Cochrane
Library

Cochrane Database of Systematic Reviews

Interventions for the treatment of borderline ovarian tumours (Review)

Faluyi O, Mackean M, Gourley C, Bryant A, Dickinson HO

Faluyi O, Mackean M, Gourley C, Bryant A, Dickinson HO.
Interventions for the treatment of borderline ovarian tumours.
Cochrane Database of Systematic Reviews 2010, Issue 9. Art. No.: CD007696.
DOI: [10.1002/14651858.CD007696.pub2](https://doi.org/10.1002/14651858.CD007696.pub2).

www.cochranelibrary.com

TABLE OF CONTENTS

ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
BACKGROUND	3
OBJECTIVES	3
METHODS	3
RESULTS	6
Figure 1.	9
Figure 2.	10
DISCUSSION	12
AUTHORS' CONCLUSIONS	14
ACKNOWLEDGEMENTS	14
REFERENCES	15
CHARACTERISTICS OF STUDIES	17
ADDITIONAL TABLES	26
APPENDICES	27
WHAT'S NEW	29
CONTRIBUTIONS OF AUTHORS	29
DECLARATIONS OF INTEREST	29
SOURCES OF SUPPORT	29
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	30
INDEX TERMS	32

[Intervention Review]

Interventions for the treatment of borderline ovarian tumours

Olusola Faluyi¹, Melanie Mackean¹, Charlie Gourley¹, Andrew Bryant², Heather O Dickinson²

¹Edinburgh Cancer Centre, Western General Hospital, Edinburgh, UK. ²Institute of Health & Society, Newcastle University, Newcastle upon Tyne, UK

Contact: Olusola Faluyi, Edinburgh Cancer Centre, Western General Hospital, Crewe Road, Edinburgh, Scotland, EH4 2XU, UK.
Sola.faluyi@luht.scot.nhs.uk, sesanfaluyi@yahoo.co.uk.

Editorial group: Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group.

Publication status and date: Edited (no change to conclusions), published in Issue 2, 2014.

Citation: Faluyi O, Mackean M, Gourley C, Bryant A, Dickinson HO. Interventions for the treatment of borderline ovarian tumours. *Cochrane Database of Systematic Reviews* 2010, Issue 9. Art. No.: CD007696. DOI: [10.1002/14651858.CD007696.pub2](https://doi.org/10.1002/14651858.CD007696.pub2).

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

The safety of conservative surgery and the benefit of additional interventions after surgery for borderline ovarian tumours are unknown.

Objectives

To evaluate the benefits and harm of different treatment modalities offered for borderline ovarian tumours.

Search methods

We searched the Cochrane Gynaecological Cancer Group Trials Register to 2009, Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2008, Issue 4), MEDLINE and EMBASE to 2009. We also searched registers of clinical trials, abstracts of scientific meetings, reference lists of included studies.

Selection criteria

Randomised controlled trials (RCTs) that compared different interventions in adult women diagnosed with borderline ovarian tumours of any histological variant.

Data collection and analysis

Two review authors independently abstracted data and assessed risk of bias.

Main results

We identified seven RCTs that enrolled 372 women. We could not pool results of trials as the treatment comparisons differed.

Six RCTs (n = 340) conducted over 15 years ago, evaluated adjuvant therapy (chemotherapy, pelvic external irradiation or intra-peritoneal radioactive isotope therapy) after radical surgery; over 87% of participants had Stage I tumours. Most participants were followed up for over 10 years. Overall and recurrence-free survival were similar between both arms of these trials, except that one trial (n = 66) showed a significantly lower survival (P = 0.03) in women who received chemotherapy (thio-TEPA). Adverse effects of treatment were incompletely reported and all six trials were at high risk of bias.

One further trial (n = 32) that recruited participants with bilateral serous tumours who were wishing fertility preservation, revealed a significantly increased chance of pregnancy (hazard ratio (HR) = 3.3, 95% CI 1.4 to 8.0) but non-significantly earlier disease recurrence (HR = 1.5, 95% CI 0.6 to 3.8) in the women who had ultra-conservative surgery (bilateral cystectomy) than in those who had conservative surgery (cystectomy and contralateral oophorectomy). This trial was at low risk of bias.

Quality of life (QoL) was not documented in any included trial. We did not find any trials that compared radical with conservative surgery or laparoscopy with laparotomy.

Authors' conclusions

We did not find evidence to support the use of any specific type of adjuvant therapy for borderline ovarian tumours. RCTs evaluating the benefit of adjuvant therapy with optimally dosed chemotherapy and newer targeted drugs are necessary, particularly for advanced borderline ovarian tumours. The low mortality from borderline ovarian tumours should make recurrence-free survival, time to recurrence and morbidity important end points in such trials.

Bilateral cystectomy may be offered to women with bilateral borderline ovarian tumours diagnosed intra-operatively who are wishing to preserve their fertility. Similarly, women who had RCTs comparing radical with conservative surgery and comparing laparoscopy with laparotomy are needed.

PLAIN LANGUAGE SUMMARY

Interventions for the treatment of borderline ovarian tumours

Women with borderline (low malignant potential) ovarian tumours do very well after surgery and recurrences may be cured by further surgery. The ideal form of initial surgical treatment for borderline ovarian tumours is controversial. Furthermore, it is not known if additional treatment after surgery reduces the risk of re-appearance of tumours or of death.

In this review, we found six trials which enrolled 340 patients who had undergone surgery for borderline ovarian tumours. These trials compared the number of deaths among women who had various forms of treatment or no additional treatment after surgery. In five of the trials, the women had tumours confined to the ovaries and most were followed up for over 10 years. Only one trial enrolled women with tumours that had spread beyond the ovary, and this trial followed patients up for less than three years, which is not long enough to detect any difference between groups receiving different treatments. None of the trials found any demonstrable benefit from any of the additional forms of treatment. However, all six trials were conducted over 15 years ago and since then platinum-based chemotherapy has become widely used to treat advanced ovarian cancer. However, only one of the trials in our review assessed this more modern type of chemotherapy. Further trials of platinum-based chemotherapy and of less toxic treatments are needed, looking at the benefit of reducing the anxiety and distress of further surgery and treatment for relapse.

One further trial, which recruited 32 women who had borderline ovarian tumours in both ovaries, compared conservative surgery (taking away the most diseased ovary and removing the tumour from the other ovary) with ultra-conservative surgery (removing the tumours without taking away either ovary). Nearly all the women who had ultra-conservative surgery became pregnant compared with half of those who had conservative surgery. Although about two thirds of the women in the trial developed similar tumours again, most women got pregnant before the disease recurred, all had their recurrences treated by further surgery, none developed invasive ovarian cancer nor died of their tumour. This small study suggests that ultra-conservative surgery by an experienced surgeon with careful follow up for recurrence may be recommended for women with bilateral borderline ovarian tumours who still intend to have children but, ideally, this approach should be evaluated in other independent trials. Despite rigorous searches, we did not find any trial directly comparing conservative surgery with radical surgery (surgery to remove all of the female reproductive organs) or comparing keyhole surgery (laparoscopy) with open surgery (laparotomy) for women with borderline ovarian tumours.

None of these trials looked at how the various treatments affected the quality of life (QoL) of the women.

BACKGROUND

Description of the condition

Ovarian tumours can be subclassified into benign (non-cancerous) tumours, malignant tumours (cancers) and borderline tumours (sometimes known as tumours of low malignant potential) (Chen 2002). Benign tumours are confined to the ovaries and can be completely cured by surgical removal of the tumour. On the other hand, malignant tumours (cancers) are usually detected at an advanced stage when they have metastasised, that is spread widely within the abdomen to invade adjacent or distant body organs (Jemal 2008; Vernooij 2008). Unfortunately, recurrences of malignant tumours are common despite optimal treatment, which includes extensive surgery to remove all visible tumour, chemotherapy and at times hormonal therapy or radiotherapy. The survival rate is only 33% within five years of diagnosis (Jemal 2008; Patridge 1996). Despite significant research into early detection of ovarian cancer by means of ultrasound scans with or without combinations of blood tests, there is as yet no validated test to screen women for ovarian cancer or borderline ovarian tumours (Bell 1998; Menon 2009).

The behaviour of borderline ovarian tumours is intermediate between that of benign and malignant tumours. Borderline tumours constitute approximately 15% to 20% of all ovarian tumours and have an age standardised incidence rate in white and black women in the United States of 2.50 and 1.55 cases per year per 100,000 women, respectively (Mink 2002). They tend to occur in younger women in the reproductive age group and are identified based on a distinct microscopic appearance with features of abnormal growth that are not as aggressive as for cancers (Prat 1999). Borderline ovarian tumours are often limited to the ovaries. However, they can spread beyond the ovaries to form non-invasive deposits within the abdomen but not as widely as for ovarian cancer (Hart 2005). Most cases of borderline ovarian tumour are cured surgically but deaths can result from recurrence within the abdomen, leading to a 5-year overall survival rate of 95% (Patridge 1996). This makes the prognosis for borderline ovarian tumours better than for ovarian cancer but worse than for benign ovarian tumours. The benefit of additional forms of therapy after surgery is not clear.

Description of the intervention

For women with borderline ovarian tumours, surgery to remove as much of the tumour as possible in order to reduce the risk of recurrence appears to be the most important aspect of treatment (Cadron 2007). In practice the extent of surgery, which is partly dependent on surgical expertise, varies widely, particularly for tumours detected at early stages. The most extensive forms of surgery involve removal of the ovaries, fallopian tubes, uterus, omentum (fatty tissue within the abdomen) and lymph nodes near the abdominal aorta; as for the treatment of advanced ovarian cancer (Wong 2007). In contrast, less extensive forms of surgery that may be limited to removal of the affected part of an ovary alone have the advantage of preserving fertility and delaying menopausal symptoms, which may be very important to the quality of life of patients in the reproductive age group (Morrice 2001). Most surgery involves open abdominal operations (laparotomy) but, for smaller tumours, keyhole surgery (laparoscopy) can be performed. Surgery by means of laparoscopy (laparoscopic surgery) increases the chances of subsequent pregnancy (Romagnolo 2006), probably

because fewer adhesions form within the abdomen. Recovery from laparoscopy is also quicker, which leads to a shorter hospital stay (Odegaard 2007). However, significant expertise is required for proper inspection of the abdomen during laparoscopy, so as not to miss co-existing invasive ovarian malignancies.

After surgery to remove all visible tumour, additional forms of treatment known as adjuvant therapy may be administered to try to reduce the risk of recurrence of borderline ovarian tumours. These include drugs which directly kill any residual tumour cells (chemotherapy), drugs which block reproductive hormonal stimuli to tumour growth (hormonal therapy) and radiation treatment (radiotherapy), which can also kill residual tumour cells (Silva 2006). Other more recently developed drugs with varying mechanisms of action against tumours may also have been tried, to reduce the risk of recurrence (experimental therapy).

Why it is important to do this review

While clear guidelines are often available for the management of ovarian cancer, less clear guidelines exist for the management of the rarer, less lethal and less researched borderline ovarian tumours (FIGO 2006). Consequently, our aim is to review the available evidence from studies on the effectiveness of treatment in improving survival and quality of life (QoL) in women with borderline ovarian tumours, which could assist in formulating guidelines for their management.

Specifically, it is vital to review previous studies to compare the risks of recurrence and survival for patients who have had different extents of surgery for borderline ovarian tumours of similar stages and co-morbidity. Furthermore, it is important to review previous studies that attempted to determine the benefits from additional treatments in the form of chemotherapy, hormonal therapy, radiotherapy or experimental therapy. It is possible that there has not been adequate research comparing the different forms of surgical treatment or evaluating the benefits of additional treatment after surgery. This review could reveal such gaps in knowledge and prompt further research on such issues in order to guide future patient management.

OBJECTIVES

To evaluate the benefits and adverse effects of different treatment modalities offered in current practice for the management of borderline ovarian tumours.

METHODS

Criteria for considering studies for this review

Types of studies

- Randomised controlled trials (RCTs)

Types of participants

Women of any age with borderline ovarian tumours of any histological variant, defined according to World Health Organization (WHO) histological diagnostic criteria (WHO 2003), were included. These criteria included ovarian epithelial hyperplasia, atypia, mitotic activity and detached cell clusters in the absence of destructive stromal invasion.

We excluded trials:

- that included women who did not have a clear histological diagnosis;
- that included women with tumours including an invasive component, unless findings for women with borderline ovarian tumours were reported separately;
- in which a second opinion on the pathological diagnosis was not sought.

Types of interventions

The following comparisons were considered.

1. Laparotomy versus laparoscopic surgical approaches.
2. Radical (total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy with or without lymphadenectomy) versus conservative surgical techniques (any form of surgery that was less than radical).
3. Adjuvant chemotherapy versus control.
4. Adjuvant hormonal therapy versus control.
5. Adjuvant radiotherapy versus control.
6. Adjuvant experimental therapy versus control. Any form of intervention for borderline ovarian cancer beyond surgery, chemotherapy, radiotherapy and hormonal therapy was to be classed as experimental therapy.

Control groups were restricted to those that received a treatment regimen which was similar in all respects to that received by the intervention group except that it did not include the intervention of interest. Control groups that received only surveillance after surgery were included.

Additionally, we considered any direct comparison between any of: adjuvant chemotherapy, adjuvant hormonal agents, adjuvant radiotherapy and experimental therapies.

Types of outcome measures

Primary outcomes

Overall survival: survival until death from all causes

Secondary outcomes

1. Recurrence-free survival
2. QoL: measured using a scale that had been validated through reporting of norms in a peer-reviewed publication
3. Fertility: proportion of women wishing to preserve fertility and who achieve pregnancy
4. Adverse events, classified according to (CTCAE 2006):
 - a. direct surgical morbidity (death within 30 days; injury to bladder, ureter, vascular, small intestine or colon; presence and complications of adhesions; intestinal obstruction; haemorrhage; local infection and sepsis)
 - b. surgically-related systemic morbidity (chest infection, febrile morbidity, thrombo-embolic events [deep vein thrombosis and pulmonary embolism], cardiac events [cardiac ischaemias and cardiac failure], stroke)
 - c. delayed discharge, unscheduled re-admission
 - d. chemotherapy toxicity
 - e. radiotherapy toxicity
 - f. hormonal treatment toxicity
 - g. others

Grades of toxicity relating to chemotherapy, radiotherapy and hormonal treatment were extracted and grouped as:

- a. haematological (leucopenia, anaemia, thrombocytopenia, neutropenia, haemorrhage)
- b. gastrointestinal (nausea, vomiting, anorexia, diarrhoea, liver toxicity, proctitis)
- c. genito-urinary
- d. skin (stomatitis, mucositis, alopecia, allergy)
- e. neurological (peripheral and central)
- f. pulmonary

Search methods for identification of studies

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

Electronic searches

See: [Cochrane Gynaecological Cancer Group](#) methods used in reviews. The following electronic databases were searched (1966 to January 2009).

- Cochrane Gynaecological Cancer Review Group Trial Register
- Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2008, Issue 4)
- MEDLINE to January 2009
- EMBASE to January 2009

The MEDLINE search strategy, based on terms related to the review topic, is presented in ([Appendix 1](#)). For databases other than MEDLINE, the search strategy was adapted accordingly and these are presented in ([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

Metaregister, Physicians Data Query, ongoing clinical trial databases (www.controlled-trials.com/rct, www.clinicaltrials.gov and www.cancer.gov/clinicaltrials) were searched. We also searched the Journal of Ovarian Research (<http://www.ovarianresearch.com/>), the World Journal of Surgical Oncology (<http://www.wjso.com>) and Gynaecologic Oncologists of Canada (<http://www.g-o-c.org>) for ongoing trials.

Handsearching

The citation lists of included studies and other relevant publications were checked through handsearching; experts in the field were contacted to identify further reports of trials. Reports of conferences were handsearched from the following sources:

- British Journal of Cancer;
- British Cancer Research Meeting;
- Annual Meeting of the International Gynecologic Cancer Society;
- Annual Meeting of the American Society of Gynecologic Oncologists;
- Annual Meeting of European Society of Medical Oncology (ESMO);

- Annual Meeting of the American Society of Clinical Oncology (ASCO);
- Annual Meetings of the European Society for Gynaecological Oncology (ESG).

Data collection and analysis

Selection of studies

All titles and abstracts retrieved by electronic searching were downloaded to the reference management database (Endnote). Duplicates were removed and the remaining references were independently examined by two review authors (OF, MM). Those studies which clearly did not meet the inclusion criteria were excluded and copies of the full text of potentially relevant references were obtained. The eligibility of retrieved papers was assessed independently by two review authors (OF, MM). Disagreements were resolved by discussion between the two review authors or by appeal to a third review author (CG, AB or HD), if necessary. Reasons for exclusion were documented.

Data extraction and management

For included studies, data were extracted as recommended in Chapter 7 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Cochrane Handbook 2008). This included data on the following.

- Author, year of publication (if published) and journal citation (including language).
- Country.
- Setting.
- Inclusion and exclusion criteria.
- Study design, methodology.
- Study population:
 - total number enrolled,
 - patient characteristics,
 - age,
 - infertility,
 - parity.
- Borderline ovarian tumour details at diagnosis:
 - FIGO stage,
 - histological cell type.

- Intervention and control details
 - Surgery details:
 - type of surgery,
 - type of surgeon (gynaec-oncologist, gynaecologist, general surgeon);
 - Chemotherapy details:
 - dose,
 - cycle length,
 - combination;
 - Radiotherapy details:
 - dose,
 - duration;
 - Hormonal therapy:
 - type,
 - duration,
 - combination;
 - Experimental therapy:
 - type,
 - duration,
 - combination.
- Risk of bias in study: see below.
- Duration of follow up.
- Outcomes, data on all primary and secondary outcomes that were reported were extracted as below for:
 - time to event (overall or recurrence-free survival) data, we extracted the log of the hazard ratio (log[HR]) and its standard error from trial reports; if these were not reported, we attempted to estimate them from other reported statistics using the methods of (Parmar 1998);
 - dichotomous outcomes (e.g. adverse events or deaths if it was not possible to use a HR), we extracted the number of patients in each treatment arm who experienced the outcome of interest and the number of patients assessed at the end point in order to estimate a risk ratio (RR).

Where possible, all data extracted were those relevant to an intention-to-treat analysis, in which participants were analysed in the groups to which they were assigned. The time points at which outcomes were collected and reported were noted.

Data were abstracted independently by two review authors (OF, MM) onto a data form specially designed for the review. Differences between review authors were resolved by discussion or by appeal to a third review author (CG, AB or HD), where necessary.

Assessment of risk of bias in included studies

The risk of bias in included RCTs was assessed using the following criteria.

Sequence generation

We coded the randomisation of participants to intervention groups as:

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

Allocation concealment

We coded the concealment of allocation sequence from treatment providers and participants as:

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

Blinding

We coded the blinding of outcome assessors as:

- Yes;
- No;
- Unclear.

Incomplete reporting of outcome data

We recorded the proportion of participants whose outcomes were not reported at the end of the study; we noted if loss to follow up was not reported.

We coded satisfactory level of loss to follow up as:

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

Selective reporting of outcomes

We noted whether reports of the study were free of the suggestion of selective outcome reporting:

- Yes, e.g. if all outcomes specified above and also pre-specified in the study were reported in the study;
- No;
- Unclear.

Other potential threats to validity

We noted whether the study was apparently free of other problems that could put it at a high risk of bias:

- Yes;
- No;
- Unclear.

Accurate classification of outcomes

We coded satisfactory diagnosis of disease recurrence as:

- Yes, if diagnostic criteria included histology;
- No, if diagnostic criteria did not include histology;
- Unclear, e.g. not reported.

The risk of bias tool was applied independently by two review authors (OF, MM) and differences resolved by discussion or by appeal to a third review author (CG, AB or HD). Results were summarised in both a risk of bias graph and a risk of bias summary. Results were interpreted in light of the findings with respect to risk of bias.

Measures of treatment effect

Where possible, we used the following measures of the effect of treatment:

- for time to event data, we used the HR to compare the risk of death or disease recurrence in the treatment group with that in the control group;
- for dichotomous outcomes, we used the RR to compare the risk of adverse events (including death) in the treatment group with that in the control group. However, we were unable to estimate finite confidence intervals for the RR if one or both treatment groups experienced no events, as in four trials ([Creasman 1982](#); [Palomba 2007](#); [Sutton 1991](#); [Trope 1993 \(Study 4\)](#)).

Dealing with missing data

We did not impute missing outcome data for any outcome.

Data synthesis

We were unable to pool the results of the included trials in meta-analyses as they all compared different interventions. Therefore, it was not relevant to assess heterogeneity between results of trials and we were unable to assess reporting biases using funnel plots or conduct any subgroup or sensitivity analyses.

RESULTS

Description of studies

Results of the search

The search strategy identified 1374 references in MEDLINE, 1398 in EMBASE, 28 in CENTRAL and 150 in the Cochrane Gynaecological Cancer Review Group Trial Register, yielding 2055 unique references. Screening of titles and abstracts identified eight references which were potentially eligible for the review. Screening of the full texts of these references excluded three for the reasons described in the table [Characteristics of excluded studies](#). One of these excluded references was a systematic review ([Swanton 2007](#)), which did not identify any further relevant trials. The remaining four references described seven RCTs which met our inclusion criteria and are described in the table [Characteristics of included studies](#). [Trope 1993 \(Study 1\)](#) was reported in two publications, by Trope et al in 1993 and Kolstad et al in 1977. We extracted data from the former as it had longer median follow up (12 years rather than five years). The search of the grey literature did not identify any additional relevant trials.

Included studies

The seven included trials ([Creasman 1982](#); [Palomba 2007](#); [Sutton 1991](#); [Trope 1993 \(Study 1\)](#); [Trope 1993 \(Study 2\)](#); [Trope 1993 \(Study 3\)](#); [Trope 1993 \(Study 4\)](#)) are described in detail in the table [Characteristics of included studies](#). They randomised a total of 372 participants, of whom 362 were assessed at the end of the trials.

All of the included trials, except that of [Palomba 2007](#), compared different forms of adjuvant therapy offered to women who had undergone radical surgery for borderline ovarian tumours. The trial of [Palomba 2007](#) compared different extents of conservative surgery for borderline ovarian tumours. We did not find any RCTs that compared conservative with radical surgery or laparotomy with laparoscopy.

Study design

Five of the seven included trials were open-label prospective RCTs on participants treated for borderline ovarian tumours ([Palomba 2007](#); [Trope 1993 \(Study 1\)](#); [Trope 1993 \(Study 2\)](#); [Trope 1993 \(Study 3\)](#); [Trope 1993 \(Study 4\)](#)). Two trials were designed to assess interventions for participants with Stage I ovarian cancer ([Creasman 1982](#)) or Stage III ovarian cancer ([Sutton 1991](#)) and participants with borderline ovarian tumours were identified retrospectively during central review of the histological samples.

Participant characteristics

Trials assessing adjuvant therapy

All participants in these trials were managed in tertiary centres, had a median age of 42 to 48 years at enrolment and had a histologically confirmed diagnosis of borderline ovarian tumour. Furthermore, in two trials ([Creasman 1982](#); [Sutton 1991](#)) all participants had the histological diagnosis reviewed by at least one other pathologist. In the trial of [Sutton 1991](#) 84% of borderline ovarian tumours were bilateral, but the proportion of bilateral tumours was not stated in the trials of [Creasman 1982](#) and [Trope 1993](#). There was a reasonably equal distribution between serous and mucinous tumours in the four trials by [Trope 1993](#), and in the 53% of participants for whom histological type was reported in [Creasman 1982](#). However, the trial of [Sutton 1991](#) had a preponderance of serous tumours while also excluding participants with Brenner's tumours (clear cell histology). For five of the trials ([Creasman 1982](#); [Trope 1993 \(Study 1\)](#); [Trope 1993 \(Study 2\)](#); [Trope 1993 \(Study 3\)](#); [Trope 1993 \(Study 4\)](#)) more than 96% of participants had Stage I tumours while the trial of [Sutton 1991](#) recruited women with Stage III tumours exclusively (which is one possible explanation for the preponderance of serous tumours in the latter study). Surgical management did not include omentectomy in the trial of [Creasman 1982](#), while details of the extent of surgery were not explicitly stated in the trials reported by [Trope 1993](#).

Trials assessing conservative surgery

The participants in the trial of [Palomba 2007](#) met stringent selection criteria including: having bilateral tumours, being younger than 35 years of age, wanting to get pregnant as soon as possible and not having factors suggestive of a possible endocrine, gynaecological or male partner contribution to infertility. More than 90% of the participants in this trial had Stage I tumours and more than 90% of the participants had tumours with serous histology.

Interventions compared

Trials assessing adjuvant treatment

The six trials on adjuvant therapy examined a range of interventions: chemotherapy (melphalan, thio-TEPA [triethylenethiophosphoramide], cis-platinum, the addition of doxorubicin to a regimen of cis-platinum and cyclophosphamide); intraperitoneal irradiation with gold (^{198}Au) or phosphorus (^{32}P); and external pelvic irradiation. We could not pool the results of the trials as the treatment comparisons differed (see summary in [Table 1](#)).

The trial of ([Creasman 1982](#)) had three treatment groups, whereas the other five trials had two groups.

Trial comparing conservative with ultra-conservative surgery

The trial of [Palomba 2007](#) compared outcomes following conservative surgery with those following ultra-conservative surgery. In women who received conservative surgery, the ovary that was mostly involved was removed and the tumour was removed from the other ovary (oophorectomy and contralateral cystectomy). In women who received ultra-conservative surgery, the tumour was removed from both ovaries but neither ovary was removed (bilateral cystectomy).

Primary outcome

All-cause mortality

All trials reported the number of deaths at the end of the trial: 1/55 (2%) in the trial of ([Creasman 1982](#)), 0/32 (0%) in the trial of ([Palomba 2007](#)), 1/32 (3%) in the trial of [Sutton 1991](#), 24/243 (10%) in the four combined trials of [Trope 1993](#). However, only 0/32 (0%), 1/55 (2%), 0/32 (0%) and 3/243 (1%) of deaths, respectively, were from borderline ovarian tumours, giving an overall death rate from borderline ovarian tumours of 4/362 (1%). Median follow up ranged from 2.6 years ([Sutton 1991](#)) to 12.3 years in the four trials of [Trope](#).

None of the trials reported HRs or RRs comparing outcomes in different arms. It was not possible to calculate such statistics in the trials of [Creasman 1982](#), [Palomba 2007](#), [Sutton 1991](#) and [Trope 1993 \(Study 4\)](#) because of the small numbers of deaths (zero or one) in each of these trials. Although studies 1 to 3 of [Trope 1993](#) reported more deaths and presented Kaplan-Meier survival plots, we were unable to calculate HRs using the methods of [Parmar 1998](#) as the survival plots did not present sufficient data to allow a precise estimate of the HR. We therefore calculated RRs for these trials, but these RRs could not allow for the differing duration of follow up of women in the trial.

Secondary outcomes

Disease recurrence

All trials except that of [Sutton 1991](#) reported disease recurrence for the cohort of enrolled patients: 1/55 (2%) in the trial of [Creasman 1982](#), 19/32 (59%) in [Palomba 2007](#) and 3/243 (1%) in the four combined trials of [Trope](#).

In the trial of [Creasman 1982](#), surveillance for tumour recurrence included six-monthly chest x-rays and pyelograms, with further imaging only as clinically indicated. Serological monitoring for tumour recurrence was not reported.

In the trial of [Palomba 2007](#), participants were followed up three-monthly for the first year, then six-monthly for at least four more years. At each appointment, serological parameters as well as a combination of transabdominal and transvaginal ultrasonography were used to monitor for tumour recurrence.

In the four trials reported by [Trope 1993](#), sequential staging investigations as surveillance for tumour recurrence were not reported. When performed, staging investigations comprised a chest X-ray and intravenous pyelography. Ultrasonography and abdominopelvic computed tomography (CT)-imaging were performed "only when clinically indicated". Furthermore, serological monitoring for tumour recurrence was not reported.

In the trial of [Sutton 1991](#), although radiological or serological surveillance for tumour recurrence was not reported, 14/32 (44%)

of participants in the trial underwent second-look surgery at the discretion of the managing surgeon.

[Palomba 2007](#) presented Kaplan-Meier survival plots and reported a HR (with 95% confidence interval (CI)) comparing treatment groups. Because of the very low number of recurrences (one or none in each treatment arm), it was not possible to calculate RRs or HRs for the other trials.

Quality of life (QoL)

None of these trials reported QoL on a validated scale.

Fertility

The trials for adjuvant therapy focused on patients who had radical surgery. Therefore, the pregnancy rate was only of relevance, and reported, in the trial of [Palomba 2007](#): 23/32 (72%) of participants became pregnant.

Adverse effects

The RCTs of [Trope 1993 \(Study 1\)](#), [Trope 1993 \(Study 2\)](#), [Trope 1993 \(Study 3\)](#), [Trope 1993 \(Study 4\)](#) and [Sutton 1991](#) provided incomplete reports on toxicity while [Creasman 1982](#) did not provide any data on toxicity (see [Table 1](#) and the table [Characteristics of included studies](#)).

Excluded studies

We excluded three references after obtaining the full text (see the table [Characteristics of excluded studies](#)). One reference ([Swanton 2007](#)) was a systematic review that yielded no further trials. We excluded the trial of [Vergote 1992](#) because it did not report outcomes for borderline ovarian tumours separately from ovarian cancer and that of [Young 1990](#) because it did not report on participants with borderline ovarian tumour by treatment arm.

Risk of bias in included studies

Only the trial by [Palomba 2007](#) was at low risk of bias. This trial satisfied five of the seven criteria that were used to assess risk of bias. For this trial, blinding of the outcome assessor was not reported and there was insufficient information to judge whether any additional risk factor for bias existed. The remaining trials were at high risk of bias as they satisfied no more than two of the criteria. All of the trials assessed an adequate proportion of their recruited women as more than 90% of those enrolled were assessed at the end point ([Figure 1](#), [Figure 2](#)). Furthermore, more than 90% of participants received the form of treatment to which they were allocated.

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete outcome data addressed?	Free of selective reporting?	Free of other bias?	Adequate classification of outcomes
Creasman 1982	?	?	?	+	?	?	+
Palomba 2007	+	+	?	+	+	?	+
Sutton 1991	?	?	?	+	?	?	?
Trope 1993 (Study 1)	?	?	?	+	?	?	?
Trope 1993 (Study 2)	?	?	?	+	?	?	?
Trope 1993 (Study 3)	?	?	?	+	?	?	?
Trope 1993 (Study 4)	?	?	?	+	?	?	?

Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

Because of the nature of the interventions compared (for example chemotherapy versus no further treatment), it was virtually impossible to blind participants or their carers to the treatment received and so we assessed only blinding of personnel who assessed the outcome of treatment. However, the lack of blinding of participants and carers may have resulted in bias.

Effects of interventions

See [Table 1](#) for summary of outcomes with the different comparisons of interventions in the included trials.

For dichotomous outcomes, we were unable to estimate finite confidence intervals for the RR if one or both treatment groups experienced no events, as in four trials ([Creasman 1982](#); [Palomba 2007](#); [Sutton 1991](#); [Trope 1993 \(Study 4\)](#)).

All-cause mortality

Ultra-conservative versus conservative surgery

The trial of [Palomba 2007](#) reported no deaths in either of the treatment groups.

Chemotherapy versus no further treatment

Melphalan versus no further treatment

The trial of [Creasman 1982](#) reported no deaths in either the chemotherapy or 'no further treatment' groups.

Thio-TEPA versus no further treatment

The trial of [Trope 1993 \(Study 3\)](#) reported significantly lower survival in women who received thio-TEPA than in those who received no further treatment. Although we estimated the risk ratio for survival to be non-significant ($P = 0.06$), the authors reported a log-rank P value of 0.03. As the log rank test uses the survival times for each woman, which were not available to us, the authors'

estimated P value is likely to be more accurate than ours. We estimated the RR comparing the risk of death in the thio-TEPA and control groups to be 4.33, 95%CI 0.94 to 19.88.

Thio-TEPA versus no further treatment (both groups received intraperitoneal radioactive isotopes following surgery)

The trial of [Trope 1993 \(Study 2\)](#) did not find any statistically significant difference in risk of death between women who received Thio-TEPA and those who received no further treatment (RR 0.95, 95% CI 0.76 to 1.20).

Radiotherapy versus no further treatment

The trial of [Creasman 1982](#) did not find any statistically significant difference in risk of death between women who received pelvic external irradiation after surgery and those who received no further treatment. The trial reported only one death, which was of a woman who received radiotherapy.

Radiotherapy versus chemotherapy

Pelvic external irradiation versus melphalan

The trial of [Creasman 1982](#) did not find any statistically significant difference in risk of death between women who received radiotherapy after surgery and those who received chemotherapy. The trial reported only one death, which was of a woman who received radiotherapy.

Intraperitoneal radioactive phosphorus (^{32}P) versus cis-platinum

The trial of [Trope 1993 \(Study 4\)](#) did not find any statistically significant difference in risk of death with overall survival being similar between women who received intraperitoneal radioactive phosphorus following surgery and those who received cis-platinum. The trial reported only two deaths, which were in woman who received cis-platinum.

Head-to-head comparison of different radiotherapy regimens

Pelvic external irradiation plus intraperitoneal radioactive gold (^{198}Au) versus pelvic external irradiation

The trial of [Trope 1993 \(Study 1\)](#) did not find any statistically significant difference in risk of death between women who received pelvic external irradiation and intraperitoneal radioactive gold after surgery and those who received pelvic external irradiation alone (comparing risk of death in intraperitoneal gold and control arms: RR 0.97, 95% CI 0.26 to 3.59).

Head-to-head comparison of different chemotherapy regimens

Cis-platinum, cyclophosphamide and doxorubicin versus cis-platinum and cyclophosphamide alone

The trial of [Sutton 1991](#) did not find any statistically significant difference in risk of death between women who received cis-platinum and cyclophosphamide in combination with doxorubicin following surgery and those who received cis-platinum and cyclophosphamide alone. The trial reported only one death, which was of a woman in the control group.

Disease recurrence

Ultra-conservative versus conservative surgery

Although the trial of [Palomba 2007](#) did not find any statistically significant difference in risk of disease recurrence between women who received ultra-conservative surgery and those who received conservative surgery (HR comparing risk of recurrence in women who received ultra-conservative and conservative surgery: 1.52, 95% CI 0.61 to 3.77), it reported a significantly shorter median time to recurrence in the ultra-conservative arm than in the conservative arm (16 months versus 48 months). This inconsistency appears to be due to two factors. Firstly, the authors used the Mann-Whitney test to compare time to recurrence in the two arms, which was not valid as this test considered only the 60% of women who had disease recurrence and ignored the other women. Secondly, the Kaplan-Meier plots suggest that the proportional hazards assumption, on which the estimates of the HR were based, may not have been valid. The percentage of women who had disease recurrence was similar in both arms of the trial (60%), although those in the ultra-conservative arm had disease recurrence earlier.

Chemotherapy versus no further treatment

Melphalan versus no further treatment

The trial of [Creasman 1982](#) reported no disease recurrences in either treatment group.

Thio-TEPA versus no further treatment

The trial of [Trope 1993 \(Study 3\)](#) did not find any statistically significant difference in risk of disease recurrence between women who received thio-TEPA following surgery and those who received no further treatment. The trial reported only one recurrence, which was of a woman who received thio-TEPA.

Thio-TEPA versus no further treatment (both groups received intraperitoneal radioactive isotopes following surgery)

The trial of [Trope 1993 \(Study 2\)](#) reported no disease recurrences in either the thio-TEPA or 'no further treatment' group.

Radiotherapy versus no further treatment

The trial of [Creasman 1982](#) did not find any statistically significant difference in risk of disease recurrence between women who received pelvic external irradiation and those who received no further treatment. The trial reported only one disease recurrence, which was in a woman who received radiotherapy.

Radiotherapy versus chemotherapy

Pelvic external irradiation versus melphalan

The trial of [Creasman 1982](#) did not find any statistically significant difference in risk of disease recurrence between women who received radiotherapy and those who received chemotherapy. The trial reported only one disease recurrence, which was in a woman who received radiotherapy.

Intraperitoneal radioactive phosphorus (^{32}P) versus cis-platinum

The trial of [Trope 1993 \(Study 4\)](#) did not find any statistically significant difference in risk of disease recurrence between women who received intraperitoneal radioactive phosphorus following surgery and those who received cis-platinum. The trial reported only one disease recurrence, which was of a woman who received cis-platinum.

Head-to-head comparison of different radiotherapy regimens

Pelvic external irradiation plus intraperitoneal radioactive gold (^{198}Au) versus pelvic external irradiation

The trial of [Trope 1993 \(Study 1\)](#) did not find any statistically significant difference in risk of disease recurrence between women who received pelvic external irradiation and intraperitoneal radioactive gold after surgery and those who received pelvic external irradiation alone. The trial reported only one disease recurrence, which was of a woman who received pelvic external irradiation and intraperitoneal radioactive gold.

Time to pregnancy post-surgery

Ultra-conservative versus conservative surgery

The trial of [Palomba 2007](#) found that ultra-conservative surgery was associated with a statistically significant increase in the chance of pregnancy compared to conservative surgery (HR 3.29, 95% CI 1.36 to 7.96). Only one woman out of 15 (7%) in the ultra-conservative surgery group failed to become pregnant compared to eight out of 17 (47%) in the control group. The median time to first pregnancy was five months for the ultra-conservative surgery arm, whereas that for the conservative surgery arm was variously reported as 8 months (in Table V) and 14 months (in the text). All of these recurrences were treated by surgery and none involved progression to invasive ovarian carcinoma.

Adverse events

Severe septic neutropenia: thio-TEPA versus no further treatment

The trial of [Trope 1993 \(Study 3\)](#) did not find any statistically significant difference in the risk of severe septic neutropenia between women who received thio-TEPA following surgery and those who received no further treatment. The trial reported only one case of severe septic neutropenia, which was in a woman who received thio-TEPA.

Grade IV granulocyte toxicity: cis-platinum, cyclophosphamide and doxorubicin versus cis-platinum and cyclophosphamide alone

The trial of [Sutton 1991](#) did not find any statistically significant difference in the risk of grade IV granulocyte toxicity between women who received the chemotherapy combination with doxorubicin following surgery and those who received cis-platinum and cyclophosphamide alone (RR 1.67, 95% CI 0.11 to 24.26).

Small intestinal toxicity: thio-TEPA versus no further treatment (both groups received intraperitoneal radioactive isotopes following surgery)

The trial of [Trope 1993 \(Study 2\)](#) did not find any statistically significant difference in the risk of small intestinal toxicity between women who received thio-TEPA and those who received no further treatment. The trial reported only two cases of small intestinal toxicity, which were both in women who received thio-TEPA.

Bone marrow toxicity: thio-TEPA versus no further treatment

The trial of [Trope 1993 \(Study 3\)](#) did not find any statistically significant difference in the risk of bone marrow toxicity between women who received thio-TEPA following surgery and those who received no further treatment. The trial reported only one case of bone marrow toxicity, which was in a woman who received thio-TEPA.

Intestinal obstruction: intraperitoneal radioactive phosphorus (³²P) versus cis-platinum

The trial of [Trope 1993 \(Study 4\)](#) did not find any statistically significant difference in the risk of intestinal obstruction between women who received intraperitoneal radioactive phosphorus and those who received cis-platinum. The trial reported four cases of intestinal obstruction, which were all in women who received intraperitoneal radioactive phosphorus.

Grade 1 neurotoxicity: intraperitoneal radioactive phosphorus (³²P) versus cis-platinum

The trial of [Trope 1993 \(Study 4\)](#) did not find any statistically significant difference in the risk of grade 1 neurotoxicity between women who received intraperitoneal radioactive phosphorus following surgery and those who received cis-platinum. The trial reported only one case of grade 1 neurotoxicity, which was in a woman who received cis-platinum.

Intraoperative blood loss: ultra-conservative versus conservative surgery

The trial of [Palomba 2007](#) did not find any statistically significant difference in intraoperative blood loss between women who received ultra-conservative and conservative surgery.

DISCUSSION

Summary of main results

We identified six RCTs that evaluated adjuvant chemotherapy or radiotherapy, or both, following radical surgery for borderline ovarian tumour. Overall survival was similar between both arms of all these trials. Three of the trials had a median follow-up period of more than 12 years. However, recurrence rates and adverse effects of treatment were incompletely documented. We did not

find any trials which compared radical with conservative surgery or laparoscopy with laparotomy.

One additional RCT recruited participants with bilateral serous borderline ovarian tumours ([Palomba 2007](#)) who wished to preserve fertility. While reporting no deaths over an eight-year follow up, the trial revealed a significantly increased chance of pregnancy but non-significantly earlier disease recurrence in women who had ultra-conservative surgery compared with those who had conservative surgery.

Overall completeness and applicability of evidence

The predominance of serous (52%) and mucinous (38%) histological variants in the trials reviewed here is consistent with the observations of a large case series ([Bostwick 1986](#)). Furthermore, as in the trials of ([Sutton 1991](#)) and ([Palomba 2007](#)), bilateral borderline ovarian tumours have been reported to be predominantly of the serous histological variant ([Nakashima 1990](#)). Even though more than 95% of the participants in five of the six adjuvant therapy trials reviewed here had Stage I tumours ([Creasman 1982](#); [Trope 1993](#)), some large case series from other centres suggest that up to 40% of patients with borderline ovarian tumour may have Stage III tumours ([Chambers 1988](#); [Leake 1992](#)). This suggests that advanced tumours may have been under-represented in the trials of adjuvant therapy reviewed here.

Since the conclusion of the trials reviewed here, the efficacy and survival benefit of platinum-containing regimens (with or without taxanes) in the management of advanced ovarian cancer have become established ([ICON 2002](#)). However, early stage ovarian cancer trials recruiting about 500 participants have shown that the benefit of platinum-containing chemotherapy regimens is confined to those at risk of residual peritoneal disease after surgical debulking ([ICON 1 2003](#); [Trimbos 2003](#)). Therefore, enrolment of participants with Stage I tumours in underpowered trials for a good prognosis tumour may explain the lack of a survival benefit of adjuvant therapy in the trials reviewed here. Unfortunately, we could not pool results of included trials as the treatment comparisons differed. Only one of the included trials evaluated the benefit of platinum-based chemotherapy ([Trope 1993 \(Study 4\)](#)) in comparison with intraperitoneal radioactive isotope. This trial administered cisplatin once every three weeks at a dose of 50 mg m⁻², which is between 50% and 66% of the dose that has been shown to be beneficial in trials of adjuvant therapy for ovarian cancer ([Muggia 2000](#); [Trimbos 2003](#)). Despite our rigorous searches, we did not find any trials of carboplatin with or without a taxane compared to no chemotherapy for borderline ovarian tumours. In a disease where overall survival is good and chemotherapy is associated with significant adverse effects, other therapies should also be considered. Hormonal therapy with inhibitors of estrogen synthesis, such as aromatase inhibitors, has been validated for estrogen-receptor positive platinum-resistant ovarian cancer ([Smyth 2007](#)). While more than 90% of serous and mucinous borderline ovarian tumours are known to express estrogen receptors ([Abu-Jawdeh 1996](#)), we found no trials evaluating inhibitors of estrogen synthesis for borderline ovarian tumours. Furthermore, some experimental agents such as histone deacetylase (HDAC) inhibitors ([Mackay 2008](#)) have also been reported to show promising activity against borderline ovarian tumours in Phase I studies. Therefore, evidence on the benefit of recently developed hormonal, chemotherapeutic agents and optimally dosed platinum-based chemotherapy as adjuvant

therapy for borderline ovarian tumours is lacking. The intestinal toxicity after abdominal radiotherapy and radio-isotope therapy, which has precluded their utilisation for ovarian cancer (Firat 2003), would discourage their further evaluation for borderline ovarian tumours.

A large case series suggested a higher recurrence rate of 54% and poorer prognosis for patients with Stage III serous borderline ovarian tumours, compared to a 6% recurrence rate for Stage I tumours (Leake 1992). Despite their small numbers, a 60% recurrence rate in 15 participants who had second-look laparotomies in the only RCT on Stage III serous borderline ovarian tumours (Sutton 1991) is consistent with that finding. In the trial of (Palomba 2007), in which more than 90% of the participants had serous tumours, the recurrence rate over eight years was also about 60% for participants who had laparoscopic conservative or ultra-conservative surgery for bilateral early stage borderline ovarian tumours and who could therefore have been at high risk of residual disease. Taken together, these trials suggest a high rate of recurrence due to residual disease from serous tumours, either because the tumours were at an advanced stage at diagnosis or because a conservative surgical technique was used, possibly with inadequate staging. Nevertheless, in the (Palomba 2007) trial, despite recurrence after conservative surgical management all patients remained alive after salvage surgery and a median follow up of 81 months. Borderline ovarian tumours are known to have a low disease-specific mortality; a previous case series with over 25-year follow up suggested that 64% of recurrent cases were surgically curable (Crispens 2002). Therefore, recurrence-free survival and toxicity from therapy, which were poorly documented in the studies reviewed here, could be more clinically relevant end points for assessing the efficacy of adjuvant therapies.

For women with bilateral borderline ovarian tumours who still intend to become pregnant, the significantly higher fertility rate for participants who had ultra-conservative compared to conservative surgery, in the trial of (Palomba 2007), would justify this form of treatment. However, further conservative surgery will not always be a possibility in some women such as those who develop invasive implants or extensive disease recurrence. In a non-systematic review of 22 case series, recurrence with transformation to invasive disease was reported to occur in less than 1% of patients (Kurman 1993). Despite earlier recurrence, the median time to first pregnancy of five months, compared to a median time to recurrence of 16 months in those who had ultra-conservative surgery (Palomba 2007), suggests a reasonable chance of pregnancy before requiring further salvage surgery. Nevertheless, appropriate surgical expertise and assisted reproductive techniques as utilised in the Palomba trial may be necessary to achieve similar pregnancy rates out with the context of a clinical trial. In the Palomba trial, ~ 90% of patients did not achieve pregnancy spontaneously as a result of which they underwent controlled hormonal ovarian stimulation and intrauterine implantation. Furthermore, 70% eventually required *in vitro* fertilization (Palomba 2010). In a previous case series of women managed conservatively for borderline ovarian tumours where ovarian stimulation techniques or *in vitro* fertilisation were applied in only ~10% of patients, only ~ 30% achieved conception (Fauvet 2005).

In contrast to the other trials reviewed here, surgery in the trial of (Palomba 2007) used a laparoscopic approach. Even though

more than 90% of tumours in that trial were reported as Stage I, a high recurrence rate of 60% was reported. It is impossible to tell if the higher recurrence rate was due to suboptimal staging through the laparoscopic approach, conservative surgery, bilaterality of tumours or the fact that serous tumours are more frequently associated with peritoneal implants. We found no trials comparing radical with conservative surgery.

Quality of the evidence

We reviewed six RCTs, assessing 340 participants, that evaluated adjuvant therapy for borderline ovarian tumours. More than 90% of participants received the treatment to which they were allocated, with loss to follow up being less than 20%. However, these trials were biased towards early stage tumours. They evaluated different interventions and no trial was adequately powered to detect differences in survival. Furthermore, adverse effects of treatment and the quality of life of participants were inadequately documented. Therefore, we cannot reach any definitive conclusions about the benefit of adjuvant therapy from these RCTs.

The RCT of (Palomba 2007) was the only trial at a low risk of bias. The only obvious risk of bias was because participants, carers and the clinical personnel who assessed outcomes were not being blinded to the type of treatment received. The authors estimated hazard ratios of time to recurrence and time to achieving the first pregnancy, correctly allowing for censoring. However, the study report contained inconsistencies in the results reported as, due to the use of inappropriate statistical tests, it was unclear whether the earlier disease recurrence in the arm that received ultra-conservative treatment was statistically significant; furthermore, the median time to pregnancy in the arm that received conservative treatment was variously reported as eight and 14 months.

Adverse effects such as intra-operative blood loss and length of hospital stay were also compared. While this trial demonstrated the benefits of an ultra-conservative surgical approach in women with bilateral serous tumours who hoped to conceive, its small size (n = 32) indicates that larger confirmatory studies are required.

Potential biases in the review process

A comprehensive search was performed, including a thorough search of the grey literature. All studies were sifted and data extracted by at least two review authors working independently. We restricted the included studies to RCTs as they provide the strongest level of evidence available. Hence we have attempted to reduce bias in the review process.

The greatest threat to the validity of the review process is likely to be publication bias, that is studies that did not find interventions to have been effective may not have been published. Furthermore, as all the RCTs of adjuvant therapy were concluded over 10 years ago, we were not able to obtain additional unpublished data relevant to the review.

Agreements and disagreements with other studies or reviews

We identified one other systematic review (Swanton 2007) on pregnancy outcomes after conservative surgery, which preceded publication of the (Palomba 2007) trial. The (Swanton 2007) review of surgical approach included 19 non-randomised studies in which

participants had either unilateral or bilateral tumours and looked at pregnancy and recurrence as outcomes. It reported an average pregnancy rate of 48%, which is slightly lower than that in the conservative arm of the (Palomba 2007) trial. It also reported a lower recurrence rate of 16% for patients who had conservative surgery, compared to 60% for the (Palomba 2007) trial. However, surgical approach differed while selection and follow-up criteria were less stringent than for the (Palomba 2007) trial. Some other non-systematic reviews including evidence from case series have concluded that there is a lack of evidence of benefit of adjuvant therapy for borderline ovarian tumours (Cadron 2007; Crispens 2003). However, while (Crispens 2003) emphasised the safety of conservative compared to radical surgery in selected patients, (Cadron 2007) concluded that radical surgery should remain the standard of care.

AUTHORS' CONCLUSIONS

Implications for practice

From the trials reviewed here, we did not find evidence to support the use of any specific treatment modality for borderline ovarian tumours. Furthermore, the high rate of tumour recurrence in the only trial in which patients had conservative surgery by laparoscopy would question the safety of this approach in women who have completed childbearing. However, patients with bilateral borderline ovarian tumours who are wishing to preserve fertility may be offered bilateral cystectomy by an experienced surgeon with an explanation of a significant risk of early recurrence within 16 months. Such patients need to be made aware that it is inadvisable to delay pregnancy as salvage radical surgery for recurrence may become necessary. Furthermore, long-term follow up with surveillance for recurrence for at least eight years is essential for patients who have undergone conservative surgery (Palomba 2007).

Implications for research

The observation of only four pre-planned RCTs, reported more than 15 years ago from a single centre, on adjuvant therapy for borderline ovarian tumours (Trope 1993 (Study 1)) suggests that the effectiveness of interventions for this tumour type is an understudied area. The rarity of this tumour type and its otherwise excellent prognosis may partly explain this. Nevertheless, given the suggestion of a higher recurrence rate for serous borderline ovarian

tumours of Stage III or above, it would appear that patients with advanced tumours should be the immediate focus for subsequent trials of adjuvant therapy. The excellent survival from Stage I tumours suggests that any trials on women with these tumours should use disease progression as a primary end point and should consider progression to invasive ovarian carcinoma and death as secondary endpoints. This would be a valid and clinically relevant early end point, provided it is precisely defined (Altman 1995). Furthermore, pre-planned analysis of the benefit of interventions for different histological variants, bilateral, micro-papillary and aneuploid tumours which may have a worse prognosis, should be incorporated. Optimally dosed platinum-based chemotherapy regimens and hormonal therapy with inhibitors of estrogen synthesis, in particular, merit further evaluation. Careful evaluation of any toxicity is essential in early stage disease where severe side effects may outweigh the benefits.

The decision on radical or conservative surgery for borderline ovarian tumour is often a choice dictated by women's wishes on preservation of fertility. However, conservative surgery could also improve the quality of life of pre-menopausal women who do not necessarily wish to preserve their fertility. Therefore, RCTs comparing outcomes after either type of surgery are probably warranted, at least in this subgroup, to quantify the level of extra risk of recurrence from conservative surgery. Furthermore, other RCTs comparing outcomes after laparoscopy and laparotomy will also be important. Stratification by tumour histology and stage, as well as radical or conservative surgical treatment, will probably be necessary in such trials.

In order to minimise the risk of bias, future studies should ensure satisfactory randomisation, concealment of the allocation sequence from participants and healthcare providers, blinding of outcome assessors to the treatment status of participants, adequate follow-up and histological diagnosis of disease recurrence. They should be reported according to the CONSORT guidelines and all outcomes specified in the trial protocol should be reported (CONSORT2010).

ACKNOWLEDGEMENTS

We thank Chris Williams for clinical and editorial advice, Jane Hayes for designing the search strategy and Gail Quinn and Clare Jess for their contribution to the editorial process. We also thank Alistair Williams for histopathological advice.

REFERENCES

References to studies included in this review

Creasman 1982 {published data only}

Creasman WT, Park R, Norris H, Disaia PJ, Morrow CP, Hreshchyshyn MM. Stage I borderline ovarian tumors. *Obstetrics and Gynecology* 1982;**59**(1):93-6.

Palomba 2007 {published data only}

Palomba S, Zupi E, Russo T, Falbo A, Del Negro S, Manguso F, et al. Comparison of two fertility-sparing approaches for bilateral borderline ovarian tumours: a randomized controlled study. *Human Reproduction* 2007;**22**(2):578-85.

Sutton 1991 {published data only}

Sutton GP, Bundy BN, Omura GA, Yordan EL, Beecham JB, Bonfiglio T. Stage III ovarian tumors of low malignant potential treated with cisplatin combination therapy (a Gynecologic Oncology Group study). *Gynecologic Oncology* 1991;**41**(3):230-3.

Trope 1993 (Study 1) {published data only}

Kolstad P, Davy M, Høeg K. Individualised treatment of ovarian cancer. *Journal of Obstetrics and Gynecology* 1977;**128**:617-25.

* Trope C, Kaern J, Vergote IB, Kristensen G, Abeler V. Are borderline tumors of the ovary overtreated both surgically and systemically? A review of four prospective randomized trials including 253 patients with borderline tumors. [Review] [27 refs]. *Gynecologic Oncology* 1993;**51**(2):236-43.

Trope 1993 (Study 2) {published data only}

Trope C, Kaern J, Vergote IB, Kristensen G, Abeler V. Are borderline tumors of the ovary overtreated both surgically and systemically? A review of four prospective randomized trials including 253 patients with borderline tumors. [Review] [27 refs]. *Gynecologic Oncology* 1993;**51**(2):236-43.

Trope 1993 (Study 3) {published data only}

Trope C, Kaern J, Vergote IB, Kristensen G, Abeler V. Are borderline tumors of the ovary overtreated both surgically and systemically? A review of four prospective randomized trials including 253 patients with borderline tumors. [Review] [27 refs]. *Gynecologic Oncology* 1993;**51**(2):236-43.

Trope 1993 (Study 4) {published data only}

Trope C, Kaern J, Vergote IB, Kristensen G, Abeler V. Are borderline tumors of the ovary overtreated both surgically and systemically? A review of four prospective randomized trials including 253 patients with borderline tumors. [Review] [27 refs]. *Gynecologic Oncology* 1993;**51**(2):236-43.

References to studies excluded from this review

Swanton 2007 {published data only}

Swanton A, Bankhead CR, Kehoe S. Pregnancy rates after conservative treatment for borderline ovarian tumours: a systematic review. [Review] [36 refs]. *European Journal of Obstetrics, Gynecology, and Reproductive Biology* 2007;**135**(1):3-7.

Vergote 1992 {published data only}

Vergote IB, Vergote De Vos LN, Abeler VM, Aas M, Lindegaard MW, et al. Randomized trial comparing cisplatin with radioactive phosphorus or whole-abdomen irradiation as adjuvant treatment of ovarian cancer. *Cancer* 1992; Vol. 69, issue 3:741-9.

Young 1990 {published data only}

Young RC, Walton LA, Ellenberg SS, Homesley HD, Wilbanks GD, Decker DG, et al. Adjuvant therapy in stage I and stage II epithelial ovarian cancer. Results of two prospective randomized trials. *The New England Journal of Medicine* 1990;**322**(15):1021-7.

Additional references

Abu-Jawdeh 1996

Abu-Jawdeh, Jacobs TW, Niloff J, Cannistra SA. Estrogen receptor expression is a common feature of ovarian borderline tumors. *Gynecologic Oncology* 1996;**60**(2):301-7.

Altman 1995

Altman DG, De Stavola BL, Love SB, Stepniowska KA. Review of survival analyses published in cancer journals. *British Journal of Cancer* 1995;**72**:511-8.

Bell 1998

Bell R, Petticrew M, Sheldon T. The performance of screening tests for ovarian cancer: results of a systematic review. *British Journal of Obstetrics and Gynaecology* 1998;**105**(11):1136-47.

Bostwick 1986

Bostwick DG, Tazelaar HD, Ballon SC, Hendrickson MR, Kempson RL. Ovarian epithelial tumors of borderline malignancy. A clinical and pathologic study of 109 cases. *Cancer* 1986;**58**(9):2052-65.

Bucher 1997

Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *Journal of Clinical Epidemiology* 1997;**50**(6):683-91.

Cadron 2007

Cadron I, Leunen K, Van Gorp T, Amant F, Neven P, Vergote I. Management of borderline ovarian neoplasms. *Journal of Clinical Oncology* 2007;**25**(20):2928-37.

Chambers 1988

Chambers JT, Merino MJ, Kohorn EI, Schwartz PE. Borderline ovarian tumors. *American Journal of Obstetrics and Gynecology* 1988;**159**(5):1088-94.

Chen 2002

Chen VW, Ruiz B, Killeen JL, Coté TR, Wu XC, Correa CN. Pathology and classification of ovarian tumors. *Cancer* 2003;**97** Suppl 10:2631-42.

Cochrane Handbook 2008

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions 5.0.0 [updated February 2008]. The Cochrane Collaboration, 2008. Available from www.cochrane-handbook.org.

CONSORT2010

Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;**340**:C332.

Crispens 2002

Crispens MA, Bodurka D, Deavers M, Lu K, Silva EG, Gershenson DM. Response and survival in patients with progressive or recurrent serous ovarian tumours of low malignant potential. *Obstetrics and Gynecology* 2002;**99**(1):3-10.

Crispens 2003

Crispens MA. Borderline ovarian tumours: a review of the recent literature. *Current Opinion in Obstetrics & Gynecology* 2003;**15**(1):39-43.

CTCAE 2006

CTCAE. Common Terminology Criteria for Adverse Events. (<http://ctep.cancer.gov/forms/CTCAEv3.pdf>) 9th August 2006; Vol. v3.0 (CTCAE).

Deeks 2001

Deeks JJ, Altman DG, Bradburn MJ. Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. In: Egger M, Davey Smith G, Altman DG (editors). *Systematic Reviews in Health Care: Meta-Analysis in Context* (2nd edition). London: BMJ Publication Group, 2001.

DerSimonian 1986

DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clinical Trials* 1986;**7**:177-88.

Fauvet 2005

Fauvet R, Poncelet C, Boccara J, Descamps P, Fondrinier E, Darai E. Fertility after conservative treatment for borderline ovarian tumors: a French multicenter study. *Fertility and Sterility* 2005;**83**(2):284-90.

FIGO 2006

Benedet JL, Pecorelli S, Ngan HYS, Hacker NF (Editors). Staging Classifications and Clinical Practice Guidelines for Gynaecological Cancers. FIGO website (http://www.igo.org/docs/staging_booklet.pdf) last accessed 18.08.2008 2006.

Firat 2003

Firat S, Murray K, Erickson B. High-dose whole abdominal and pelvic irradiation for treatment of ovarian carcinoma: long-term toxicity and outcomes. *International Journal of Radiation Oncology, Biology, Physics* 2003;**57**(1):201-207.

Hart 2005

Hart WR. Borderline epithelial tumors of the ovary. *Modern Pathology* 2005;**18 Suppl 2**:33-50.

Higgins 2003

Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**:557-60.

ICON 1 2003

ICON 1. International collaborative ovarian neoplasm trial 1: A randomized trial of adjuvant chemotherapy in women with early-stage ovarian cancer. *Journal of the National Cancer Institute* 2003;**95**(2):125-32.

ICON 2002

ICON 2002. Paclitaxel plus carboplatin versus standard chemotherapy with either single-agent carboplatin or cyclophosphamide, doxorubicin and cisplatin in women with ovarian cancer: the ICON3 randomised trial. *Lancet* 2002;**360**:505-15.

Jemal 2008

Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, Thun MJ. Cancer Statistics. *CA: A Cancer Journal for Clinicians* 2008;**58**:71-96.

Kurman 1993

Kurman RJ, Trimble CL. The behavior of serous tumors of low malignant potential: are they ever malignant?. *International Journal of Gynecological Pathology* 1993;**12**(2):120-27.

Leake 1992

Leake JF, Currie JL, Rosenshein NB, Woodruff JD. Long-term follow-up of serous ovarian tumors of low malignant potential. *Gynecologic Oncology* 1992;**47**(2):150-8.

Mackay 2008

Mackay H, Hirte HW, Covens A, MacAlpine K, Wang L, Tsao MS, et al. A phase II trial of the histone deacetylase inhibitor belinostat (PXD 101) in patients with platinum resistant epithelial ovarian tumours and micro-papillary/borderline (LMP) ovarian tumours. A PMH phase 2 consortium trial. *Journal of Clinical Oncology* 2008;**26 Suppl**:5518.

Menon 2009

Menon U, Gentry-Maharaj A, Hallett R, Ryan A, Burnell M, Sharma A, et al. Sensitivity and specificity of multimodal and ultrasound screening for ovarian cancer, and stage distribution of detected cancers: results of the prevalence screen of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). *Lancet Oncology* 2009;**10**(4):327-40.

Mink 2002

Mink PJ, Sherman ME, Devesa SS. Incidence patterns of invasive and borderline ovarian tumors among white women and black women in the United States. *Cancer* 2002;**95**:2380-9.

Morrice 2001

Morrice P, Camatte S, El Hassan J, Pautier P, Duvillard P, Castaigne D. Clinical outcomes and fertility after conservative treatment of ovarian borderline tumors. *Fertility and Sterility* 2001;**75**(1):92-6.

Muggia 2000

Muggia FM, Braly PS, Brady MF, Sutton G, Niemann TH, Lentz SL, et al. Phase III randomized study of cisplatin versus paclitaxel

versus cisplatin and paclitaxel in patients with suboptimal stage III or IV ovarian cancer: A Gynecologic Oncology group study. *Journal of Clinical Oncology* 2000;**18**(1):106-15.

Nakashima 1990

Nakashima N, Nagasaka T, Oiwa N, Nara Y, Fukata S, Fukatsu T, et al. Ovarian epithelial tumors of borderline malignancy in Japan. *Gynecologic Oncology* 1990;**38**(1):90-8.

Odegaard 2007

Ødegaard E, Staff AC, Langebrekke A, Engh V, Onsrud M. Surgery of borderline tumors of the ovary: retrospective comparison of short-term outcome after laparoscopy or laparotomy. *Acta Obstetrica et Gynaecologica Scandinavica* 2007;**86**(5):620-6.

Palomba 2007

Palomba S, Zupi E, Russo T, Falbo A, Del Negro S, Manguso F, et al. Comparison of two fertility-sparing approaches for bilateral borderline ovarian tumours: a randomized controlled study. *Human Reproduction* 2007;**22**(2):578-85.

Palomba 2010

Palomba S, Falbo A, Del Negro S, Rocca M, Russo T, Cariati F, Annunziata G, et al. Ultra-conservative fertility-sparing strategy for bilateral borderline ovarian tumours. *Human Reproduction* 2010; Vol. epub.

Parmar 1998

Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Statistics in Medicine* 1998;**17**(24):2815-34.

Partridge 1996

Partridge EE, Phillips JL, Menck HR. The National Cancer Data Base report on ovarian cancer treatment in United States hospitals. *Cancer* 1996;**78**(10):2236-46.

Prat 1999

Prat J. Ovarian tumors of borderline malignancy (tumors of low malignant potential): a critical appraisal. *Advances in Anatomical Pathology* 1999;**6**(5):247-74.

Romagnolo 2006

Romagnolo C, Gadducci A, Sartori E, Zola P, Maggino T. Management of borderline ovarian tumors: Results of an Italian multicenter study. *Gynecologic Oncology* 2006;**101**:255-60.

Silva 2006

Silva EG, Gershenson DM, Malpica A, Deavers M. The recurrence and the overall survival rates of ovarian serous borderline neoplasms with noninvasive implants is time dependent. *American Journal of Surgical Pathology* 2006;**30**(11):1367-71.

Smyth 2007

Smyth JF, Gourley C, Walker G, Mackean MJ, Stevenson A, Williams AR, et al. Antiestrogen therapy is active in selected ovarian cancer cases: the use of letrozole in estrogen receptor-positive patients. *Clinical Cancer Research* 2007;**13**(12):3617-22.

Trimbos 2003

Trimbos JB, Parmar M, Vergote I, Guthrie D, Bolis G, Colombo N, et al. International Collaborative Ovarian Neoplasm 1, European Organisation for Research and Treatment of Cancer Collaborators - Adjuvant chemotherapy in ovarian neoplasm. Impact of adjuvant chemotherapy and surgical staging in early-stage ovarian carcinoma: European Organisation for Research and Treatment of cancer-Adjuvant chemotherapy in ovarian neoplasm trial. *Journal of the National Cancer Institute* 2003;**95**(2):113-25.

Vernooij 2008

Vernooij F, Heintz AP, Witteveen PO, van der Heiden-van der Loo M, Coebergh JW, van der Graaf Y. Specialized care and survival of ovarian cancer patients in The Netherlands: nationwide cohort study. *Journal of National Cancer Institute* 2008;**100**(6):399-406.

WHO 2003

Tavassoli FA, Develli P. World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Breast and Female Genital Organs. WHO Press. 5. Lyon: IARC, 2003:117-37.

Wong 2007

Wong HF, Low JJ, Chua Y, Busmanis I, Tay EH, Ho TH. Ovarian tumors of borderline malignancy: a review of 247 patients from 1991 to 2004. *International Journal of Gynecologic Cancer* 2007;**17**(2):342-9.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Creasman 1982

Methods	Multi-centre RCT in the USA.
Participants	55 women with Stage I borderline (low malignant potential) lesions of the ovary. The median age at entry to the study was 42 years (range:19-74). All 55 women were diagnosed with FIGO Stage I disease.

Creasman 1982 (Continued)

The tumour histological type was serous in 14 (25%) women, mucinous in 13 (24%), endometrioid in 2 (4%) but was not reported in the remaining 26 (47%) women.

Median parity was 2 with a range of 0 to 9.

Interventions	<ul style="list-style-type: none"> • Radiotherapy (n = 13): Women received 5000 rads to the pelvis over 5 to 6 weeks with a daily dose of 160 to 200 rads 5 times per week either from x-ray generators producing a peak photon energy of 1meV or more or from cobalt-60 radiators. The margins of the radiation portals were defined as follow; <ul style="list-style-type: none"> • 1) superior: the upper margin of the sacroiliac joint. • 2) inferior: the upper third of the obturator foramen. • 3) lateral: 1cm beyond the lateral margins of the bony pelvis at the widest plane of the pelvis. • Chemotherapy (n = 17): Received 0.2 mg/kg melphalan orally daily 5 days every 4 weeks for 18 months, if the white blood cell count was greater than 3000/mm³ and platelet count at least 150,000/mm³. • Observation (n = 25): Received no further treatment <p>If subsequent therapy was given, it commenced within 8 weeks of surgery.</p>
Outcomes	<ul style="list-style-type: none"> • Overall Survival and Disease-specific survival <p>The mean follow-up period was 3 years (Range: 1 to 7 years).</p>
Notes	<p>Some patients did not undergo omentectomy, therefore could have had undiagnosed stage III disease.</p> <p>There was only one reported death in the study.</p> <p>Although the study was prospective and randomised, the distribution of patients into the 3 treatments regimens was unequal. This was because they were initially randomised with patients who had Stage I invasive carcinoma lesions.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not reported, "The patients were randomized to the 3 post surgical categories: no further therapy (25 patients), pelvic radiation therapy (13 patients), and chemotherapy (17 patients)".
Allocation concealment?	Unclear risk	Not reported.
Blinding? All outcomes	Unclear risk	Not reported.
Incomplete outcome data addressed? All outcomes	Low risk	% analysed: 55/55 (100%).
Free of selective reporting?	Unclear risk	Insufficient information to permit judgement.
Free of other bias?	Unclear risk	Insufficient information to determine if further risk of bias exists.
Adequate classification of outcomes	Low risk	"An autopsy was performed ... based on post-mortem".

Palomba 2007

Methods	Single-centre RCT.
Participants	<p>Young women with bilateral borderline ovarian tumours who have the desire to conceive as soon as possible.</p> <p>The median age at study entry was 26.6 years (range: 20-35).</p> <p>FIGO Stage: I: 29 (91%) [IB 21 (66%); IC 8 (25%)]; II: 1 (3%); III: 1 (3%); IV: 1 (3%).</p> <p>Tumour grade: 1: 27 (84%); 2: 3 (9%); 3: 2 (7%).</p> <p>The tumour histological type was serous in 29 (91%) women and mucinous in 3 (9%) women.</p> <p>Median parity was 0 with a range of 0 to 1.</p>
Interventions	<p>All surgical procedures were performed by the same experienced laparoscopist following the same standardised procedure for each intervention. Peritoneal fluid was collected and processed for cytological examination in all cases.</p> <ul style="list-style-type: none"> • Ultra-conservative surgery (n = 15) <p>Bilateral cystectomy was performed.</p> <ul style="list-style-type: none"> • Conservative surgery (n = 17) <p>Oophorectomy plus contralateral cystectomy was performed. The side to perform the oophorectomy was decided by the surgeon after laparoscopic access according to the ovary mostly involved. Salpingectomy was performed in the presence of macroscopic involvement of the tube.</p> <p>Systematic pelvic and para-aortic lymphadenectomy were performed only in selected cases for either arm, with macroscopic pelvic and peritoneal involvement (advanced stages).</p> <p>A blood sample was taken from each patient for calculating haemoglobin variation (Δ Hb), 3 and 24 h after surgery.</p>
Outcomes	<ul style="list-style-type: none"> • Overall survival • Recurrence free survival • Pregnancy • Adverse events: Salvage surgery • Toxicity: <p>Median follow-up period was: 81 months (range, 60-96 months).</p>
Notes	<p>The authors used the Mann-Whitney test to compare time to recurrence in the two arms (see table V), which is not valid as this test considers only the 60% of women who had disease recurrence and ignores other women.</p> <p>The Kaplan-Meier plot for time to recurrence (Figure 2A) suggests that the proportional hazards assumption on which the estimates of the HR were based may not have been valid.</p> <p>“Exclusion criteria were age over 35 years, FSH > 15 UI/L, obesity [body mass index (BMI, kg/m²) >30], unilateral adnexal tumour, absence of remnant ovarian parenchyma [as detected by transvaginal ultrasonography (USG)], other pre-malignancies or malignancies, major medical conditions, psychiatric disorders, organic pelvic diseases, previous pelvic surgery, clinical tumour stage > I, tumour size over 8 cm, history of infertility, oligo-anovulatory cycles, tubal and male factor infertility (as determined by hysterosalpingogram and semen analysis). Patients were also excluded when not compliant to close post-surgical follow-up”.</p> <p>Intra-operative blood loss (72.8ml versus 81.1ml) was similar for the conservative and ultra-conservative surgical arms (P = 0.18).</p>

Palomba 2007 (Continued)

Hospital stay (3 days in either arm) and time to return to work (15 days in either arm) were similar between the ultra-conservative and conservative surgical arms.

The median time to first recurrence was 16 and 48 months for ultra-conservative and conservative surgery arms respectively ($P = 0.358$).

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	"The randomization was carried out using computer software (University of Catanzaro) to generate a random allocation to two independent groups".
Allocation concealment?	Low risk	"The random allocation sequence was concealed in closed and dark envelope until the interventions were assigned".
Blinding? All outcomes	Unclear risk	Not reported.
Incomplete outcome data addressed? All outcomes	Low risk	For all outcomes: % analysed 32/32 (100%). Originally 40 women were randomised to each group, but intra-operative examination of frozen sections during surgery detected borderline ovarian tumours in only 32 women.
Free of selective reporting?	Low risk	All measures seem to be reported in results section and adequate statistical measures have been used (HRs for survival data).
Free of other bias?	Unclear risk	Insufficient information to determine if further risk of bias exists.
Adequate classification of outcomes	Low risk	"The follow-up visits included physical and gynaecologic examinations, trans-abdominal and transvaginal USG and blood sample assay. All blood samples were obtained in the morning during early follicular phase (3rd day) of the menstrual cycle, serum tumoural markers and FSH levels were measured."

Sutton 1991

Methods	Multi-centre RCT in the USA.
Participants	<p>32 women with borderline ovarian tumours were included in an extension to a trial that had originally excluded borderline cases.</p> <p>The mean age at study entry was 48 years (range 25 to 75).</p> <p>All 32 women were diagnosed with FIGO Stage III disease.</p> <p>The tumour histological type was serous in 30 (94%) women and mucinous in 2 (6%) women.</p>
Interventions	<ul style="list-style-type: none"> Triple-agent chemotherapy: Received 50mg/m² cis-platinum, 500mg/m² cyclophosphamide and 50mg/m² doxorubicin (n = 12). Double-agent chemotherapy: Received 50mg/m² cisplatin and 1000mg/m² cyclophosphamide (n=20). <p>Drugs were administered every 3 weeks for eight courses.</p>

Sutton 1991 (Continued)

The median follow-up period was 2.6 years (range: 0.3 to 6.2 years).

Outcomes	<ul style="list-style-type: none">• Overall survival anddisease-specific survival• Toxicity.	
Notes	One patient assigned to the intervention arm did not start chemotherapy and was lost to follow up. Eight of 14 patients had persistent disease at second-look laparotomy. Not stated by intervention arm.	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not reported.
Allocation concealment?	Unclear risk	Not reported.
Blinding? All outcomes	Unclear risk	Not reported.
Incomplete outcome data addressed? All outcomes	Low risk	% analysed: 27/32 (84%). However, 5 women were lost to follow up, "In addition to the patient lost to follow-up after initial surgery, four patients were lost to follow-up at 6.2, 6.9, 13.2, and 48.2 months after surgery. None had clinically apparent disease".
Free of selective reporting?	Unclear risk	Insufficient information to permit judgement.
Free of other bias?	Unclear risk	Insufficient information to determine if further risk of bias exists.
Adequate classification of outcomes	Unclear risk	Not reported.

Trope 1993 (Study 1)

Methods	Single-centre RCT (1970 to 1974).
Participants	<p>74 women with histologically proven Stage I-II borderline ovarian tumours without residual tumour after primary laparotomy who received no previous non-surgical treatment. Women with known intraperitoneal adhesions or a previous or concomitant malignant lesion were excluded.</p> <p>The median age in the hospital at study entry in all 4 trials was 48 years (range 15-81 years).</p> <p>All women were diagnosed with FIGO Stage I or II disease.</p> <p>The tumour histological type was serous in 34 (46%), mucinous in 32 (43%), any other type in 5 (7%) or unspecified in 3 (4%).</p>
Interventions	<ul style="list-style-type: none"> • External irradiation and intraperitoneal radioactive gold (n = 38): Received 100 mCi of ¹⁹⁸Au dissolved in 1000 ml of physiological saline (n=38). A catheter with multiple outlets was placed in the upper abdomen either at laparotomy or laparoscopy. A separate stab wound was secured by a purse-string suture. One litre of saline was run into the peritoneal cavity over 24 hr. The isotope colloid was premixed in 1 litre of saline and instilled on the first postoperative day. The catheter was withdrawn immediately after flushing with 200 ml of saline and the purse-string suture was secured to prevent

Trope 1993 (Study 1) *(Continued)*

leaking. In addition, the patients were treated with 3000 rads of external megavoltage irradiation to the pelvis

- **External irradiation (n = 33):** Received external irradiation alone (pelvic field; dose 5000 rads).

The median follow-up period for the 4 trials by Trope et al was 147 months (range: 4 to 246 months).

Outcomes	<ul style="list-style-type: none"> • Overall survival • Disease-specific survival/disease recurrence • Toxicity.
Notes	<p>This group of randomised patients constituted 49% of all borderline ovarian tumours treated during the study period.</p> <p>No patients were lost to follow up. Analysis of outcomes was done in 1991.</p> <p>3 Stage 1 patients were excluded as they did not receive the treatment to which they were assigned.</p> <p>None of the excluded patients relapsed.</p> <p>The results section states that 19 women died of intercurrent disease and one died of ovarian cancer. However, the Kaplan-Meier (KM) plot clearly shows that the total number of women who died in the trial was 8 (4 in each group).</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not reported.
Allocation concealment?	Unclear risk	Not reported.
Blinding? All outcomes	Unclear risk	Not reported.
Incomplete outcome data addressed? All outcomes	Low risk	% analysed: 71/74 (96%).
Free of selective reporting?	Unclear risk	Insufficient information to permit judgement.
Free of other bias?	Unclear risk	Insufficient information to determine if further risk of bias exists.
Adequate classification of outcomes	Unclear risk	Not reported.

Trope 1993 (Study 2)

Methods	Single-centre RCT (1975 to 1977).
Participants	<p>42 women with histologically proven Stage I-II borderline ovarian tumours without residual tumour after primary laparotomy. They had no previous non-surgical treatment. Women with known intraperitoneal adhesions or a previous or concomitant malignant lesion were excluded.</p> <p>The median age at study entry in all 4 trials was 48 years (range: 15 to 81 years).</p> <p>All women were diagnosed with FIGO Stage I or II disease.</p>

Interventions for the treatment of borderline ovarian tumours (Review)

Trope 1993 (Study 2) (Continued)

The tumour histological type was serous in 28 (67%), mucinous in 13 (31%) or unspecified in 1 (2%).

Interventions	<p>Both groups received intraperitoneal instillation of radioactive gold (^{198}Au, the same doses as described above: see study 1) or later of radioactive phosphorus (^{32}P as described below: see study 4).</p> <ul style="list-style-type: none"> • Radio-isotope and chemotherapy (n = 21): Received two courses of 60 mg thio-TEPA 2 weeks apart, followed by 15 mg every second week intramuscularly for 6 months. • Radio-isotope (n = 20): Received no further treatment. <p>The median follow-up period for the 4 trials by Trope et al was 147 months (range: 4 to 246 months).</p>
Outcomes	<ul style="list-style-type: none"> • Overall survival • Disease-specific survival/disease recurrence • Toxicity.
Notes	<p>1 Stage I patient was excluded as treatment was not given due to postoperative sub-ileus.</p> <p>None of the excluded patients relapsed. No patients were lost to follow up. Analysis of outcomes was done in 1991.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not reported.
Allocation concealment?	Unclear risk	Not reported.
Blinding? All outcomes	Unclear risk	Not reported.
Incomplete outcome data addressed? All outcomes	Low risk	% analysed: 41/42 (98%).
Free of selective reporting?	Unclear risk	Insufficient information to permit judgement.
Free of other bias?	Unclear risk	Insufficient information to determine if further risk of bias exists.
Adequate classification of outcomes	Unclear risk	Not reported.

Trope 1993 (Study 3)

Methods	Single-centre RCT (1978 to 1981).
Participants	<p>68 women with histologically proven Stage I-II borderline ovarian tumours without residual tumour after primary laparotomy. They had no previous non-surgical treatment. Women with known intraperitoneal adhesions, a previous or concomitant malignant lesion were excluded.</p> <p>The median age in the hospital at study entry in all 4 trials was 48 years (range: 15-81 years).</p> <p>All women were diagnosed with FIGO Stage I or II disease.</p>

Trope 1993 (Study 3) (Continued)

The tumour histological type was serous in 29 (44%), mucinous in 34 (51%) or any other type in 3 (5%).

Interventions	<ul style="list-style-type: none"> • Chemotherapy (n=27): Received two courses of 60 mg thio-TEPA 2 weeks apart, followed by 15 mg every second week intramuscularly for 6 months. • Control (n=39): No further treatment. <p>The median follow-up period for the 4 trials by Trope et al was 147 months (range: 4 to 246 months).</p>
Outcomes	<ul style="list-style-type: none"> • Overall survival • Disease-specific survival/disease recurrence • Toxicity.
Notes	<p>2 stage I patients were excluded as they did not manage to receive the treatment.</p> <p>None of the excluded patients relapsed. No patients were lost to follow up. Analysis of outcomes was done in 1991.</p> <p>The total number of deaths in the trial was unclear. It was reported that "7 patients dies of intercurrent disease, and 1 patient randomized to thio-TEPA died of ovarian cancer. One Stage Ia patient treated with thio-TEPA died of bone marrow toxicity" (see page 239). The KM plot appeared to indicate 7 deaths. Hence we are unclear whether the total number of deaths was 7, 8 or 9; we assumed it was 8.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not reported.
Allocation concealment?	Unclear risk	Not reported.
Blinding? All outcomes	Unclear risk	Not reported.
Incomplete outcome data addressed? All outcomes	Low risk	% analysed: 66/68 (97%).
Free of selective reporting?	Unclear risk	Insufficient information to permit judgement.
Free of other bias?	Unclear risk	Insufficient information to assess whether an important risk of bias exists.
Adequate classification of outcomes	Unclear risk	Not reported.

Trope 1993 (Study 4)

Methods	Single-centre RCT (1982-1988).
Participants	<p>69 women with histologically proven Stage I-II borderline ovarian tumours without residual tumour after primary laparotomy. They had no previous non-surgical treatment. Women with known intraperitoneal adhesions, a previous or concomitant malignant lesion were excluded.</p> <p>The median age in the hospital at study entry in all 4 trials was 48 years (range: 15-81 years).</p> <p>All women were diagnosed with FIGO Stage I or II disease.</p>

Interventions for the treatment of borderline ovarian tumours (Review)

Trope 1993 (Study 4) *(Continued)*

The tumour histological type was serous in 23 (35%), mucinous in 40 (62%) or any other type in 2 (3%).

Interventions	<ul style="list-style-type: none"> • Chemotherapy (n=32): Cis-platinum (50 mg/m² intravenously), repeat courses every 3 weeks for 6 cycles. • Radio-isotope therapy (n=33): Intraperitoneal ³²P given as a suspension of ³²P-labeled colloids containing chromic hydroxide particles with diameters between 0.1 and 1 µm. Patients weighing less than 50kg, 50-59 kg or more than 70 kg, received 260 MBq (7.0 mCi), 300 MBq (8.1 mCi), 330 MBq (8.9 mCi), and 370 MBq (10 mCi) respectively. <p>The median follow-up period for the 4 trials by Trope et al was 147 months (range: 4 to 246 months).</p>
Outcomes	<ul style="list-style-type: none"> • Overall survival • Disease-specific survival/disease recurrence • Toxicity.
Notes	<p>2 stage I and 2 stage II patients in the ³²P arm were excluded and were treated with external beam irradiation instead of ³²P because of extensive intraperitoneal adhesions.</p> <p>None of the excluded patients relapsed. No patients were lost to follow up. Analysis of outcomes was done in 1991. 1 patient died of ovarian cancer.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not reported.
Allocation concealment?	Unclear risk	Not reported.
Blinding? All outcomes	Unclear risk	Not reported.
Incomplete outcome data addressed? All outcomes	Low risk	% analysed: 65/69 (94%).
Free of selective reporting?	Unclear risk	Insufficient information to permit judgement.
Free of other bias?	Unclear risk	Insufficient information to determine if further risk of bias exists.
Adequate classification of outcomes	Unclear risk	Not reported.

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

Study	Reason for exclusion
Swanton 2007	Systematic review which yielded no further included trials.
Vergote 1992	This was an RCT which inadvertently included a subgroup of 67 patients with borderline ovarian tumours whose outcomes were not reported separately from those of patients with invasive cancer.

Study	Reason for exclusion
Young 1990	This article reported on two RCTs in patients with early ovarian cancer. Even though central pathology review identified 51 patients with borderline ovarian tumours, the outcomes on these were not reported by treatment arm.

ADDITIONAL TABLES

Table 1. Summary of trial comparisons, outcomes and follow up

Trial ID and comparison	Deaths	Disease recurrence l	Time to pregnancy post-surgery	Adverse events	Duration of follow up
Creasman 1982	a) 1/13 (8%) versus 0/25 (0%)	a) 1/13 (8%) versus 0/25 (0%)	Not reported	Not reported	Mean: 3 yrs Range: 1-7 yrs.
a) External pelvic irradiation versus. no further treatment					
b) Chemotherapy (melphalan) versus no further treatment	b) 0/17 (0%) versus 0/25 (0%)	b) 0/17 (0%) versus 0/25 (0%)			
c) External pelvic irradiation versus chemotherapy (melphalan)	c) 1/13 (8%) versus 0/17 (0%)	c) 1/13 (8%) versus 0/17 (0%)			
Palomba 2007	0/15 (0%) versus 0/17 (0%)	9/15 (60%) versus 10/17 (59%)	14/15 (93%) versus 9/17 (53%)	Intra-operative blood loss (ml): 72.8 (IQR=11.4; range: 64.2–92.7) versus 81.1 (IQR=15.9; range: 64.4–102.3). Hospital stay (days): 3.0 (IQR=0.0; range: 3.0–6.0) versus 3.0 (IQR=2.0; range: 3.0–6.0).	Median: 81 months Range: 60-96 months.
Ultra-conservative versus conservative surgery					
Sutton 1991	0/12 (0%) versus 1/20 (5%)	Not reported	Not reported	Grade IV granulocyte toxicity: 1/12 (8%) versus 1/20 (5%)	Median: 2.6 yrs Range: 0.3-6.2 yrs.
Cis-platinum, cyclophosphamide and doxorubicin versus cis-platinum and cyclophosphamide alone					
Trope 1993 (Study 1)	4/36 (11%) versus 4/35 (11%)	1/36 (3%) versus 0/35 (0%)	Not reported	Not reported	For all 4 Trope trials combined: Median: 147 months Range: 14 - 246 months
Pelvic external irradiation + ¹⁹⁸ Au ip versus pelvic external irradiation					

Table 1. Summary of trial comparisons, outcomes and follow up *(Continued)*

Trope 1993 (Study 2)	3/21 (14%) versus 2/20 (10%)	0/21 (0%) versus 0/20 (0%)	Not reported	Small intestinal toxicity: 2/21 (10%) versus 0/20 (0%) Bone marrow toxicity (grade 4): 1/21 (5%) versus 0/20 (0%)
Thio-TEPA versus no further treatment (both groups re- ceived intraperitoneal isotopes)				
Trope 1993 (Study 3)	6/27 (22%) versus 2/39 (5%)	1/27 (4%) versus 0/39 (0%)	Not reported	Severe septic neutropenia (grade 4): 1/27 (4%) versus 0/39 (0%) Bone marrow toxicity (grade 3): 1/27 (4%) versus 0/39 (0%)
Thio-TEPA versus no further treatment				
Trope 1993 (Study 4)	0/33 (0%) versus 2/32 (6%)	0/33 (0%) versus 1/32 (3%)	Not reported	Intestinal obstruction: 4/33 (12%) versus 0/32 (0%) Grade 1 neurotoxicity: 0/33 (0%) versus 1/32 (3%)
Intraperitoneal ³² P versus <i>cis</i> - platinum				

APPENDICES

Appendix 1. MEDLINE search strategy

MEDLINE Ovid 1950 to week 3 2009

1. exp Ovarian Neoplasms/
2. (ovar* adj5 (cancer* or neoplas* or carcinom* or malignan* or tumor* or tumour*)).mp.
3. 1 or 2
4. (atypical adj proliferative).mp.
5. borderline.mp.
6. micropapillary.mp.
7. (low adj malignan*).mp.
8. (semi adj malignan*).mp.
9. 4 or 5 or 6 or 7 or 8
- 10.3 and 9
- 11.(ovar* adj5 cystadeno*).mp.
- 12.10 or 11

- 13."randomized controlled trial".pt.
- 14."controlled clinical trial".pt.
- 15.randomized.ab.
- 16.placebo.ab.
- 17."drug therapy".fs.
- 18."surgery".fs.
- 19."therapy".fs.
- 20."radiotherapy".fs.
- 21.randomly.ab.
- 22.trial.ab.
- 23.groups.ab.
- 24.exp Cohort Studies/
- 25.cohort*.mp.
- 26.(case adj series).mp.
- 27.13 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
- 28.12 and 27
- 29.Animals/
- 30.Humans/
- 31.29 not (29 and 30)
- 32.28 not 31

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

ab=abstract

fs=floating subheading

Appendix 2. EMBASE search strategy

EMBASE Ovid 1980 to 2009 week 2

1. Ovary Tumor/
2. (ovar* adj5 (cancer* or neoplas* or carcinom* or malignan* or tumor* or tumour*)).mp.
3. 1 or 2
4. (atypical adj proliferative).mp.
5. borderline.mp.
6. micropapillary.mp.
7. (low adj malignan*).mp.]
8. (semi adj malignan*).mp.
9. 4 or 5 or 6 or 7 or 8
- 10.3 and 9
- 11.(ovar* adj5 cystadeno*).mp.
- 12.10 or 11
- 13.exp Controlled Clinical Trial/
- 14.randomized.ab.
- 15.placebo.ab.
- 16.dt.fs.
- 17.su.fs.
- 18.th.fs.
- 19.rt.fs.
- 20.randomly.ab.
- 21.trial.ab.
- 22.groups.ab.
- 23.exp Cohort Analysis/
- 24.cohort*.mp.

25.(case adj series).mp.
26.13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25
27.12 and 26
28.exp Animal/
29.Human/
30.28 not (28 and 29)
31.27 not 30

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

fs=floating subheading

ab=abstract

Appendix 3. CENTRAL search strategy

CENTRAL Issue 4 2008

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. atypical adj proliferative
5. borderline
6. micropapillary
7. low adj malignan*
8. semi adj malignan*
9. (#4 OR #5 OR #6 OR #7 OR #8)
- 10.(#3 AND #9)
- 11.ovar* near/5 cystadeno*
- 12.(#10 OR #11)

WHAT'S NEW

Date	Event	Description
26 February 2014	Amended	Contact details updated.

CONTRIBUTIONS OF AUTHORS

OF, CG and MM drafted the clinical sections of the protocol; AB and HD drafted the methodological sections of the protocol; OF, MM, AB and HD performed data extraction. All authors contributed to writing the review.

DECLARATIONS OF INTEREST

None

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Department of Health, UK.

NHS Cochrane Collaboration programme Grant Scheme CPG-506

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Restriction to RCTs

The search strategy identified seven RCTs that met our inclusion criteria, so we restricted the review to RCTs as they provide the best level of evidence. In the protocol we had stated the following.

"Since borderline ovarian tumours are rare we expect to find few RCTs so non-randomised studies with concurrent comparison groups will be included:

- Quasi-randomised trials, non-randomised trials, prospective and retrospective comparative cohort studies, and case series of 30 or more patients that allow concurrent comparisons of different treatments.

Case-control studies, uncontrolled observational studies and case series of fewer than 30 patients will be excluded."

Searches

In the protocol, we stated:

"The main investigators of any relevant ongoing trials will be contacted for further information, as will any major co-operative trials groups active in this area."

However, we did not find any relevant ongoing trials or active trial groups, so we did not make these contacts.

Data extraction

None of the included trials reported adjusted results, so we were unable to extract these. In the protocol we had stated the following.

"Both unadjusted and adjusted statistics will be extracted, if reported. If adjusted statistics are reported, we will record the variables used in adjustment."

Risk of bias

In the protocol, we stated that "We coded satisfactory level of loss to follow-up for each outcome". We were unable to do this as loss to follow up was not reported separately for each outcome in the included papers.

Risk of bias was not examined in non-randomised studies as the review was restricted to RCTs. In the protocol we stated the following.

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

Cohort selection

1. Were relevant details of criteria for assignment of patients to treatments provided?
 - a. Yes
 - b. No
 - c. Unclear
2. Was the group of women who received the experimental intervention representative?
 - a. Yes, if they were representative of women with borderline ovarian tumours
 - b. No, if group of patients was selected
 - c. Unclear, if selection of group was not described
3. Was the group of women who received the comparison intervention representative?
 - a. Yes, if drawn from the same population as the experimental cohort
 - b. No, if drawn from a different source
 - c. Unclear, if selection of group not described

Comparability of treatment groups

1. Were there no differences between the two groups or were differences controlled for, in particular with reference to age, parity, infertility, FIGO stage, histology?
 - a. Yes, if at least three of these characteristics were reported and any reported differences were controlled for
 - b. No, if the two groups differed and differences were not controlled for.
 - c. Unclear, if fewer than three of these characteristics were reported even if there were no other differences between the groups, and other characteristics had been controlled for."

Quality of life

Quality of life was not reported in any of the trials so the following sections in the protocol, which discussed the handling of data for continuous outcomes, were removed as they were unnecessary.

"Data extraction and management

- For continuous outcomes (e.g. quality of life measures), we will extract the final value and standard deviation of the outcome of interest and the number of patients assessed at endpoint in each treatment arm at the end of follow up, in order to estimate the mean difference between treatment arms and its standard error.

Measures of treatment effect

- For continuous outcomes, we will use the mean difference between treatment arms if all trials measured the outcome on the same scale, otherwise standardised mean differences will be used."

Dealing with missing data

In the protocol, we stated:

"If data were missing or only imputed data were reported we contacted trial authors to request data on the outcomes only among participants who were assessed".

This was not done as none of the trials imputed missing data. Although some of the outcomes that we specified were not reported in included trials, we did not contact trial authors as all trials except one were reported on over 15 years ago. The most recent trial ([Palomba 2007](#)) reported all the outcomes we specified.

Data synthesis

We were unable to pool the results of the included trials in meta-analyses as they all compared different interventions. Therefore, it was not relevant to assess heterogeneity between results of trials and we were unable to assess reporting biases using funnel plots or conduct any subgroup analyses or sensitivity analyses. The following sections of the protocol were therefore removed.

"Assessment of heterogeneity

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

Assessment of reporting biases

Funnel plots corresponding to meta-analysis of the primary outcome will be examined to assess the potential for small study effects such as publication bias. If these plots suggest that treatment effects may not be sampled from a symmetric distribution, as assumed by the random effects model, further meta-analyses will be performed using fixed effects models.

Data synthesis

Where sufficient clinically similar studies were available, their results will be pooled in meta-analyses. Adjusted summary statistics will be used if available; otherwise unadjusted results will be used.

- For time-to-event data, HRs will be pooled using the generic inverse variance facility of RevMan 5.
- For any dichotomous outcomes, the RR will be calculated for each study and these were then pooled

If any trials had multiple treatment groups, the 'shared' comparison group will be divided into the number of treatment groups and comparisons between each treatment group and the split comparison group will be treated as independent comparisons.

Random effects models with inverse variance weighting will be used for all meta-analyses ([DerSimonian 1986](#)).

If possible, studies making different comparisons will be synthesised using the methods of [Bucher 1997](#).

Subgroup analysis and investigation of heterogeneity

Subgroup analyses will be performed, grouping the trials by:

- Histology (Serous versus others)
- Follow up (Median < 5 years versus > 5 years)

Factors such as age, type of intervention, stage, length of follow up and adjusted/unadjusted analysis were considered in interpretation of any heterogeneity.

Sensitivity analysis

Sensitivity analyses will be performed excluding (i) studies at high risk of bias and (ii) using unadjusted results."

INDEX TERMS**Medical Subject Headings (MeSH)**

Chemotherapy, Adjuvant; Neoplasm Staging; Ovarian Neoplasms [pathology] [surgery] [*therapy]; Quality of Life; Radiotherapy, Adjuvant; Randomized Controlled Trials as Topic

MeSH check words

Adult; Female; Humans; Pregnancy