; respiratory complications such as atelectasis (lung collapse), infection, adult respiratory distress syndrome; blood loss; and intraoperative ureteric, bowel and bladder injury. In the postoperative period, these women may require a longer hospital stay and recovery time, with an increased risk of infection (chest, wound, urine), venous thromboembolic disease, poorer mobility and poorer nutritional status. The cost-effectiveness of such surgery would also require evaluation.

There is also a suggestion from one before-after study that a structured shift to an ultra-radical upfront primary surgical approach may not improve survival in surgically treated women (Falconer 2020). In this population-based cohort study, women with suspected advanced EOC near Stockholm in Sweden were included via the Swedish Quality Registry for Gynecologic Cancer (SQRGC) and the National Cancer Registry (NCR). Women were selected in two sets of three-year cohorts, based on the year of their diagnosis (a before cohort or an after cohort 2 change in surgical treatment algorithm) and were followed for at least three years. Five-year overall survival (OS) in non-surgically and surgically treated women was analysed. After a median follow-up of around 28 months in 752 women, the complete resection rate increased from 37% to 67% as well as proportion of non-surgically treated women (from 24% to 33%). This study also demonstrated that a shift to ultra-radical surgery increased the proportion of non-surgically treated women. However, this study was not a 'controlled' before-after study and as a consequence was prone to bias. The use of historical controls are known to overestimate the benefit of new treatments. Before-after studies also have a high risk of bias because there may be unidentified differences between the intervention and control groups that may affect changes in the outcome measure (Sterne 2022).

Why it is important to do this review

To our knowledge, there have been no comprehensive and rigorous systematic reviews on ultra-radical (extensive) surgery versus standard surgery. There is no consensus in clinical guidelines, and there is widespread variation in surgical practice globally with varying rates of survival (Norell 2020). Willingness to undertake more-extensive surgery was correlated with three-year survival by distant stage, and clinicians from higher performing countries appeared to be more likely than those from lower performing countries to be proponents of 'ultra-radical' surgery (Norell 2020). Guidelines from Belgium in 2016 supported the use of radical surgical techniques to obtain resection of all macroscopic tumour (Vergote 2016).

Given the differences in opinion regarding the role of extensive debulking surgery in ovarian cancer treatment, we aimed to systematically review the available evidence for ultra-radical surgery in ovarian cancer management.

OBJECTIVES

To evaluate the effectiveness and morbidity associated with ultra-radical/extensive surgery in the management of advanced-stage epithelial ovarian cancer.

METHODS

Criteria for considering studies for this review

Types of studies

- Randomised controlled trials (RCTs)

As we expected to find few, if any, RCTs of surgical interventions (Johnson 2008), we included the following types of non-randomised studies with concurrent comparison groups.

- Quasi-randomised trials, non-randomised studies, prospective and retrospective cohort studies, and case series of 100 or more participants

We excluded case-control studies, uncontrolled observational studies and case series of fewer than 100 participants.

In order to minimise selection bias, we decided to include only studies that used statistical adjustment for baseline case mix (e.g. age, performance status, grade, etc.) using multivariate analyses.

Types of participants

Women diagnosed with stage III and IV EOC. Women having ultra-radical surgery as part of upfront primary debulking surgery (PDS) or interval debulking surgery (IDS; surgery halfway through the course of chemotherapy) were included.

There is evidence that a high percentage of so-called 'ovarian' high-grade serous carcinomas arise in the fimbrial end of the

fallopian tube. Serous tubal intraepithelial carcinoma is considered a precursor lesion (Harley 2014).

Women with other concurrent malignancies women with recurrent disease were excluded.

Types of interventions

- Intervention: ultra-radical surgery defined as total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, removal of enlarged lymph nodes (para-aortic, pelvic, obturator) and one or more of the following: upper abdominal surgery (splenectomy, diaphragmatic or peritoneal stripping, liver resection), bowel surgery or stoma formation (excluding localised colonic resection) or urinary tract surgery, peritonectomy (en bloc or excision of nodules, depending on disease involvement).
- Comparison: standard surgery defined as total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy either with or without removal of enlarged lymph nodes (para-aortic, pelvic, obturator), localised colonic resection and debulking of any other superficial tumour plaques.

The types of interventions defined above have been widely described in the literature and in the published NICE guidance on ultra-radical (extensive) surgery for advanced ovarian cancer (NICE 2013).

Two included studies in the review also included some elements of extensive surgery in the standard surgery group: segmental small bowel resection (Chang 2012a), and rectosigmoid resection and appendectomy (Luyckx 2012). It was decided to include these two studies, because these surgical additions are common practice in some countries such as Belgium (Vergote 2016).

Types of outcome measures

Primary outcomes

- Overall survival (OS): survival until death from all causes. Survival was assessed from the time when women were enrolled in the study. One study reported disease-specific survival rather than death from any cause (Aletti 2006a). We additionally added this as an outcome in the review.

Secondary outcomes

- Progression-free survival (PFS).
- Disease-free survival (DFS).
- Optimal cytoreduction, defined as residual tumour less than 1 cm, or complete cytoreduction.
- Death within 30 days of intervention.
- Adverse events classified according to CTCAE 2017:
  - direct surgical morbidity: for example, vascular injury, injury to bladder, ureter, small bowel or colon, presence and complications of adhesions, febrile morbidity, intestinal obstruction, anastomotic leak, haematoma, collection, local infection.
  - surgically related systemic morbidity, for example, chest/wound/urine infection, thromboembolic events (deep vein thrombosis and pulmonary embolism), cardiac events (cardiac ischaemia, myocardial infarction and cardiac failure), cerebrovascular accident, transfusion reaction, pulmonary oedema;
  - recovery: delayed discharge, unscheduled re-admission.
- Quality of life (QoL) measured using a scale that has been validated through reporting of norms in a peer-reviewed publication.

Search methods for identification of studies

We sought papers in all languages and carried out translations when necessary.

Electronic searches

See: Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group methods used in reviews.

For this review update, we searched the following electronic databases on 25 November 2021:

- the Cochrane Central Register of Controlled Trials (CENTRAL; 2021, Issue 11), in the Cochrane Library;
- MEDLINE via Ovid (November 2010 to November week 3 2021);
- Embase via Ovid (November 2010 to 2021 week 46).

The CENTRAL, MEDLINE and Embase search strategies are presented in Appendix 1, Appendix 2, and Appendix 3.

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

Searching other resources

Unpublished and grey literature

We searched metaRegister, Physicians Data Query, the ISRCTN Registry (www.controlled-trials.com/rct), ClinicalTrials.gov (www.clinicaltrials.gov), and the National Cancer Institute Register (www.cancer.gov/clinicaltrials) for ongoing trials. We used search terms derived from the main searches.

Reference lists

We searched reference lists of all included studies for additional studies.

Handsearching

We handsearched abstracts of meetings from the International Gynaecological Cancer Society (2000 to 2020), the British Gynaecological Cancer Society (2008 to 2021), European Society of Gynaecological Oncology (2003, 2005, 2009, 2015 and 2019) and the Society of Gynecologic Oncology (2009, 2010, 2015 and 2019) to identify unpublished studies.

Data collection and analysis

Selection of studies

We downloaded all titles and abstracts retrieved by electronic searching to the reference management database Endnote and removed duplicates. Three review authors (AB, PB, SH) independently examined the remaining references. We excluded those studies that clearly did not meet the inclusion criteria and obtained copies of the full text of potentially relevant references. Three review authors (AB, PB, SH) independently assessed the eligibility of retrieved papers. We resolved disagreements by discussion between the three review authors

and, when necessary, with fourth and fifth review authors (RN, KG). We documented reasons for exclusion in the Characteristics of excluded studies table.

Data extraction and management

For included studies, we recorded the following data.

- Author, year of publication and journal citation (including language).
- Country.
- Setting.
- Inclusion and exclusion criteria.
- Study design, methodology.
- Study population, abstracted by treatment arm if possible:
  - total number enrolled;
  - participant characteristics;
  - age;
  - ethnicity;
  - comorbidities;
  - response to neoadjuvant chemotherapy.
- Ovarian cancer details at diagnosis:
  - FIGO stage (III or IV);
  - histological cell type;
  - differentiation.
- Previous treatment (neoadjuvant chemotherapy subgroup analysis: responders versus non-responders).
- Surgical details:
  - type of surgeon (gynae-oncologist, gynaecologist, general surgeon);
  - type of surgery (ultra-radical (extensive) versus standard).
- Risk of bias in study (see below).
- Duration of follow-up.
- Outcomes (see above) – OS, PFS, QoL and adverse events.
  - For each outcome:
    - outcome definition (with diagnostic criteria if relevant);
    - unit of measurement (if relevant);
    - for scales: upper and lower limits, and whether high or low score is good.
  - For results: number of participants allocated to each intervention group.
  - For each outcome of interest: sample size; missing participants.

We extracted data on outcomes as follows.

- For time to event data (OS), we extracted the log of the hazard ratio (HR) and its standard error from trial reports; if these were not reported, we attempted to estimate the log (HR) and its standard error using the methods of Parmar 1998.

We reported the HR and its 95% confidence interval (CI). For adjusted statistics, we noted the variables used in adjustment. Where possible, all data extracted were those relevant to an intention-to-treat analysis, in which participants were analysed in groups to which they were assigned. We noted the time points at which outcomes were collected and reported.

Two review authors (PB, SH) independently extracted data onto a data abstraction form specially designed for the review. We resolved differences between review authors by discussion or appeal to a third review author (RN), when necessary.

Assessment of risk of bias in included studies

We used the Risk of Bias In Non-randomised Studies of Interventions (ROBINS-I) tool to assess bias in our included studies (Sterne 2016). According to the ROBINS-I, non-randomised studies of interventions (NRSI) aim to mimic a target trial (i.e. a hypothetical pragmatic RCT), which may not be feasible or ethical to conduct. Bias in this sense is defined as "systematic difference between the results of the NRSI and the results expected from the target trial". Given that the NRSIs included in our study were concerned with the effect of having undergone ultra-radical or standard surgery and not the effect of having been assigned to a surgery type, we may further specify that bias is the systematic difference between the results of NRSIs and the per-protocol effect of a target trial.

The ROBINS-I rates bias along seven domains (see Appendix 4):

- confounding;
- selection of participants into the study;
- classification of interventions;
- deviation from intended interventions;
- missing data;
- measurement of outcomes; and
- selection of reported result.

Responses to signalling questions lead to the formulation of domain-specific risk of bias ratings – no information, low, moderate, serious and critical risk of bias – which then guide the judgement for an overall risk of bias rating. We also added additional signalling questions to the ones in ROBINS-I domains in accordance with additional criteria for confounding and selection of women so that we were confident in our judgements (Taggart 2001). These additional criteria for confounding included an assessment of the comparability of treatment groups to see if there were no differences between the two groups or that differences had been controlled for, in particular with reference to age, FIGO stage, histological cell type, differentiation, previous treatment (neoadjuvant chemotherapy – responders versus non-responders) and type of surgeon (gynae-oncologist, gynaecologist, general surgeon). At least three of these characteristics were reported and any reported differences were controlled for. To aid signalling questions in selection of women into the study, we assessed whether relevant details of criteria for assignment of women to treatments was provided and whether the group of women who received each intervention were representative and were not selected by a subset of the population. If these additional signalling questions were questionable in any way, then the risk of bias judgement in that domain would be of serious or critical concern, which is above a 'high' risk of bias judgement.

Three review authors (AB, PB, SH) independently applied the risk of bias tool and resolved differences by discussion or by appeal to a fourth review author (RN, KG). We tabulated results and presented them in a risk of bias graph.

Measures of treatment effect

We used the following measures of the effect of treatment.

- For time to event data, we used the HR with 95% CI.

Unit of analysis issues

We did not expect or encounter any unit of analysis issues.

Dealing with missing data

We did not impute missing outcome data for any outcomes. For the primary outcome, if data were missing or only imputed outcome data were reported, we contacted study authors to request data on the outcomes among participants who were assessed.

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 analysis (see below). If there was evidence of substantial heterogeneity, we investigated and reported the possible reasons for this.

Assessment of reporting biases

We did not examine funnel plots corresponding to meta-analysis of the primary outcome to assess the potential for small-study effects due to an insufficient number of included studies. If there had been evidence of small-study effects, we would have considered publication bias as only one of a number of possible explanations. If these plots had suggested that treatment effects may not have been sampled from a symmetric distribution, as assumed by the random-effects model, we would have performed a sensitivity analysis using the fixed-effect model.

Data synthesis

If there were sufficient clinically similar studies available, we pooled their results in a meta-analysis. We used adjusted summary statistics as specified in Types of studies.

- For time-to-event data, we pooled HRs using the generic inverse variance facility of Review Manager 5 (Review Manager 2014).

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

Subgroup analysis and investigation of heterogeneity

We performed subgroup analysis, grouping the studies by:

- reporting of survival (overall and disease-specific; progression and disease-free);
- radicality of procedures in the ultra-radical groups.

We considered factors such as age, FIGO stage, type of surgery (upfront primary debulking surgery (PDS) or IDS), type of surgeon and length of follow-up in interpretation of any heterogeneity.

Sensitivity analysis

We planned to perform a sensitivity analysis excluding studies at high risk of bias, but all three studies were at a high risk of bias. However, we did perform sensitivity analyses including only women with more-extensive disease (with carcinomatosis).

Summary of findings and assessment of the certainty of the evidence

We presented the overall certainty of the evidence for each outcome according to the GRADE approach, which takes into account issues related to internal validity (risk of bias, inconsistency, imprecision, publication bias) and to external validity such as directness of results (see Summary of findings 1 based on the methods described the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019). 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

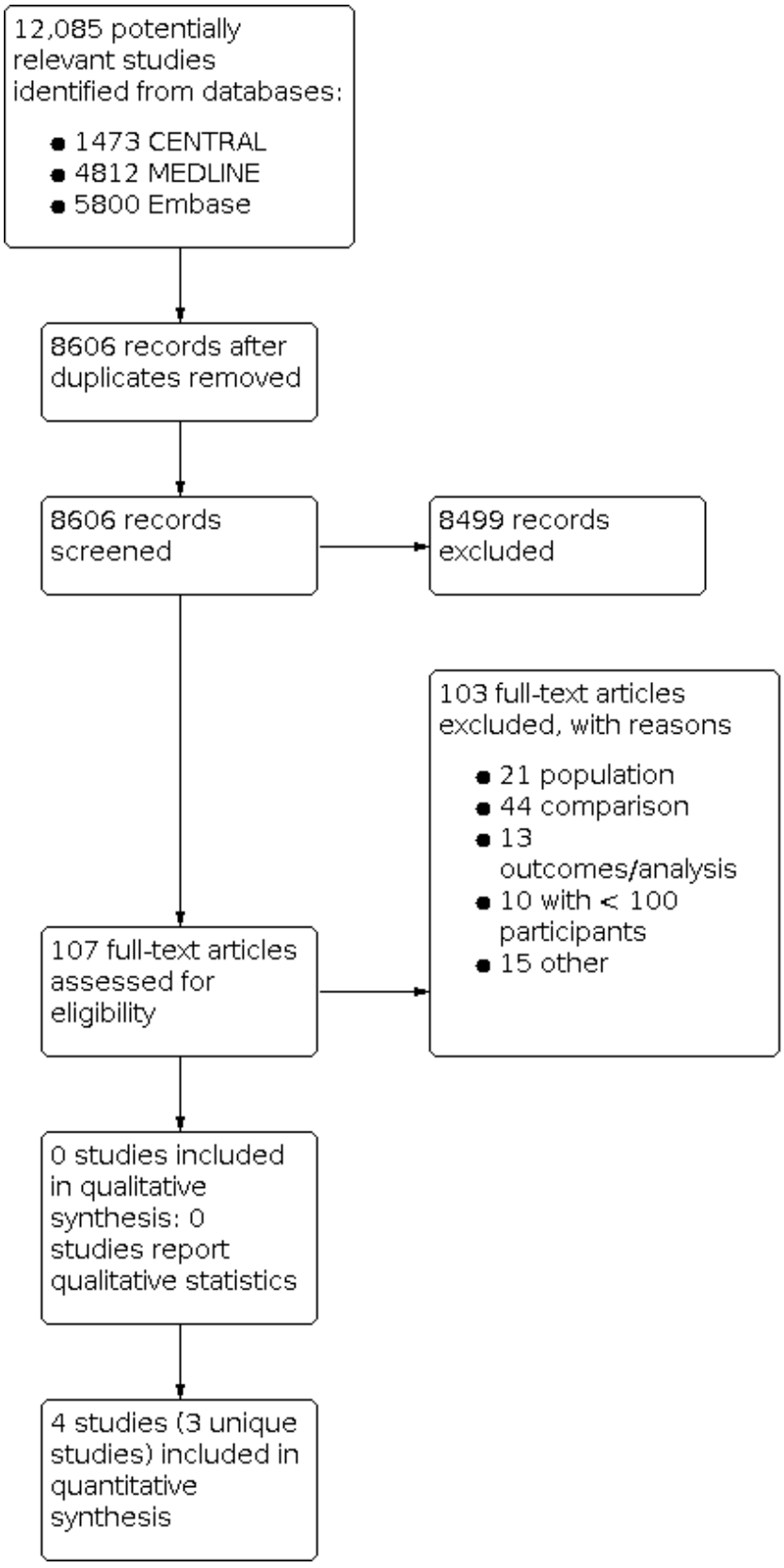
Description of studies

Results of the search

When the search results were merged into EndNote and duplicates were removed, there were 8606 unique references. The title and abstract screening identified 107 references as potentially eligible. The full-text screening excluded 103 of these, with the reasons for exclusion presented in the Characteristics of excluded studies table. We included four references reporting on three studies that met our inclusion criteria (Aletti 2006a; Chang 2012a; Luyckx 2012).

The PRISMA flow diagram of the search results is presented in Figure 1.

Figure 1. Study flow diagram up to 25 November 2021.



Searches of the grey literature did not identify any additional relevant studies.

The three included studies are described in the Characteristics of included studies table (Aletti 2006a; Chang 2012a; Luyckx 2012). While it did not meet the inclusion criteria, we also identified a study worthy of discussion that measured the introduction of ultra-radical surgery on a population level (Falconer 2020). The analysis had a before-after design but was excluded as it was not a controlled study. Details of this study are given in Agreements and disagreements with other studies or reviews.

Included studies

All three included studies (924 women) compared ultra-radical or extensive surgery with standard surgery. The two most recent studies also included some elements of extensive surgery in the standard surgery group: segmental small bowel resection (Chang 2012a), and rectosigmoid resection and appendectomy (Luyckx 2012). We decided to include these two studies, because these surgical additions are common practice in some countries such as Belgium (Vergote 2016).

All studies enrolled women who underwent primary surgery and adjusted their analyses in attempts to reduce selection bias in assignment of participants to surgical treatment. All studies were considered to have a high risk of bias. Despite each study reporting multivariate analyses, confounding by indication could not be excluded. In addition, in all cases, the adjusted HRs were derived from prognostic models, which seem to have been assessed based on significance testing and not on the inclusion of putative confounders in the analysis, irrespective of statistical significance.

Design

All three studies reported retrospective analyses of participants identified from surgical or medical records (Aletti 2006a; Chang 2012a; Luyckx 2012). Aletti 2006a reported a retrospective analysis of 194 women from the Mayo clinic in Minnesota (USA), Chang 2012a (203 women) was set in South Korea (Ajou University Hospital, Republic of Korea) and Luyckx 2012 (527 women) analysed data from seven gynaecological oncology centres in France.

Participants

The median age at diagnosis of advanced EOC ranged from 54 years in Chang 2012a to 64 years in Aletti 2006a (ages across studies ranged from 24 to 90 years). About 65% to 82% of participants had a serous histological tumour cell type. Most participants had Grade IIIC tumour (84% to 100%) and 93% of women had tumour Grade III in Aletti 2006a whereas the proportion with Grade III in the other two studies was lower (49 to 58% based on non-missing observations), with over a third having tumour Grade II in these studies. Ascites varied across studies with Aletti 2006a reporting mean ascites of 2076 mL and median of 1000 mL (range 0 mL to 12,000 mL). In Chang 2012a, 45% of women had ascites greater than 1000 mL, which was in contrast to Luyckx 2012 where median ascites was 50 mL (range 0 mL to 8000 mL). In terms of residual disease after primary surgery, Luyckx 2012 had most favourable outcome with 71% being cytoreduced to microscopic disease and 18.5% of remaining women having optimal cytoreduction (residual disease less than 1 cm). The other two studies were fairly similar with around two-thirds of women being optimally or completely cytoreduced with the remaining third or so having residual disease greater than 1 cm. Two studies reported American Society of Anesthesiologists (ASA) score at baseline: Aletti 2006a (48% had ASA scores 1 to 2 and 49% had ASA scores 3 to 4 with remaining scores unknown) and Chang 2012a (56% had ASA scores 1 to 2 and 39% had ASA scores 3 to 4, with remaining scores unknown). Two studies also reported extent of disease: 144 (74%) women had carcinomatosis in Aletti 2006a and 149 (73%) had carcinomatosis in Chang 2012a. Luyckx 2012 reported the extent of peritoneal carcinomatosis with a median peritoneal cancer index of 10. Approximately 39% had no upper abdominal lesions, 40% had abdominal lesions of 2.5 cm or less, and 21% had upper abdominal lesions greater than 2.5 cm.

Interventions

All three studies compared ultra-radical or extensive surgery with standard surgery. However, the two more recent studies additionally included some elements of extensive surgery in the standard surgery group: segmental small bowel resection (Chang 2012a), and rectosigmoid resection and appendectomy (Luyckx 2012). Aletti 2006a and Chang 2012a included only surgery from upfront primary debulking surgery whereas Luyckx 2012 included a mixture of PDS and IDS.

Aletti 2006a performed initial surgery for diagnosis, staging and surgical cytoreduction. Ultra-radical surgery was defined as having any diaphragmatic surgery, bowel resection, splenectomy or extensive abdominal peritoneal stripping or resection and was compared to standard surgery defined as hysterectomy, complete omentectomy, stripping of pelvic peritoneum or limited resection of peritoneal-based nodules. Participants were first classified by the extent of peritoneal dissemination. Those with tumour nodules diffusely covering most of the bowel serosal surfaces and the parietal peritoneum of the abdomen and pelvis were classified as having carcinomatosis. The centre's division of gynaecological surgery contained a mixed group of surgeons, some being more likely to carry out ultra-radical surgery but all sharing a uniform referral base with similar patient demographics, practising at a single institution where each surgeon had access to identical services and nursing support. The mean length of follow-up was 3.5 years and median was 2.7 years (range 0.02 to 10.5 years). For the overall cohort of 194 women, 83 (42%) received ultra-radical surgery and 111 (57%) received standard surgery. For the subset of 144 women with worse disease (carcinomatosis), 68 (47%) underwent ultra-radical surgery and 76 (53%) received standard surgery.

Radical cytoreductive procedures in Chang 2012a included radical oophorectomy with or without rectosigmoid colectomy, total omentectomy, multiple bowel resections, diaphragm peritonectomy or resection, liver resection, splenectomy, distal pancreatectomy and gastric resection. Simple surgery included total abdominal hysterectomy, bilateral salpingo-oophorectomy, peritoneal biopsies or excisions, infracolic omentectomy, pelvic lymphadenectomy, para-aortic lymphadenectomy and segmental resection of small bowel. After surgery, all participants received adjuvant platinum-based chemotherapy in combination with paclitaxel for six to nine cycles. The median length of follow-up was 43 months (range 1 to 124 months).

Luyckx 2012 defined ultra-radical surgery as involving standard surgery plus upper abdominal surgery such as stripping of the

diaphragmatic peritoneum and splenectomy alone (group 2A in the study), or a combination of digestive tract resections (right colon and caecum, total colectomy and others), organ resection (spleen, gallbladder, partial gastrectomy and others), coeliac lymph node dissection, and total abdominal peritoneum stripping in addition to standard surgery (group 2B in the study). The comparison group was standard surgery with hysterectomy, bilateral salpingo-oophorectomy, rectosigmoid resection, infragastric omentectomy, pelvic and aortic lymphadenectomy and, when applicable, appendectomy (group 1 in the study). The median length of follow-up was 49 months.

Outcomes reported

Survival

Two studies reported outcomes for survival. One study applied a multivariate analysis of OS adjusting the HR for surgery type, age (continuous), FIGO stage and residual disease (Chang 2012a). Although not reported in the original paper, Aletti 2006a provided estimates of the HR from a multivariable Cox model, comparing five-year disease-specific survival (DSS) (event being death from advanced ovarian cancer) in the ultra-radical surgery group with that in the standard surgery group for all 194 women and for the 144 women with carcinomatosis. The HR for DSS in Aletti 2006a including all 194 women was adjusted for: age, ASA score, carcinomatosis, mesenteric involvement, diaphragmatic involvement, ascites, residual disease and operative time. The HR for DSS in the subset of 144 women with carcinomatosis was adjusted for: age, ASA score, tumour grade, residual disease and operative time. Luyckx 2012 reported cox regression estimates for OS but did not include type of surgery in their multivariate model as it was not significant in univariate analysis.

Progression-free survival

Chang 2012a reported PFS and adjusted the HR for FIGO stage, tumour grade, residual disease and surgery type.

Disease-free survival

Luyckx 2012 reported an HR for disease-free survival (DFS) and adjusted for FIGO stage, tumour grade, presence of upper abdominal disease, amount of residual disease, and timing of surgery (primary or interval) and surgery type.

Death within 30 days of intervention

Aletti 2006a and Chang 2012a reported perioperative death within 30 days. In this review, we used 'death within 30 days' as a secondary outcome measure because this cut-off has been widely used in the literature and would include people who died of complications directly related to surgery that may only manifest one to two weeks after surgery.

Adverse events

Chang 2012a reported postoperative morbidity defined as infected lymphocyst, thromboembolism, intestinal obstruction, anastomostic leakage, ureteral injury, sepsis, intra-abdominal abscess, pneumothorax, postoperative death within 30 days, or a combination of these. Luyckx 2012 and Aletti 2006a did not report adverse events by type of surgery.

None of the studies reported recurrence rate, QoL or (loco)regional control.

For further details see the Characteristics of included studies table.

Excluded studies

We excluded 103 references after obtaining the full text for the following reasons (see Characteristics of excluded studies table).

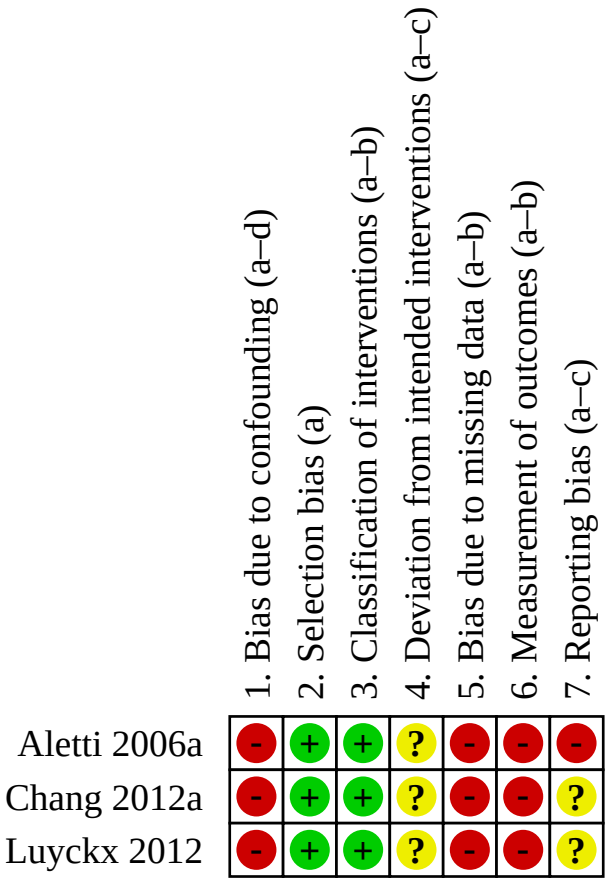
- In 12 studies, a comparison of ultra-radical and standard surgery was not possible (Aletti 2006b; Aletti 2009a; Bahra 2013; Bertelsen 1990; Eisenkop 2001; Eisenkop 2003; Grimm 2017; Laios 2019; Pelissier 2018; Vidal 2016; Wimberger 2007; Yildirim 2014).
- In 22 studies, the comparison was not of interest to our study (Chua 2011; Clark 2012; Clark 2014; Favero 2014; Ferrero 2014; Fotopoulou 2012; Gremeau 2014; Guyon 2014; Hamilton 2011; Hwang 2014; Hudry 2013; Janda 2014; Kato 2013a; Kehoe 2013; Li 2014; Perri 2013; Pushpalatha 2011; Qin 2012; Rouzier 2010; Sandadi 2014; Scalici 2014; Sehouli 2010).
- Participants in the comparison (standard surgery) group also had extensive bowel surgery (which is classified as ultra-radical) in 13 studies (Aletti 2006b; Canlorbe 2018; Chi 2004; Eisenhauer 2006; Eisenkop 1993; Eisenkop 1998; Elgamal 2019; Eoh 2017; Filippova 2019; Gockley 2019; Kommoss 2010; Kuhn 1998; Tozzi 2019), diaphragmatic stripping in two studies (Tsolakidis 2010a; Tsolakidis 2010b), ultra-radical with splenectomy in one study (Davies 2019), and extensive upper abdominal surgery in two studies (Chi 2009; Oseledchyk 2016).
- In three studies, the intervention was a specific form of ultra-radical surgery, but it was unclear whether those in the comparison group received a different form of ultra-radical surgery or standard surgery (Aletti 2006c; Cai 2007; Eisenkop 2006).
- In three studies, there was no ultra-radical surgery performed (Chang 2012b; Cormier 2012; Park 2011).
- Four studies included participants with recurrent disease (Bristow 1999; Kato 2013b; Kolev 2014; van de Laar 2014), whereas in one study it was unclear whether women with recurrent disease were included (von Hugo 1989).
- Ten studies analysed data by descriptive statistics, no multivariate analysis was performed (Barlin 2013; Chereau 2011; Eng 2018; Soo Hoo 2015; McCann 2011; Muallem 2018; Phillips 2018; Sagara 2019; Zamurovic 2013; Zapardiel 2012).
- Ten studies included fewer than 100 participants in their analyses (Angioli 2012; Butler 2012; Kim 2011; Liu 2013a; Pathiraja 2011; Pathiraja 2013; Ratnavelu 2014; Stefanović 2011; Sundar 2014; Wat 2012).
- Four studies included people with borderline tumours (Kristensen 2014), germ cell tumours (Liu 2013b), only stages pT1-2 (Oshita 2013), and where those with suboptimal debulking were excluded (Rodriguez 2013).
- Thirteen studies were conference abstracts and the full text was not available to make a decision (Campos 2014; Cummins 2019; Jiang 2013; Liberale 2019; Lee 2017; Martinez 2014; Rodriguez 2012; Sundar 2018; Sundar 2019; Suzuki 2008; Szczesny 2016; Wallace 2016; Wright 2012), one of which reported outcomes that were not of interest (Wright 2012).
- In Ren 2015 (Jiang 2013 in abstract form), the type of surgery was not included as a variable in a multivariable analysis of PFS.
- One study was an uncontrolled before-after study, but forms part of the discussion in Agreements and disagreements with other studies or reviews (Falconer 2020).

Risk of bias in included studies

We did not identify any RCTs, so we did not apply Cochrane's risk of bias tool (we planned to use ROB-1) for the assessment of these types of studies. Instead, we used the ROBINS-I tool to assess bias in our included studies (Sterne 2016).

The risk of bias assessments of the three included comparative observational studies are summarised in Table 1 and Figure 2. All studies had critical bias due to confounding because no known prognostic factors could be identified that would have the potential for confounding the effect on intervention. In Chang 2012a, adjusted HRs were derived from a prognostic model. No details were presented on how modelling was performed, but this seems to have been done based on significance testing (and not on including putative confounders in the analysis, irrespective of statistical significance). The adjusted HRs for Luyckx 2012 were derived from a prognostic model based on univariate significance testing ($P < 0.10$) and not on including putative confounders in the analysis, irrespective of statistical significance. In addition, the data were collected retrospectively.

Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



All three studies were at low risk of bias in selection of participants into the study. In all three, the intervention and follow-up occurred simultaneously as outcomes would be observed immediately after the cytoreductive surgery. Additionally, there was no evidence of selection into the study due to variables measured after the intervention, since participants were included retrospectively.

In all three studies, bias in classification of interventions was low because the intervention statuses were clearly defined as either having: aggressive surgery or not (Aletti 2006a), simple versus radical surgical procedure (Chang 2012a), or standard surgery versus standard surgery plus relatively routine upper abdominal surgery versus ultra-radical surgery (Luyckx 2012).

All three studies were at unclear risk of bias due to deviations from intended interventions. There was no evidence of any deviations from interventions or usual practice but these may either be due to omission or that deviations did not happen.

In all three studies, there was no differential follow-up or missing data reported and no participants were reportedly omitted due to

missing data. Although there is no reason to believe there was a serious bias due to missing data, they were still not comparable to a randomised trial. Therefore, we rated bias due to missing data as moderate to high.

All three studies were at critical bias in measurement of outcomes. In Aletti 2006a, the multivariate analysis adjusted for variables that were measured after the time origin in some of the analyses, namely extent of residual disease and operative time (Altman 1995). Residual disease was also used as an adjustment prognostic factor in the other two included studies (Chang 2012a; Luyckx 2012). This is likely to distort the estimate of survival as this adjustment is made after surgery and is a key prognostic factor.

Only one study was at critical bias in selection of the reported result. In Aletti 2006a, the authors reported DSS rather than OS, which is a more appropriate and reliable outcome measure and did not report any QoL data, or state if there were any predefined outcome measures prior to data analysis. Therefore, it is possible that the outcomes may have been selectively reported. DSS is not a good outcome measure to use for several reasons, for example the coding of death certificates is notoriously prone to error. Also data were reported in a subset of the 144 women with carcinomatosis (more-extensive disease) only. There was unclear evidence of selective reporting in the other studies as no protocol was available (Chang 2012a; Luyckx 2012). However, all outcomes mentioned in the methods section seemed to have been reported in the results section.

Effects of interventions

See: **Summary of findings 1** Ultra-radical (extensive) surgery compared to standard surgery in women with stage IIIc or IV ovarian cancer

We only identified very low-certainty evidence for all outcomes reported in the review, but mainly due to relatively few women being included due to stringent inclusion criteria. A breakdown of adverse events was not adequately reported in two studies (Aletti 2006a; Luyckx 2012) and QoL was not reported in any of the three included studies. Although a secondary outcome, none of the studies reported 'Optimal cytoreduction' in any multivariate analyses. We did not present any unadjusted results for this as it is likely that 'optimal cytoreduction' will be higher in ultraradical surgery and would not be a fair comparison.

Survival (overall and disease-specific)

Upfront primary debulking surgery

Meta-analysis of two studies (397 women) found that women who underwent radical procedures as part of PDS had 40% less chance of mortality compared to women who underwent standard surgery (adjusted HR 0.60, 95% CI 0.43 to 0.82; I^2 = 0%; very low-certainty evidence; Analysis 1.1; Summary of findings 1) (Aletti 2006a; Chang 2012a). Aletti 2006a reported the five-year DSS rather than categorising deaths by any cause. In Chang 2012a, the median OS (unadjusted) was 66 months in the ultra-radical surgery group and 38 months in the standard surgery group. The five-year DSS rate (unadjusted) was 46% in the ultra-radical surgery group compared with 13% in the standard surgery group.

The results were robust to a sensitivity analysis which included two studies assessing 283 participants with more-extensive disease (carcinomatosis), which found that women who underwent radical procedures as part of PDS had 39% less chance of mortality compared to women who underwent standard surgery (adjusted HR 0.61, 95% CI 0.44 to 0.85; I^2 = 0%; very low-certainty evidence; Analysis 1.2; Summary of findings 1) (Aletti 2006a; Chang 2012a).

Upfront primary and interval debulking surgery

One study, which included women with stage IIIC and IV disease, reported a comparison of radical versus standard surgical procedures associated with both PDS and IDS procedures (Luyckx 2012). The study authors did not report the magnitude of effect in multivariate analyses and only included variables associated with P < 0.05 on univariate analysis in Cox regression model. The study found no difference in the risk of mortality between women undergoing radical surgery versus standard surgery (403 women) or ultra-radical versus standard surgery (424 women), in univariate analyses. Multivariate analyses were not reported and, therefore, the certainty of the evidence was not assessable and remained very low.

Progression-free survival

Upfront primary debulking surgery

Chang 2012a, which assessed 203 participants, found that women who underwent radical procedures as part of PDS had nearly 40% less chance of disease progression or death compared to women who underwent standard surgery (adjusted HR 0.62, 95% CI 0.42 to 0.92; very low-certainty evidence; Analysis 1.3; Summary of findings 1). The median PFS (unadjusted) was 18 in the ultra-radical surgery group and 11 months in the standard surgery group. The results were robust to a sensitivity analysis assessing a subset of 139 women with carcinomatosis, which found that women who underwent radical procedures as part of PDS had nearly 50% less chance of disease progression or death compared to women who underwent standard surgery (adjusted HR 0.52, 95% CI 0.33 to 0.82; very low-certainty evidence; Analysis 1.4; Summary of findings 1).

Disease-free survival

Upfront and interval debulking surgery

One study, which included women with stage IIIC and IV disease, reported DFS for a comparison of radical versus standard surgical procedures associated with both PDS and IDS procedures (Luyckx 2012). A combined analysis in one study (Luyckx 2012), assessing 527 women, found that those who underwent radical procedures were associated with increased chance of disease progression or death than those who received standard surgery (adjusted HR 1.60, 95% CI 1.11 to 2.31; I^2 = 0%; very low-certainty evidence; Analysis 1.5; Summary of findings 1). In absolute and unadjusted terms, the DFS was 19.3 months in the standard surgery group (group 1), 15.8 months in group 2A and 15.9 months in group 2B (the two ultra-radical surgery groups) (see Characteristics of included studies table for details of groups).

Death within 30 days of surgery

Upfront debulking surgery

None of the studies reporting death within 30 days of surgery used any statistical adjustment.

In Aletti 2006a, three women died within 30 days of their standard surgical procedure whereas there were no reported cases of perioperative mortality in the ultra-radical surgery group (very low-certainty evidence).

In Chang 2012a, perioperative death within 30 days occurred in 0/119 (0%) in the ultra-radical surgery group versus 1/84 (1.2%) in the standard surgery group (very low-certainty evidence).

In total there were only four deaths within 30 days of surgery in both studies and none in the ultra-radical group so we did not report a risk ratio (planned outcome of choice a priori) to avoid potentially misleading results with so few deaths (Summary of findings 1).

Adverse events

Upfront debulking surgery

Chang 2012a did not use any statistical adjustment for any adverse events.

In Chang 2012a, there was postoperative morbidity in 32/84 (38.1%) women in the ultra-radical surgery group versus 14/119 (11.8%) women in the standard surgery group (RR 3.24, 95% CI 1.84 to 5.68; very low-certainty evidence).

Women who underwent ultra-radical surgery had significantly larger median estimated blood loss (800 mL with ultra-radical surgery versus 500 mL with standard surgery; P = 0.03), were more likely to receive a intraoperative or postoperative blood transfusion (intraoperative: 25% with ultra-radical surgery versus 17.6% with standard surgery; postoperative: 39.3% with ultra-radical surgery versus 26.1% with standard surgery; P = 0.01), had longer median days in the intensive care unit (1.5 days with ultra-radical surgery versus 0.8 days with standard surgery; P < 0.01), and were more likely to experience postoperative morbidity (38% with ultra-radical surgery versus 11.8% with standard surgery; P < 0.01) than those who underwent standard surgery (very low-certainty evidence; Summary of findings 1).

Operative time

Upfront debulking surgery

Chang 2012a did not use any statistical adjustment for operative times between groups.

In Chang 2012a, women who underwent ultra-radical surgery had significantly longer median operative times than those who had standard surgery (307 with ultra-radical surgery versus 235 minutes with standard surgery; P < 0.01). This outcome was not specified in the summary of findings table.

DISCUSSION

Summary of main results

We found three studies that met our inclusion criteria (Aletti 2006a; Chang 2012a; Luyckx 2012). These studies reported retrospective data for 924 women with advanced EOC (stage III/IV) who underwent either ultra-radical or standard surgery. Two studies reported on women who exclusively received PDS (Aletti 2006a; Chang 2012a), whereas Luyckx 2012 included women who had received both PDS and IDS procedures.

Of the six outcomes examined, only survival (overall and disease-specific and progression/disease-free), and perioperative mortality were reported in more than one study. There is from two observational retrospective studies providing very low-certainty evidence that ultra-radical surgery compared to standard surgery was associated with better OS in multivariate analyses (Chang 2012a). However, the evidence for better OS was not corroborated in Luyckx 2012, as surgery type was not found to be associated with OS in a univariate analysis. In contrast, we also found evidence from Luyckx 2012 that ultra-radical surgery was associated with worse DFS compared to standard surgery. We found that ultra-radical surgery was no better than standard surgery regarding DSS in multivariate analysis (Aletti 2006a).

In women with advanced-stage ovarian cancer, a difference in perioperative mortality between ultra-radical surgery and standard surgery could neither be demonstrated nor refuted due to the low number of reported deaths within 30 days of surgery. We found that there is very low-certainty evidence that these participants who underwent ultra-radical surgery may be more likely to experience postoperative morbidity, have longer operative time, greater estimated blood loss, more likely to have intraoperative or postoperative blood transfusions, and longer stay in the intensive care unit compared to those who underwent standard surgery (Chang 2012a).

In summary, across the three studies, we found insufficient evidence in assessing ultra-radical surgery versus standard surgery.

We did not identify any RCTs or comparative observational studies that used statistical adjustment that addressed recurrence rate, QoL or (loco)regional control.

Overall completeness and applicability of evidence

The included studies did not adequately address the objectives of the review, with outcomes being incompletely reported or not reported at all (e.g. QoL). The settings of the three studies spread across three countries: USA, France and South Korea.

We assumed that the decision to perform standard or ultra-radical procedures in these three retrospective studies was determined by the surgeon's discretion unless the study authors explicitly stated the reasons. Furthermore, descriptive information on participant and disease characteristics were not reported by type of surgery. Thus, confounding by indication cannot be ruled out. Significance at univariate analyses was the primary method for variable selection in multivariate analyses for all three studies, highlighting the exploratory nature of these studies with regards to identifying potential confounders. Putative confounders, irrespective of statistical significance on their own, should always be reported in statistical models. Depending on the outcome, selected variables included a combination of age, FIGO stage, residual disease, ASA score, operative time, timing of surgery, tumour grade, or a combination of these in addition to surgery type. Prognostic factors that are commonly known (or could, in principle, be known) before the operation is performed (e.g. age, ASA score, carcinomatosis, mesenteric involvement, diaphragmatic involvement, ascites) are moderating variables and it is valid to adjust for them. It may even be necessary to adjust for them as they may confound the assignment to type of surgery.

The sensitivity analysis including women with carcinomatosis appeared to suggest that in women with more-extensive disease, there is more benefit of radical surgery. Despite the certainty of the evidence being very low, there was a suggestion that unless there is some indication of both the preprocedure extent of disease and the postprocedure residual disease, it is difficult to define the value of surgery. FIGO staging may simply be too crude to use to define extent of disease for most cases.

One included study reported DSS, which included deaths from ovarian cancer and deaths from surgical treatment (Aletti 2006a). Adjusted HRs for OS, which was this review's strict primary outcome, was only reported in Chang 2012a, although we combined these outcomes for the meta-analysis with the assumption that deaths from other causes would be minimal (potentially a dubious assumption but we did present the different outcomes as a subgroup for transparency).

One limitation observed was the inclusion of potential mediating variables in the multivariate models reported in the identified studies The extent of residual disease is likely to be a consequence of both the initial extent of disease (e.g. the pattern rather than the stage and bulk) and the type of surgery (e.g. the degree of surgical radicality). If residual disease is a putative risk factor for survival, then it is likely to be the case that residual disease is a potential mediator in the hypothesised causal pathway from surgery type to survival. As such, residual disease does not meet the criteria for a confounder (Kyriacou 2016), and its inclusion in multivariate models would reduce the effect of surgery type on survival.

Women with advanced ovarian cancer are generally in poor health and have a relatively short life expectancy. A good QoL after treatment is therefore an important issue in this group of women, but unfortunately this review was unable to assess this important outcome but the results of the recent SOCQER-2 study are discussed below under Agreements and disagreements with other studies or reviews (Sundar 2021).

Quality of the evidence

Overall, the certainty of the evidence was very low for all outcomes because the review found only three relevant NRSs, all of which were at high risk (critical) of bias (GRADE Working Group 2004). This severely limits any conclusions. The three included studies analysed 874 women, but not all could be included in the same pooled analyses. All three studies were at critical risk of bias, largely because they were retrospective in nature. Participant characteristics were not reported by surgical group so it was not possible to assess whether the groups receiving different types of surgery were similar prior to surgery. However, the univariate analysis showed which factors were important predictors of survival individually and analysis of the type of surgery that adjusted for these prognostic factors and generally gave similar effect estimates for survival estimates to the unadjusted results, suggesting that prognostic factors were likely balanced between surgical groups. However, it is possible that factors not significant in univariate analysis could influence the estimates of effect in the multivariate model. Furthermore, the dichotomy of several covariates is also questionable and variables that were not considered in the analysis, such as comorbidities and ethnicity, could also influence results.

There were also other contributing factors to downgrade the level of evidence to providing very low-certainty evidence. We had concerns that residual disease after surgery had been adjusted for in the Cox models for survival in all three included studies. When assessing the effect of ultra-radical versus standard surgery, the extent of residual disease is likely to be a consequence of whether ultra-radical or standard surgery was performed; therefore, adjusting for extent of residual disease is likely to dilute the estimate of the effect of the type of surgery. 'Extent of residual disease' is a mediating variable, on the causal pathway between type of surgery and outcome (Altman 1995). Likewise, operative time which was included in the Cox model in Aletti 2006a is also a mediating variable. Prognostic factors that are known (or could in principle be known) before the operation is performed (e.g. age, ASA score, carcinomatosis, mesenteric involvement, diaphragmatic involvement, ascites) are moderating variables and it is completely valid to adjust for them. Indeed, it is necessary to adjust for them and they formed part of our inclusion criteria because they are probably confounded with assignment to treatment group. A separate prognostic review assessing residual disease as a prognostic factor in this area has been conducted (Bryant 2021). This review shows the prognostic impact of achieving NMRD.

In the included studies, as well as many that were excluded, there appeared to be an over-interpretation of statistical significance. For example, in Aletti 2006a, the adjusted HR was 0.64 (95% CI 0.40 to 1.04). The HR in women with carcinomatosis was 0.64 (95% CI 0.41 to 0.98). The former was somewhat dismissed because it was "not statistically significant" but the authors were more convinced by the latter. This carries through into the conclusions where ultra-radical surgery is deemed to be beneficial for women with carcinomatosis, but not for others. However, the point estimates are in this instance identical. The reason the former is not significant and the latter is, could simply be because the former was adjusted for a large number of factors (Higgins 2019; Schisterman 2009). We reflected this in our certainty of the evidence judgements, although the power of meta-analyses did provide us as review authors increased scope to make slightly more generalised conclusions (than single study authors) as there was a suggestion that women with carcinomatosis may have benefited from more radical surgery.

There were also many other factors affecting assignment to the surgical groups. It may have been the case that surgeons were more likely to perform ultra-radical surgery if women are in better health or they are themselves more experienced. We suggest that because the adjusted and unadjusted HRs are similar, the prognostic factors may be well balanced at baseline. Nonetheless, we have been cautious and this is reflected in the certainty of evidence judgements. While the groups may be well balanced, it is possible that the ultra-radical group started off healthier and their apparently better survival in upfront surgery was an artefact. However, this is not possible to ascertain and more evidence of better certainty is needed.

Aletti 2006a reported disease-specific OS. We assumed this to be DSS, as DSS and OS are different. OS counts all deaths (from whatever cause) as an event; DSS counts only deaths from ovarian cancer as an event. This raises the question about how disease-specific survival counts deaths from other causes, where presumably such deaths are censored. DSS is not a non-ideal outcome measure to use due to the potentially poor and error-

prone coding of death certificates. Furthermore, if someone dies because of the treatment they receive, this may not be counted as a death from ovarian cancer, but it is just as important to the patient as a death from ovarian cancer. Thus the evaluation of the relative benefits of the treatments should include these deaths. DSS was not one of our prespecified outcomes, however we chose to subgroup by DSS in the meta-analysis.

Potential biases in the review process

We performed a comprehensive search, including a thorough search of the grey literature and at least two review authors independently sifted and extracted data for all studies. The review included NRSs and was not restricted to RCTs, which provide the strongest level of evidence available. We made every attempt to minimise bias in the review process. We anticipated that selection bias was likely to be a real problem due to the non-randomised assignment of women to surgery as it was likely that treatment allocation depended on the clinical indication and the level of surgical expertise available. We attempted to minimise this bias by only including RCTs or quasi-RCTs or NRSs of sufficient quality that adjusted for baseline differences between the groups receiving different types of surgery. Unfortunately, we were only able to include three studies of such quality that met the inclusion criteria.

A further threat to the validity of the review is likely to be the possibility of publication bias. Studies that did not find a statistically significant difference between treatments may not have been published. We were unable to assess this possibility as the analysis was restricted to just three included studies.

Agreements and disagreements with other studies or reviews

One before-after study suggested that a structured shift to an ultra-radical upfront primary surgical approach may not improve survival in surgically treated women (Falconer 2020). In this population-based cohort study, women with suspected advanced EOC near Stockholm in Sweden were included via the Swedish Quality Registry for Gynecologic Cancer (SQRGC) and the NCR. Women were selected in two sets of three-year cohorts, based on the year of their diagnosis (a 'before' cohort or an 'after' cohort with a change in surgical treatment algorithm) and were followed for at least three years. Five-year OS in non-surgically and surgically treated women was analysed. After a median follow-up of around 28 months in 752 women, the complete resection rate increased from 37% to 67% as well as the proportion of non-surgically treated women, from 24% to 33%. This study also demonstrated that a shift to ultra-radical surgery was associated with an increase in the proportion of non-surgically treated women. However, this study was not a 'controlled' before-after study and as a consequence was prone to bias (Goodacre 2015). The use of historical controls are known to overestimate the benefit of new treatments. Before-after studies also have a high risk of bias because there may be unidentified differences between the intervention and control groups that may affect changes in the outcome measure (Sterne 2022).

One of the excluded studies evaluated the impact of different prognostic factors for surgical outcome and evaluated the impact of surgical outcome on survival in women with advanced-stage ovarian cancer (Wimberger 2007). In this prospective study, 798 women with FIGO IIB-IV disease from 136 centres within Germany were operated on and then randomised to receive either cisplatin plus paclitaxel or carboplatin plus paclitaxel chemotherapy. Complete surgical data were obtained from 761 women and were analysed using multivariable logistic regression. Complete cytoreduction with no macroscopic residual tumour was achieved in 29.8% of women, with a significant improved OS compared to women with visible, including small, remaining disease (P < 0.0001). In women with FIGO stages IIIC and IV, complete cytoreduction was less likely in older women, those with a higher preoperative tumour load, worse performance status, and peritoneal carcinomatosis. FIGO stage was not an independent factor for complete cytoreduction in this group of women. The authors identified a subgroup of 71 centres (referred to as type A) which demonstrated the capability of performing ultra-radical surgery having carried out pelvic or para-aortic lymphadenectomy (or both) and peritoneal stripping in at least one of the enrolled participants in the study. This group included 534 (69.8%) women. The remaining 65 centres were identified as type B centres and treated 227 women. A higher percentage of women with worse performance status were treated in type A centres (53.9% in type A versus 43.6% in type B; P = 0.009). Type A centres more often achieved complete cytoreduction compared to type B centres (32.8% in type A versus 22.9% in type B; P = 0.007). Treatment in type A centres was associated with greater OS compared to treatment in type B centres (45.2 months in type A versus 35 months in type B; P = 0.045).

Their results suggest an advantage for aggressive primary surgery and complete cytoreduction in women with more advanced disease when operated on in experienced centres. Although this study was excluded from the review because the comparative groups were by treatment centres that contained a mixed case load of ultra-radical and standard surgery, it does provide some evidence that aggressive primary cytoreductive surgery can negate the effects of aggressive tumour biology in advanced ovarian cancer, with a subsequent improvement in OS.

In Aletti 2006a, the authors reported that radical procedures were performed at the same rate regardless of age (49% for age less than 65 years versus 51% for age greater than 65 years; P = 0.45) and that participants with better ASA scores (1 or 2 versus 3 or 4) were more likely to have aggressive procedures performed (59% with ASA 1 or 2 versus 36% with ASA 3 or 4; P = 0.005), which implies the overall medical condition of the participant at least partially influences the decision to perform aggressive surgery. However, the numbers of women in each surgical group were not reported. For further details, see the Characteristics of included studies table.

One recent review of guidelines showed clear international differences in ovarian cancer survival and these differences in treatment could be contributing to survival disparities (Norell 2020). The objective of the review by Norell and colleagues was to compare clinical practice guidelines and patterns of care across seven high-income countries. They included guidelines widely used in routine ovarian cancer treatment. The review also included an expert questionnaire component, which included questions on surgical practice and was validated and tested by an expert clinical working group. Guideline and survey results were crudely compared with three-year survival by 'distant' stage using Spearman's rank order correlation.

Norell 2020 compared 27 guidelines, and 119 clinicians completed the survey. Guideline-related measures varied between countries but did not correlate with survival internationally. Reported

patterns of surgical care varied internationally, including for rates of extensive/'ultra-radical' surgery, and perceived barriers to optimal cytoreduction. When surveyed, Norwegian and Australian clinicians either agreed or strongly agreed with ultra-radical surgery, whereas clinicians from Canada and the UK agreed with ultra-radical surgery to a lesser extent, with some respondents either disagreeing or strongly disagreeing with this approach. When crudely compared, willingness to undertake extensive/ultra-radical surgery correlated with three-year survival by distant stage (Spearman's rank correlation coefficient (r_s) = 0.94, P = 0.017). Norell 2020 reported that most guidelines that were identified did not explicitly recommend ultra-radical (extensive) surgery, but clinicians from higher-performing countries were more likely than those from lower-performing countries to be proponents of 'ultra-radical' surgery. Norwegian clinicians were least likely to perceive age as a barrier to achieving optimal cytoreduction and Norway demonstrated the highest survival in elderly women with distant-stage disease. In the UK, where clinicians perceived a lack of supportive care, survival for these women was lower. Women with advanced ovarian cancer are more likely to have severe comorbidities and higher mortality, and historically, elderly women were less likely to receive comprehensive surgical treatment. One Dutch study recently found that older participants and those with advanced disease were significantly less likely to receive any cancer-directed treatment (Zijlstra 2019). It was also noted by the authors of Norell 2020 that available resources and operating theatre time may influence a surgeons' ability to perform extensive surgery and could impact patient outcomes. They also added that it is this subcategory of elderly women with advanced disease where survival is lowest and where significant differences exist.

Guidelines from Belgium in 2016 provided recommendations based on scientific evidence for the diagnosis, treatment and follow-up of epithelial ovarian, fallopian tube and primary peritoneal cancer (Vergote 2016). The report stated that clinicians were encouraged to interpret their recommendations in the context of the individual patient situation and her own values and preferences. Furthermore, in the absence of good-quality evidence on optimal treatment options, patient participation in clinical trials was to be encouraged as much as possible. The guidelines reported by Vergote 2016 acknowledged that the evidence was limited, but suggested that it supports the use of radical surgical techniques (such as diaphragm resection, peritoneal stripping, splenectomy, etc.) to obtain complete resection of all macroscopic tumour. The guidelines showed the prognostic value of debulking to no macroscopic disease at the end of surgery and supporting evidence from the use of radical surgery. The guidelines formulated a strong recommendation (despite low level of evidence) that complete debulking should be the aim of cytoreductive surgery (PDS or IDS) and that the term optimal should no longer be used as old definitions of optimal surgery (residual disease less than 2 cm or less than 1 cm). We are more cautious in the interpretations in our systematic review than the guidelines we identified. While the results of the guidelines are compelled to make recommendations, our review is restricted to the inclusion of just three NRSs and we were bound by systematic review reporting guidance (Higgins 2019).

The guidelines reported by Norell 2020 also accounted for the experience of patient representatives. The influence of radical surgery on long-term QoL was reported not to be a major drawback, the survival benefit weighing more importantly in the overall balance. The SOCQER-2 study reported QoL as a primary outcome, which was a prospective, non-randomised multicentre observational study run across the UK, India and Australia (Sundar 2021). Women were eligible if they had suspected or confirmed EOC with radiological spread beyond pelvis and if primary or delayed debulking surgery was planned.

The SOCQER-2 study found that women with late-stage ovarian cancer had no important differences in European Organisation for Research and Treatment of Cancer Quality of Life of Cancer Patients – 30 (EORTC QLQ-C30) global scores measured across six weeks, six months and 12 months' postsurgery when undergoing surgery of varying complexity, despite a higher preoperative disease burden in people undergoing more radical surgical procedures (Sundar 2021). Across all groups of women receiving all forms of complex surgery (categorised by surgery complexity scores (SCS) and grouped into low, intermediate and high), global QoL showed a small but significant improvement by 12 months postoperatively. Women who underwent the most complex surgery (high-SCS group) had small-to-moderate detriments in EORTC QLQ-C30 physical function, role function and emotional function at six weeks postsurgery compared with women undergoing less-extensive surgery (intermediate- and low-SCS groups), but by six to 12 months' postsurgery, these functions were comparable across all SCS categories. Most women undergoing high-SCS surgery without disease progression experienced a positive change in QoL by 12 months' postsurgery. There were no clinically meaningful differences in QoL among women undergoing surgery of different complexities. The authors of the study concluded that women undergoing high-complexity surgery can be reassured that by 12 months' postsurgery most will have better QoL after than immediately before surgery (Sundar 2021).

The authors of SOCQER-2 found that women who underwent low-complexity surgery had higher rates of residual disease and lower survival compared with those with a similar disease burden undergoing surgery of intermediate complexity (Sundar 2021). However, there was no statistical adjustment performed in these analyses. Postoperative residual disease was associated with poorer OS, particularly in women undergoing low-complexity surgery, but again they made no statistical adjustment. Sundar 2021 acknowledged potential selection bias, but since research nurses carried out recruitment to the SOCQER-2 study, that systematic bias introduced by surgeons recruiting women whom they believed would recover well after extensive surgery was unlikely.

AUTHORS' CONCLUSIONS

Implications for practice

We found only very low-certainty evidence comparing ultra-radical and standard surgery in women with advanced ovarian cancer and also subgroups with carcinomatosis. The evidence suggested that ultra-radical surgery may result in better survival, but results are based on retrospective studies, at critical risk of bias, in relatively few women. Results for progression/disease-free survival were inconsistent and evidence was sparse. Quality of life (QoL) and morbidity was not reported in the two groups, but the results of the SOCQER-2 (Surgery in Ovarian Cancer – Quality of Life Evaluation Research – 2) study are promising for those undertaking high-complexity surgery (Sundar 2021). This study was the only one

to adequately investigate QoL and it concluded that there can be confidence in clinical practice that the use of high-complexity surgery in advanced ovarian cancer will not have a detrimental effect on global QoL compared with less-complex surgery.

While we were unable to reach definite conclusions about the relative benefits and adverse effects of the two types of surgery in our review (that applied stringent inclusion criteria), the guidelines that we identified are worthy of consideration (Norell 2020; Vergote 2016). These guidelines generally supported the use of radical surgical techniques to obtain no macroscopic residual disease in appropriate women.

Implications for research

To date, most studies of ultra-radical (extensive) surgery for advanced-stage ovarian cancer have assessed residual disease as an outcome rather than survival. Other studies that have assessed the role of ultra-radical surgery have not compared it with standard surgery and have included women with recurrent disease, making this a heterogeneous group of women and hence limiting the inferences that can be made about the role of ultra-radical surgery. In order to aid existing guidelines, the role of ultra-radical surgery in the management of advanced-stage ovarian cancer could be addressed through the conduct of a sufficiently powered randomised controlled trial comparing ultra-radical and standard surgery.

If randomised controlled trials are not feasible, high-quality non-randomised studies should be designed to add to the existing evidence base in the review. Such studies should include all women diagnosed within a fixed population and agree criteria for prognostic factors that will form the key adjustment in analyses. Population-level, multicentre studies are important in this area as what works or does not work in one institution may be very different from what works elsewhere. It would be important to test the effect of ultra-radical surgical adoption on the rates of surgery and the effects on those women who do not undergo surgery. Multivariable analysis should allow for baseline prognostic factors, but not for variables (such as extent of residual disease or operating time) that were recorded after women were assigned to surgical groups. The experience of the treating surgeon should also be factored in.

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CHARACTERISTICS OF STUDIES

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

Aletti 2006a

Study characteristics	
Methods	Retrospective cohort study of consecutive participants identified from surgical records. Surgery carried out at Mayo Clinic, Minnesota (USA)
Participants	Women with FIGO stage IIIC ovarian cancer, where disease status was extracted from surgical exploration notes.

Aletti 2006a *(Continued)*

	Age at study entry: mean 64.4 years; median 64 years; range 24–87 years All women presented with FIGO stage IIIC: 194/194 (100%) Tumour cell type: serous 126 (64.9%), mucinous: 4 (2.1%), endometrioid: 18 (9.3%), clear cell: 7 (3.6%), mixed: 17 (8.8%), seroanaplastic: 17 (8.8%), Müllerian origin: 2 (1%) Tumour grade: 1: 1 (0.5%), 2: 13 (6.7%), 3: 180 (92.8%) ASA score: 1: 7 (3.6%), 2: 87 (44.8%), 3: 88 (45.4%), 4: 7 (3.6%), unknown: 5 (2.6%) Ascites: mean 2076 mL, median 1000 mL, range 0–12,000 mL Extent of disease: carcinomatosis: 144 (74.2%), diaphragm involvement: 137 (70.6%), mesentery: 138 (71.1%), cul-de-sac: 163 (84%), omentum: 168 (86.6%), ascites: 160 (82.5%) Residual disease: no gross visible: 46 (23.7%); 0–1 cm: 85 (43.8%); 1–2 cm: 22 (11.3%); > 2 cm: 41 (21.1%) Baseline details for 144 women with carcinomatosis were not reported. However, it is known that 68 (47.2%) women underwent ultra-radical surgery and 76 (52.8%) underwent standard surgery.
Interventions	Initial surgery performed for diagnosis, staging and surgical cytoreduction. **Intervention:** ultra-radical surgery: if any diaphragmatic surgery, bowel resection, splenectomy or extensive abdominal peritoneal stripping or resection. **Comparison:** standard surgery: hysterectomy, complete omentectomy, stripping of pelvic peritoneum or limited resection of peritoneal-based nodules.
Outcomes	• Disease-specific overall survival • Perioperative mortality Disease-specific survival: HR for death from advanced epithelial ovarian cancer (adjusted for age, ASA score, carcinomatosis, mesenteric involvement, diaphragmatic involvement, ascites, residual disease and operative time): 0.64 (95% CI 0.40 to 1.04). Provided through personnel communication with the study authors. Median disease-free survival: 15.9 with ultra-radical surgery; 19.3 months with standard surgery; significant; not adjusted
Notes	Follow-up: mean: 3.5 years; median: 2.7 years; range: 0.02–10.5 years Participants were first classified by the extent of peritoneal dissemination. Those with tumour nodules diffusely covering most of the bowel serosa surfaces and the parietal peritoneum of the abdomen and pelvis were classified as having carcinomatosis. In multivariate analysis, only residual disease and radical surgery were independent factors predicting participant survival (Table 4). Quote: "When examining the effect of radical surgery on all patients with carcinomatosis (n = 144), we observed an improved disease-specific overall survival rate (38% versus 9%; log-rank test, P=0.001) favouring patients who underwent radical procedures versus non-radical procedures (Fig. 3)". Quote: "Radical procedures were performed at the same rate regardless of age (49% for age 65 years versus 51% for age 65 years; P = 0.45). Patients with better ASA scores (1 or 2 versus 3 or 4) were more likely to have aggressive procedures performed (59% versus 36%, respectively; P = 0.005), which implies the overall medical condition of the patient at least partially influences the decision to perform aggressive surgery". Quote: "The 5-year disease-specific overall survival rate was 46% compared with 13% for patients with radical and non-radical surgeries, respectively (log-rank test, P = 0.001; Fig. 4A)". Quote: "The rate of optimal resection (residual disease 1 cm) was 84.5% compared with 51% on the basis of surgeon tendency to use radical procedures".

Aletti 2006a *(Continued)*

Quote: "Our division of gynaecologic surgery shares a uniform referral base with similar patient demographics, and we practice at a single institution where each surgeon has access to identical services and nursing support".

Risk of bias

Bias	Authors' judgement	Support for judgement
1. Bias due to confounding (a–d)	High risk	Domain had a critical risk of bias: no known prognostic factors that have potential for confounding of the effect on intervention. Information was collected retrospectively.
2. Selection bias (a)	Low risk	Intervention and follow-up start were simultaneous as a rule for cytoreductive surgery. No evidence of selection into the study due to variables measured after the intervention since participants were included retrospectively.
3. Classification of interventions (a–b)	Low risk	Well-defined surgical interventions based on aggressive surgery (yes versus no).
4. Deviation from intended interventions (a–c)	Unclear risk	No evidence of any deviations from interventions or usual practice but may be due to omission or that deviations did not happen.
5. Bias due to missing data (a–b)	High risk	Domain had moderate-to-high risk of bias: no differential follow-up or missing data reported; no participant selection due to missing data reported. In some respects, there was no reason to believe there was serious bias due to missing data as the study was sound for a non-randomised study with regard to this domain but cannot be considered comparable to a well-performed randomised trial. Therefore, it was sensible to judge the missing data domain at moderate-to-high risk of bias.
6. Measurement of outcomes (a–b)	High risk	Domain had a critical risk of bias: disease-specific survival is not a good outcome measure to use for several reasons, namely the coding of death certificates is notoriously error-prone. If someone dies because of the treatment they receive, this may not be counted as a death from ovarian cancer. But it is just as important to the patient as a death from ovarian cancer and the evaluation of the relative benefits of the treatments should include these deaths. The study authors would have had access to data for death from all causes.
7. Reporting bias (a–c)	High risk	Domain had a critical risk of bias: there is a serious problem in the multivariate analysis. It adjusted for variables that were measured after the time origin, namely extent of residual disease and operative time (Altman 1995). Also data were reported in a subset of the 144 women with carcinomatosis (more-extensive disease) only.

Chang 2012a

Study characteristics

Methods	Retrospective review of medical records. The decision to perform simple or radical procedures was determined by the surgeon.
Participants	Consecutive women with FIGO stage IIIC and IV primary epithelial ovarian, fallopian tube or peritoneal cancer who underwent primary cytoreductive surgery at Ajou University Hospital, Republic of Korea (enrolment 1 January 2000 to 31 December 2011). Age: median 54 years; range 30–78 years

Chang 2012a *(Continued)*

	FIGO stage IIIC: 189 (93.1%); IV: 14 (6.9%) Tumour cell type: serous 167 (82.3%), mucinous: 4 (2.0%), endometrioid: 5 (2.5%), clear cell: 9 (4.4%), mixed: 18 (8.9%) ASA score 1–2: 114 (56.2%); 3–4: 80 (39.4%); 9 not available Tumour grade 1: 26 (12.8%), 2: 72 (35.5%), 3: 100 (49.3%), unknown: 5 Ascites > 100 mL: 92 (54.7%) Peritoneal carcinomatosis 149 (73.4%) Residual disease: no gross visible: 63 (31.0%); 0–1 cm: 67 (37.9%); > 1 cm: 63 (31.0%) Median BMI: 23.3 (range 11.7–35.2) Carcinomatosis: 149 (73.4%) Baseline details not presented according to type of surgery.
Interventions	**Intervention:** radical cytoreductive procedures included radical oophorectomy with or without rectosigmoid colectomy, total omentectomy, multiple bowel resections, diaphragm peritonectomy or resection, liver resection, splenectomy, distal pancreatectomy, and gastric resection. **Comparison:** simple surgery included total abdominal hysterectomy, bilateral salpingo-oophorectomy, peritoneal biopsies or excisions, infracolic omentectomy, pelvic lymphadenectomy, para-aortic lymphadenectomy, and segmental resection of small bowel. After surgery, all participants received adjuvant platinum-based chemotherapy plus paclitaxel for 6–9 cycles.
Outcomes	Overall survival, progression-free survival and adverse events Ultra-radical versus standard surgery Median operative time (minutes): 307 versus 235; P < 0.01 Median estimated blood loss (mL): 800 versus 500; P = 0.03 Intra- or postoperative blood transfusion: 25% versus 17.6%; P = 0.01 Median stay in intensive care unit (days): 1.5 versus 0.8; P < 0.01 Postoperative mortality within 30 days: 1 versus 0 Any postoperative morbidity: 38% versus 11.8%; P < 0.01 Postoperative morbidity defined as infected lymphocyst, thromboembolism, intestinal obstruction, anastomotic leakage, ureteral injury, sepsis, intra-abdominal abscess, pneumothorax or postoperative death within 30 days.
Notes	Follow-up: median 43 months; range 1–124 months Retrospective non-randomised study. The decision to perform simple or radical procedures was determined by the surgeon. Confounding by indication could not be excluded. Participant and disease characteristics not reported per type of surgery. Blinding not reported. Adjusted HRs were derived from a prognostic model. No details on how modelling was performed, but this seems to have been done based on significance testing (and not on including putative confounders in the analysis, irrespective of statistical significance).
Risk of bias	

Chang 2012a *(Continued)*

Bias	Authors' judgement	Support for judgement
1. Bias due to confounding (a–d)	High risk	Domain had a critical risk of bias: (quote) "The decision to perform simple or radical procedures was determined by the surgeon's discretion". Confounding by indication could not be excluded. Also, no known prognostic factors that had potential for confounding of the effect on intervention. Information was collected retrospectively.
2. Selection bias (a)	Low risk	Intervention and follow-up start were simultaneous as a rule for cytoreductive surgery. No evidence of selection into the study due to variables measured after the intervention since participants were included retrospectively.
3. Classification of interventions (a–b)	Low risk	Well-defined surgical interventions based on type of surgical procedure (simple versus radical).
4. Deviation from intended interventions (a–c)	Unclear risk	No evidence of any deviations from interventions or usual practice – which may either be an error of omission or that deviations did not happen.
5. Bias due to missing data (a–b)	High risk	Domain had a moderate-to-high risk of bias: all selected participants seem to have been included in the analyses. No differential follow-up or missing data reported; no participant selection due to missing data reported. There was no reason to believe there was a serious bias due to missing data as the study was sound for a non-randomised study with regard to this domain but could not be considered comparable to a well-performed randomised trial. Therefore, it was sensible to judge the missing data domain at moderate-to-high risk of bias.
6. Measurement of outcomes (a–b)	High risk	Domain had a critical risk of bias: adjusted HRs were derived from a prognostic model. No details on how modelling was performed, but this seems to have been done based on significance testing (and not on including putative confounders in the analysis, irrespective of statistical significance). Also, adjustment were made for residual disease and this was likely to distort the estimate of survival as this adjustment was made after surgery and was a key prognostic factor.
7. Reporting bias (a–c)	Unclear risk	Difficult to judge. No protocol available. All outcomes mentioned in the methods section seemed to have been reported in the results section.

Luyckx 2012

Study characteristics	
Methods	Retrospective review of medical records of patients treated in 7 French gynaecological oncology and surgery centres.
Participants	Women with FIGO stage IIIC and IV (pleural invasion only) ovarian, tubal or peritoneal epithelial carcinoma who underwent either primary or interval debulking. All had ≥ 6 cycles of carboplatin plus paclitaxel (enrolment 1 January 2003 to 31 December 2007) Age: median 59 years; range 24–90 years FIGO stage IIIC: 441 (83.7%); IV: 86 (16.3%) Tumour cell type: serous papillary 382 (72.8%), mucinous: 11 (2.1%), endometrioid: 54 (10.3%), clear cell: 13 (2.5%), undifferentiated 54 (10.3%), other: 11 (2.1%) Tumour grade 1: 34 (8.3%), 2: 138 (33.8%), 3: 236 (57.8%), unknown: 119

Luyckx 2012 *(Continued)*

	Ascites: median 50 mL; range 0–8000 mL Residual disease: no gross visible: 374 (71.1%), 0–1 cm: 97 (18.5%), > 1 cm: 55 (10.5%) Peritoneal cancer index: median 10.0 Upper abdominal lesion: 0 mm: 175 (38.5%); 0–25 mm: 182 (40.0%); > 25 mm: 97 (21.4%) Baseline details not presented according to type of surgery.
Interventions	**Intervention 1:** ultra-radical surgery involving a combination of digestive tract resections (right colon and caecum, total colectomy, and others), organ resection (spleen, gallbladder, partial gastrectomy, and others), coeliac lymph node dissection, and total abdominal peritoneum stripping in addition to standard surgery (group 2B in the study). **Intervention 2:** standard surgery plus relatively routine upper abdominal surgery (group 2A in the study). **Comparison:** standard surgery with hysterectomy, bilateral salpingo-oophorectomy, rectosigmoid resection, infragastric omentectomy, pelvic and aortic lymphadenectomy, and, when applicable, appendectomy (group 1 in the study).
Outcomes	Overall survival, disease-free survival
Notes	Follow-up: median 49 months Retrospective non-randomised study. We assume that the decision to perform simple or radical procedures was determined by the surgeon. Confounding by indication could not be excluded. Participant and disease characteristics not reported per type of surgery. Blinding not reported (but may not be relevant to this research question). Sample also included a mixture of primary and interval debulking surgery. Adjusted HRs were derived from a prognostic model. Characteristics were selected based on statistical significance in the univariate analysis (P < 0.10) and not on including putative confounders in the analysis, irrespective of statistical significance.

Risk of bias

Bias	Authors' judgement	Support for judgement
1. Bias due to confounding (a–d)	High risk	Domain had a critical risk of bias: no known prognostic factors that have potential for confounding of the effect on intervention. Information collected retrospectively.
2. Selection bias (a)	Low risk	Intervention and follow-up start were simultaneous as a rule for cytoreductive surgery. No evidence of selection into the study due to variables measured after the intervention since participants were included retrospectively.
3. Classification of interventions (a–b)	Low risk	Well-defined surgical interventions based on type of surgical procedure: group 1: standard surgery; group 2A: standard surgery plus relatively routine upper abdominal surgery; group 2B: ultra-radical surgery
4. Deviation from intended interventions (a–c)	Unclear risk	No evidence of any deviations from interventions or usual practice but may be due to omission or that deviations did not happen.
5. Bias due to missing data (a–b)	High risk	Domain had a moderate-to-high risk of bias: all selected participants may have been included in the analyses but this could not be confirmed. Therefore, it was sensible to judge the missing data domain as being at moderate-to-high risk of bias.
6. Measurement of outcomes (a–b)	High risk	Domain had a critical risk of bias: adjusted HRs are derived from a prognostic model based on univariate significance testing (P < 0.10) and not on including putative confounders in the analysis, irrespective of statistical significance. Al-

Luyckx 2012 *(Continued)*

		so, adjustment were made for residual disease and this was likely to distort the estimate of survival as this adjustment was made after surgery and was a key prognostic factor.
7. Reporting bias (a–c)	Unclear risk	Difficult to judge. No protocol available. All outcomes mentioned in the methods section seemed to have been reported in the results section.

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

Study	Reason for exclusion
Aletti 2006b	Participants in comparison standard surgery group also had extensive bowel surgery, which is ultra-radical. It was also unclear whether women with recurrent disease were included.
Aletti 2006c	Intervention was ultra-radical (removal of tumour from diaphragm), but unclear whether those in comparison group received different form of ultra-radical surgery.
Aletti 2009a	Comparison of ultra-radical versus standard surgery groups not possible – low complexity scores also included possible small bowel resection.
Aletti 2009b	Comparison of ultra-radical versus standard surgery groups not possible – low complexity scores also included possible small bowel resection.
Angioli 2012	< 100 participants in analysis.
Bahra 2013	Comparison not possible.
Barlin 2013	No multivariate analysis.
Bartl 2018	No comparator.
Bertelsen 1990	Comparison of ultra-radical versus standard surgery groups not possible. It was also unclear whether women with recurrent disease were included.
Bristow 1999	Women with recurrent disease also included.
Butler 2012	< 100 participants; conference abstract.
Cai 2007	Comparisons were made between bowel resection versus no bowel resection regardless of the nature of surgery, so those in the no bowel resection group may have still received a form of ultra-radical surgery. It was also unclear whether women with recurrent disease were included.
Campos 2014	Conference abstract.
Canlorbe 2018	Participants in comparison standard surgery group also had extensive bowel surgery, which is ultra-radical. It was also unclear whether women with recurrent disease were included.
Chang 2012b	No ultra-radical surgery.
Chereau 2011	Mixed FIGO stages; no multivariate analysis.
Chi 2004	Participants in comparison standard surgery group also had extensive bowel surgery, which is ultra-radical. It was also unclear whether women with recurrent disease were included.

Study	Reason for exclusion
Chi 2009	Comparison between standard surgery and ultra-radical surgery groups not possible as all women underwent extensive upper abdominal surgery.
Chua 2011	Comparison not of interest.
Clark 2012	Outcomes not of interest; conference abstract.
Clark 2014	Comparison not of interest.
Cormier 2012	No ultra-radical surgery; conference abstract.
Cummins 2019	Conference abstract.
Davies 2019	Participants in comparison standard surgery group also had extensive bowel surgery, which is ultra-radical. It was also unclear whether women with recurrent disease were included.
Eisenhauer 2006	Participants in comparison standard surgery group also had extensive bowel surgery, which is ultra-radical. Also unclear if women with recurrent disease included.
Eisenkop 1993	Participants in comparison standard surgery group also had extensive bowel surgery or diaphragmatic stripping (or both) which is ultra-radical. It was also unclear whether women with recurrent disease were included.
Eisenkop 1998	Participants in comparison standard surgery group also had extensive bowel surgery or diaphragmatic stripping (or both) which is ultra-radical. Women with recurrent disease were also included.
Eisenkop 2001	Comparison of ultra-radical versus standard surgery groups not possible.
Eisenkop 2003	Comparison of ultra-radical versus standard surgery groups not possible. Women with recurrent disease were also included.
Eisenkop 2006	Comparisons were made between splenectomy versus no splenectomy regardless of the nature of surgery, so those in the no splenectomy group may have still received a form of ultra-radical surgery. Women with recurrent disease were also included.
Elgamal 2019	Participants in comparison standard surgery group also had extensive bowel surgery, which is ultra-radical. It was also unclear whether women with recurrent disease were included.
Eng 2018	No multivariate analysis.
Eoh 2017	Participants in comparison standard surgery group also had extensive bowel surgery, which is ultra-radical. It was also unclear whether women with recurrent disease were included.
Falconer 2020	Uncontrolled before-after study.
Favero 2014	Comparison not of interest.
Ferrero 2014	Comparison not of interest.
Filippova 2019	Participants in comparison standard surgery group also had extensive bowel surgery, which is ultra-radical. It was also unclear whether women with recurrent disease were included.
Fotopoulou 2012	Comparison not of interest; conference abstract.
Gockley 2019	Participants in comparison standard surgery group also had extensive bowel surgery, which is ultra-radical. It was also unclear whether women with recurrent disease were included.

Study	Reason for exclusion
Gremeau 2014	Comparison not of interest.
Grimm 2017	No comparator.
Guyon 2014	Comparison not of interest.
Hamilton 2011	Comparison not of interest.
Hudry 2013	Comparison not of interest.
Hwang 2014	Mixed population; comparison not of interest.
Janda 2014	Comparison not of interest.
Jiang 2013	Abstract form only but appeared to be same study as Ren 2015 where multivariate analysis did not include surgery type.
Kato 2013a	Comparison not of interest.
Kato 2013b	Population not of interest.
Kehoe 2013	Comparison not of interest.
Kim 2011	Comparison not of interest.
Kolev 2014	Recurrent cancer.
Kommoss 2010	Comparison between groups not possible as both groups also included participants undergoing bowel resection.
Kristensen 2014	Borderline tumours.
Kuhn 1998	Participants in comparison standard surgery group also had extensive bowel surgery or diaphragmatic stripping (or both), which is ultra-radical. Women with recurrent disease were also included.
Laios 2019	No comparator.
Lee 2017	Conference abstracts.
Li 2014	Comparison not of interest.
Liberale 2019	Conference abstract.
Liu 2013a	Germ cell tumours; < 100 participants.
Liu 2013b	Germ cell tumours; article in Chinese.
Martinez 2014	Conference abstract.
McCann 2011	No multivariate analysis.
Muallem 2018	No multivariate analysis.
Oseledchyk 2016	Participants in comparison standard surgery group also had extensive bowel surgery, which is ultra-radical. It was also unclear whether women with recurrent disease were included.

Study	Reason for exclusion
Oshita 2013	Included only stages pT1-2.
Park 2011	No ultra-radical surgery; conference abstract.
Pathiraja 2011	< 100 participants; conference abstract.
Pathiraja 2013	< 100 participants; outcomes not of interest.
Pelissier 2018	No comparator.
Perri 2013	Comparison not of interest.
Phillips 2018	No multivariate analysis.
Pushpalatha 2011	Comparison not of interest.
Qin 2012	No meta-analysis; comparison not of interest.
Ratnavelu 2014	< 100 participants; conference abstract.
Ren 2015	Multivariate analysis did not include surgery type.
Rodriguez 2012	Women with suboptimal debulking were excluded (see also full publication Rodriguez 2013).
Rodriguez 2013	Women with suboptimal debulking were excluded.
Rouzier 2010	Mixed population; comparison not of interest.
Sagara 2019	No multivariate analysis.
Sandadi 2014	Comparison not of interest.
Scalici 2014	Comparison not of interest.
Sehouli 2010	Comparison not of interest.
Soo Hoo 2015	No multivariate analysis.
Stefanović 2011	< 100 participants.
Sundar 2014	< 100 participants; conference abstract.
Sundar 2018	Conference abstract.
Sundar 2019	Conference abstract.
Suzuki 2008	Conference abstract.
Szczesny 2016	Conference abstract.
Tozzi 2019	Participants in comparison standard surgery group also had extensive bowel surgery, which is ultra-radical. It was also unclear whether women with recurrent disease were included.
Tsolakidis 2010a	Comparison between 'standard surgery' and 'ultra-radical surgery' groups not possible as all women underwent diaphragmatic stripping.

Study	Reason for exclusion
Tsolakidis 2010b	Comparison between standard surgery and ultra-radical surgery groups not possible as all women underwent diaphragmatic stripping.
van de Laar 2014	Protocol for a new study; applies to recurrent cancer.
Vidal 2016	No comparator.
von Hugo 1989	Unclear if women with recurrent disease were included.
Wallace 2016	No comparator.
Wat 2012	< 100 participants; conference abstract.
Wimberger 2007	Comparison of ultra-radical versus standard surgery groups not possible, as the comparative groups include participants who had both types of surgery.
Wright 2012	Outcomes not of interest.
Yildirim 2014	No comparator.
Zamurovic 2013	No multivariate analysis.
Zapardiel 2012	No multivariate analysis.

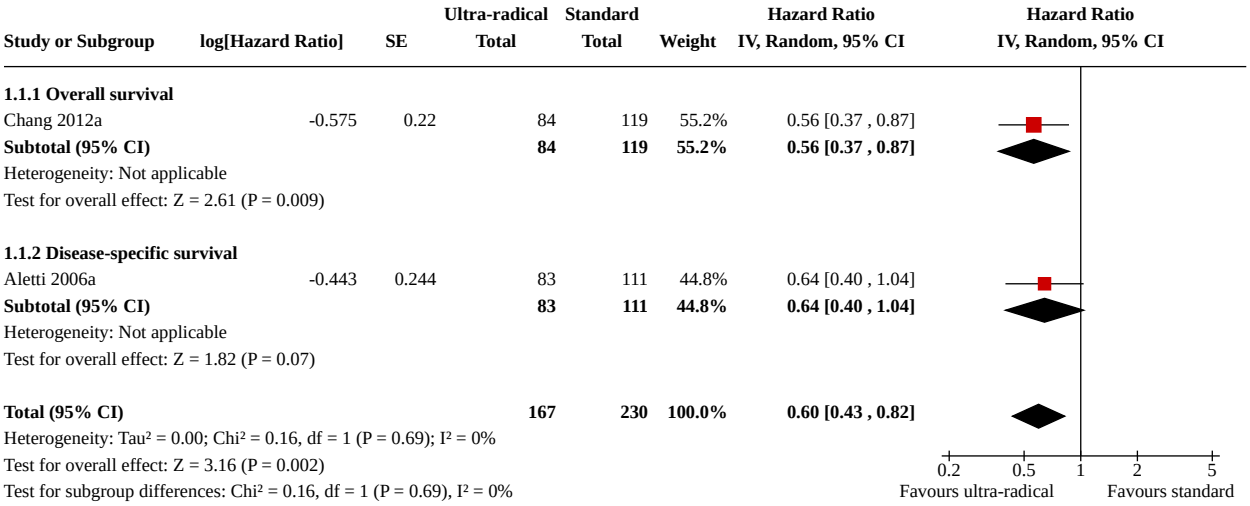
DATA AND ANALYSES

Comparison 1. Ultra-radical versus standard surgery (upfront surgery)

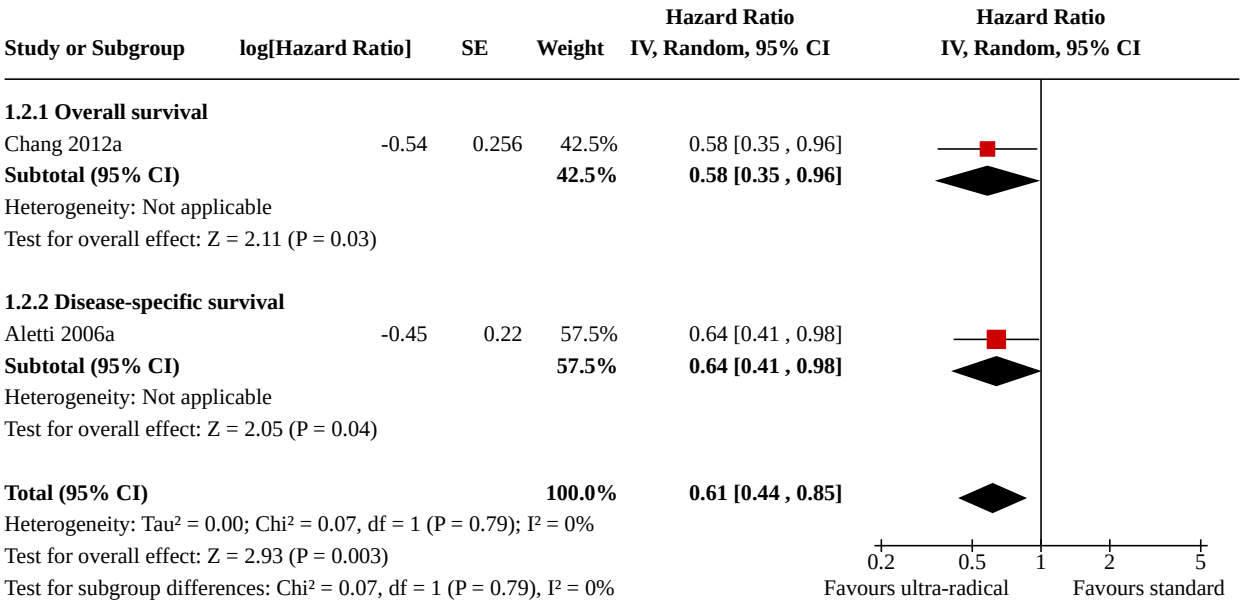
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Survival	2	397	Hazard Ratio (IV, Random, 95% CI)	0.60 [0.43, 0.82]
1.1.1 Overall survival	1	203	Hazard Ratio (IV, Random, 95% CI)	0.56 [0.37, 0.87]
1.1.2 Disease-specific survival	1	194	Hazard Ratio (IV, Random, 95% CI)	0.64 [0.40, 1.04]
1.2 Survival: women with carcinomatosis (upfront surgery)	2		Hazard Ratio (IV, Random, 95% CI)	0.61 [0.44, 0.85]
1.2.1 Overall survival	1		Hazard Ratio (IV, Random, 95% CI)	0.58 [0.35, 0.96]
1.2.2 Disease-specific survival	1		Hazard Ratio (IV, Random, 95% CI)	0.64 [0.41, 0.98]
1.3 Progression-free survival	1		Hazard Ratio (IV, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3.1 Upfront primary debulking surgery	1		Hazard Ratio (IV, Random, 95% CI)	Totals not selected
1.4 Progression-free survival: women with carcinomatosis (upfront surgery)	1		Hazard Ratio (IV, Random, 95% CI)	Subtotals only
1.5 Disease-free survival	1	527	Hazard Ratio (IV, Random, 95% CI)	1.60 [1.11, 2.31]
1.5.1 Mix of upfront and interval debulking surgical procedures – including group 2A	1	258	Hazard Ratio (IV, Random, 95% CI)	1.54 [0.91, 2.60]
1.5.2 Mix of upfront and interval debulking surgical procedures – including group 2B	1	269	Hazard Ratio (IV, Random, 95% CI)	1.66 [1.00, 2.78]

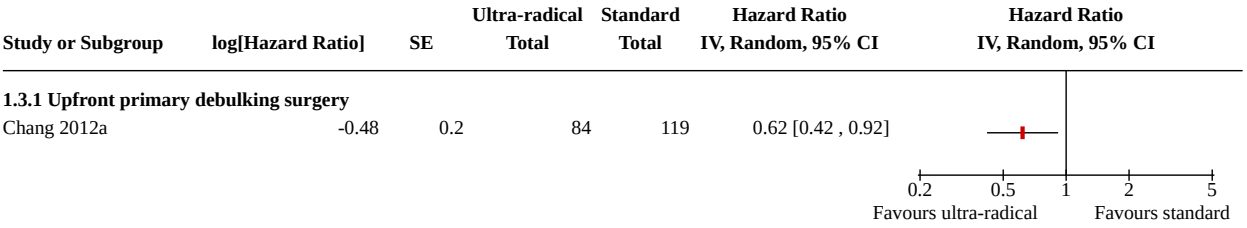
Analysis 1.1. Comparison 1: Ultra-radical versus standard surgery (upfront surgery), Outcome 1: Survival



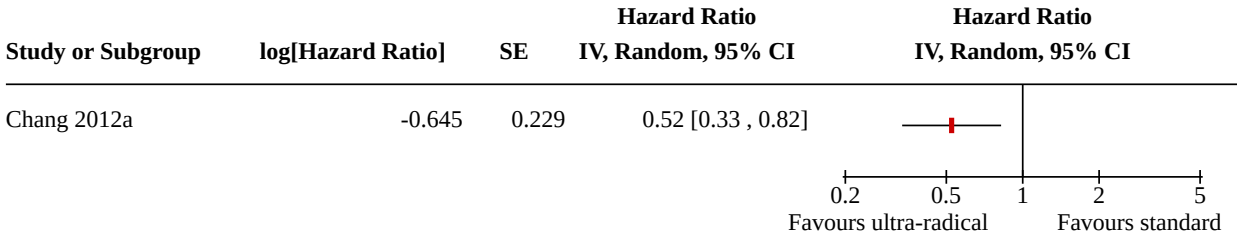
Analysis 1.2. Comparison 1: Ultra-radical versus standard surgery (upfront surgery), Outcome 2: Survival: women with carcinomatosis (upfront surgery)



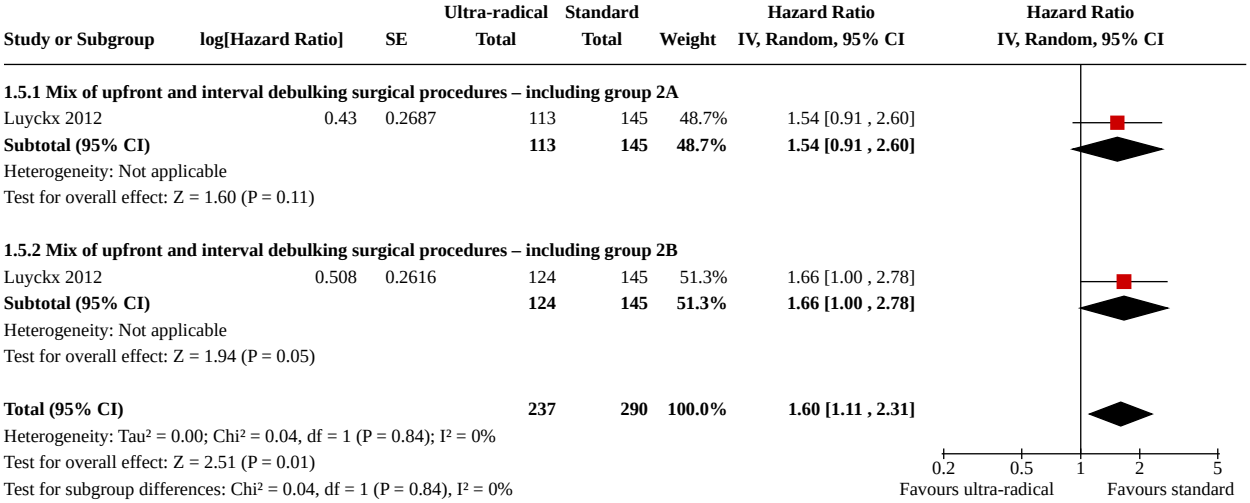
Analysis 1.3. Comparison 1: Ultra-radical versus standard surgery (upfront surgery), Outcome 3: Progression-free survival



Analysis 1.4. Comparison 1: Ultra-radical versus standard surgery (upfront surgery), Outcome 4: Progression-free survival: women with carcinomatosis (upfront surgery)



Analysis 1.5. Comparison 1: Ultra-radical versus standard surgery (upfront surgery), Outcome 5: Disease-free survival



ADDITIONAL TABLES

Table 1. Summary of Risk Of Bias In Non-randomised Studies of Interventions (ROBINS-I)

Author	Confounding	Selection bias	Classification of interventions	Deviation	Missing data	Measuring outcomes	Reporting bias
Aletti 2006a	Critical	Low	Low	Unclear	Moderate/high	Critical	Critical
Chang 2012a	Critical	Low	Low	Unclear	Moderate/high	Critical	Unclear
Luyckx 2012	Critical	Low	Low	Unclear	Moderate/high	Critical	Unclear

Risk of bias in included non-randomised studies was assessed using the ROBINS-I tool as outlined in Appendix 4(Sterne 2016).

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor Ovarian Neoplasms explode all trees
#2 ovar* near/5 (cancer* or neoplas* or carcinom* or malignan* or tumor* or tumour*)
#3 (#1 OR #2)
#4 MeSH descriptor Surgical Procedures, Operative explode all trees
#5 surg*
#6 Any MeSH descriptor with qualifier: SU
#7 (#4 OR #5 OR #6)
#8 debulk*
#9 cytoreduc*
#10 ultradical or ultra-radical or ultra radical
#11 MeSH descriptor Omentum explode all trees
#12 omentum
#13 bowel
#14 abdom*
#15 MeSH descriptor Spleen explode all trees
#16 spleen
#17 MeSH descriptor Liver explode all trees
#18 liver
#19 MeSH descriptor Diaphragm explode all trees
#20 diaphragm*
#21 MeSH descriptor Lymph Nodes explode all trees
#22 lymph next node*
#23 MeSH descriptor Peritoneum explode all trees
#24 peritone*
#25 MeSH descriptor Urinary Tract explode all trees
#26 urinary next tract
#27 (#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR 23 OR #24 OR #25 OR #26)
#28 (#7 AND #27)
#29 MeSH descriptor Splenectomy explode all trees
#30 splenectomy
#31 MeSH descriptor Hysterectomy explode all trees
#32 abdom* near/5 hysterectomy
#33 abdominohysterectomy
#34 MeSH descriptor Lymph Node Excision explode all trees
#35 lymph next node next excision
#36 bilateral next salpingo next oophorectomy
#37 omentectomy
#38 MeSH descriptor Surgical Stomas explode all trees
#39 stoma
#40 (#29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39)
#41 (#28 OR #40)
#42 (#3 AND #41)

Appendix 2. MEDLINE search strategy

1. exp Ovarian Neoplasms/
2. (ovar* adj5 (cancer* or neoplas* or carcinom* or malignan* or tumor* or tumour*)).mp.
3. 1 or 2
4. exp Surgical Procedures, Operative/
5. surg*.mp.
6. surgery.fs.
7. 4 or 5 or 6
8. debulk*.mp.
9. cytoreduc*.mp.
10. (ultraradical or ultra-radical or ultra radical).mp.
11. exp Omentum/

12.omentum.mp.
13.bowel.mp.
14.abdom*.mp.
15.exp Spleen/
16.spleen.mp.
17.exp Liver/
18.liver.mp.
19.exp Diaphragm/
20.diaphragm*.mp.
21.exp Lymph Nodes/
22.(lymph adj node*).mp.
23.exp Peritoneum/
24.peritone*.mp.
25.exp Urinary Tract/
26.(urinary adj tract).mp.
27.8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
28.7 and 27
29.exp Splenectomy/
30.splenectomy.mp.
31.exp Hysterectomy/
32.(abdom* adj5 hysterectomy).mp.
33.abdominohysterectomy.mp.
34.exp Lymph Node Excision/
35.(lymph adj node adj excision).mp.
36.(bilateral adj salpingo adj oophorectomy).mp.
37.omentectomy.mp.
38.exp Surgical Stomas/
39.stoma.mp.
40.29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39
41.28 or 40
42.3 and 41
43."randomized controlled trial".pt.
44."controlled clinical trial".pt.
45.randomized.ab.
46.randomly.ab.
47.trial.ab.
48.groups.ab.
49.exp Cohort Studies/
50.cohort*.mp.
51.(case adj series).mp.
52.43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51
53.42 and 52
54.Animals/
55.Humans/
56.54 not (54 and 55)
57.53 not 56

key: mp = title, original title, abstract, name of substance word, subject heading word

Appendix 3. Embase search strategy

1. exp Ovary Tumor/
2. (ovar* adj5 (cancer* or neoplas* or carcinom* or malignan* or tumor* or tumour*)).mp.
3. 1 or 2

4. exp Surgery/
5. surg*.mp.
6. su.fs.
7. 4 or 5 or 6
8. debulk*.mp.
9. cytoreduc*.mp.
10. (ultraradical or ultra-radical or ultra radical).mp.
11. exp Omentum/
12. omentum.mp.
13. bowel.mp.
14. abdom*.mp.
15. exp Spleen/
16. spleen.mp.
17. exp Liver/
18. liver.mp.
19. exp Diaphragm/
20. diaphragm*.mp.
21. exp Lymph Node/
22. (lymph adj node).mp.
23. exp Peritoneum/
24. peritone*.mp.
25. exp Urinary Tract/
26. (urinary adj tract).mp.
27. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
28. 7 and 27
29. exp Splenectomy/
30. splenectomy.mp.
31. exp Hysterectomy/
32. (abdom* adj5 hysterectomy).mp.
33. abdominohysterectomy.mp.
34. exp Lymphadenectomy/
35. (lymph adj node adj excision).mp.
36. (bilateral adj salpingo adj oophorectomy).mp.
37. omentectomy.mp.
38. exp Stoma/
39. stoma.mp.
40. 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39
41. 28 or 40
42. 3 and 41
43. exp Controlled Clinical Trial/
44. randomized.ab.
45. randomly.ab.
46. trial.ab.
47. groups.ab.
48. exp Cohort Analysis/
49. cohort*.mp.
50. (case adj series).mp.
51. 50 or 49 or 46 or 45 or 43 or 44 or 48 or 47
52. 42 and 51
53. exp Animal/
54. Human/
55. 53 not (53 and 54)

56.52 not 55

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

ab=abstract

fs=floating subheading

Appendix 4. ROBIN-1 domains

Risk of bias in included non-randomised studies was assessed using the ROBINS-I tool (Sterne 2016).

1. **Bias due to confounding**
   a. Baseline confounding – when one or more preintervention prognostic factors predict the intervention received at start of follow-up.
   b. Time-varying confounding – when the intervention received can change over time.
   c. Residual confounding – when a confounding domain is measured with error.
   d. Unmeasured confounding – when confounding domain has not been measured or controlled in the analysis.
2. **Selection bias**
   a. Bias in selection of participants into the study.
3. **Classification of interventions**
   a. Differential misclassification – intervention status is related to subsequent outcome or to the risk of the outcome.
   b. Non-differential misclassification – unrelated to outcome.
4. **Deviation from intended interventions**
   a. Considerations for co-interventions.
   b. Considerations for fidelity of implementation of intended interventions.
   c. Considerations for adherence to intervention.
5. **Bias due to missing data**
   a. Differential missingness.
   b. Whether proportions of individuals in whom adverse effects may be prevalent have been excluded.
6. **Measurement of outcomes**
   a. Differential measurement error – measurement error related intervention status.
   b. Non-differential measurement error – unrelated to the intervention received.
7. **Reporting bias**
   a. Selective outcome reporting.
   b. Selective analysis reporting.
   c. Selection of a subgroup from a larger cohort.

WHAT'S NEW

Date	Event	Description
18 May 2022	New search has been performed	Updated to include two new studies
6 April 2022	New citation required but conclusions have not changed	Updated search on 10 November 2021

HISTORY

Protocol first published: Issue 2, 2009
Review first published: Issue 4, 2011

Date	Event	Description
1 August 2016	New search has been performed	Search updated, no new studies included

Date	Event	Description
17 June 2015	New search has been performed	Search updated; two new studies included
11 February 2015	Amended	Contact details updated.
26 February 2014	Amended	Contact details updated.
28 July 2011	Amended	Author contact details updated

CONTRIBUTIONS OF AUTHORS

KG and RN drafted the clinical and discussion sections of the review.

AB, SH and PK data extracted items for inclusion in the review.

AB and SH drafted the methodological, results and discussion sections of the review.

AB and SH performed the GRADE judgements with other co-authors acting as arbiters.

SH and AB are joint first authors on the review.

RN initiated the research concept and was the lead senior clinical author.

All authors agreed the final version.

DECLARATIONS OF INTEREST

SH: none known.

AB: none known.

PK: none known.

KG: performs surgery for advanced ovarian cancer surgery, but has no conflicts of interest to declare.

RN: performs surgery for advanced ovarian cancer surgery, but has no conflicts of interest to declare.

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- NIHR, UK

  NHS Cochrane Collaboration Programme Grant Scheme CPG-506

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We added the following study constraint in the Types of studies section, as it was apparent that selection bias would have been problematic.

We added disease-free survival as a secondary outcome.

"In order to minimise selection bias, we decided to include only studies that used statistical adjustment for baseline case mix (e.g. age, performance status, grade, etc.) using multivariate analyses."

We removed discussion of unadjusted results from the data synthesis, subgroup analysis, and investigation of heterogeneity and sensitivity analysis sections as we do not plan to use unadjusted results in future updates due to the risk of selection bias.

Three studies met the inclusion criteria for the review and did not report dichotomous or continuous outcomes. Should more studies be identified for updates of the review, we will use the following methods.

Data extraction and management

Data on outcomes will be extracted as below.

- For dichotomous outcomes (e.g. adverse events or deaths, if it was not possible to use a hazard ratio), we will extract the number of patients in each treatment arm who experienced the outcome of interest and the number of participants assessed at endpoint, in order to estimate a risk ratio (RR).
- For continuous outcomes (e.g. QoL measures), we will extract the final value and standard deviation of the outcome of interest and the number of participants assessed at endpoint in each treatment arm at the end of follow-up, in order to estimate the mean difference between treatment arms and its standard error.

Measures of treatment effect

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

- For dichotomous outcomes, we will use the risk ratio.
- For continuous outcomes, we will use the mean difference between treatment arms.

Data synthesis

If sufficient clinically similar studies are available, we will pool their results in a meta-analysis and use adjusted summary statistics.

- For any dichotomous outcomes, we will calculate the risk ratio for each study and then pool them.
- For continuous outcomes, we will pool the mean differences between the treatment arms at the end of follow-up if all trials measured the outcome on the same scale, otherwise we will pool standardised mean differences.

We will assess the risk of bias in included RCTs using the Cochrane RoB tool (Higgins 2019). This includes assessment of:

- sequence generation;
- allocation concealment;
- blinding (where assessment of blinding was restricted to blinding of outcome assessors, since it is generally not possible to blind participants and treatment providers to surgical interventions);
- incomplete outcome data; we coded a satisfactory level of loss to follow-up for each outcome as:
- yes, if less than 20% of participants were lost to follow-up and reasons for loss to follow-up were similar in both treatment arms;
- no, if more than 20% of participants were lost to follow-up or reasons for loss to follow-up differed between treatment groups;
- unclear if loss to follow-up was not reported;
- selective reporting of outcomes;
- other possible sources of bias.

However, we only identified three non-randomised studies, so it was more appropriate to use the ROBIN-I risk of bias tool (Sterne 2016), so this superseded the default tool used to assess risk of bias in trials (Higgins 2019).

Sensitivity analysis

We performed post hoc sensitivity analyses including only women with more extensive disease (with carcinomatosis) as there were a substantial proportion of women with this.

INDEX TERMS

Medical Subject Headings (MeSH)

*Carcinoma, Ovarian Epithelial [pathology] [surgery]; Controlled Clinical Trials as Topic; *Cytoreduction Surgical Procedures; Disease Progression; Observational Studies as Topic; *Ovarian Neoplasms [pathology] [surgery]; Treatment Outcome

MeSH check words

Female; Humans