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Maintenance chemotherapy for ovarian cancer (Review)

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[Intervention Review]

Maintenance chemotherapy for ovarian cancer

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ABSTRACT

Background

This review is an update of a previously published review in the Cochrane Database of Systematic Reviews (2010, Issue 9 and 2013, Issue 6). Epithelial ovarian cancer accounts for about 90% of all cases of ovarian cancer. Debulking surgery and six courses of platinum-based chemotherapy results in complete clinical remission (CCR) in up to 75% of cases. However, 75% of the responders will relapse within a median time of 18 to 28 months and only 20% to 40% of women will survive beyond five years. It has been suggested that maintenance chemotherapy could assist in prolonging remission. To date, there has not been a systematic review on the impact of maintenance chemotherapy for epithelial ovarian cancer.

Objectives

To assess the effectiveness and toxicity of maintenance chemotherapy for epithelial ovarian cancer and to evaluate the impact on quality of life (QoL).

Search methods

In the original review we searched the Cochrane Gynaecological Cancer Review Group Specialised Register, Cochrane Central Register of Controlled Trails (CENTRAL, the Cochrane Library 2009, Issue 1), MEDLINE, Embase, PubMed, CBMdisc, CNKI and VIP (to May 2009). We collected information from ongoing trials, checked reference lists of published articles and consulted experts in the field. For the first update the searches were extended to October 2012 and for this update to February 2017.

Selection criteria

Randomised controlled trials (RCTs) comparing maintenance chemotherapy with no further intervention, maintenance radiotherapy or other maintenance therapy.

Data collection and analysis

Two review authors independently assessed trials for eligibility and quality and extracted data. We analysed overall survival (OS) and progression-free survival (PFS) rates as dichotomous variables. Toxicity and QoL data were extracted where present. All analyses were based on intention-to-treat (ITT) on the endpoint of survival. We also analysed data by subgroups of drugs.

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Main results

No new studies were found for inclusion in this update from the latest searches. We included eight trials (1644 women). When all chemotherapy regimens were combined, meta-analysis indicated no significant difference in three-, five- and 10-year OS or PFS. For five-year OS, the combined risk ratio (RR) was 1.03 (95% confidence interval (CI) 0.96 to 1.10; 4 studies, 899 participants; moderate-certainly evidence) and for the five-year PFS, the combined RR was 1.06 (95% CI 0.97 to 1.17; 3 studies, 761 participants; moderate-certainly evidence). Results were very similar when trials of different regimens were analysed. Comparing chemotherapy with radiotherapy, only the RR for 10-year PFS in pathological complete remission (PCR) was in favour of whole abdominal radiotherapy 0.51 (95% CI 0.27 to 1.00), while three- and five-year OS rates have no significant difference between the two groups.

Authors' conclusions

There is no evidence to suggest that the use of platinum agents, doxorubicin or paclitaxel used as maintenance chemotherapy is more effective than observation alone. Further investigations regarding the effect of paclitaxel used as maintenance chemotherapy are required.

PLAIN LANGUAGE SUMMARY

Maintenance chemotherapy for ovarian cancer

Background

Of all the gynaecological cancers, ovarian cancer has the highest death rate and epithelial ovarian cancer accounts for about 90% of all cases. Surgery and six courses of platinum-based chemotherapy is the standard treatment and 75% of the women may not have any evidence of disease at the end of this treatment. However, 75% of the women who respond to initial treatment will relapse within 18 to 28 months and only 20% to 40% of all women will survive beyond five years.Some doctors suggest giving maintenance chemotherapy for epithelial ovarian cancer. Maintenance chemotherapy refers to the chemotherapy given to women who have achieved remission after initial surgery and induction chemotherapy.The aim of maintenance chemotherapy is to prolong the duration of remission and improve the overall length of survival. Some studies indicate that maintenance chemotherapy can improve the time without cancer progression, while others do not show any effect.

The aim of the review

The aim of this review was to estimate whether using maintenance chemotherapy is better than observation alone for women with epithelial ovarian cancer.

What are the main findings?

We identified eight trials that used different types of chemotherapy (e.g. platinum agents, doxorubicin, topotecan or paclitaxel) but there was not sufficient evidence to prove any of the drugs were better than observation alone. An important consideration for women with advanced disease is the balance between the benefit of treatment and the harms or adverse effects that these treatments may cause. There were insufficient data to comment on the overall impact of the maintenance chemotherapy on clinical benefit from the women's perspective.

Quality of the evidence

We tried to identify all trials and both published and unpublished data in this review; thereby minimising the influence of publication bias. The included trials are graded as moderate quality but this meta-analysis currently provides a reliable assessment of the average treatment effect of platinum and doxorubicin among women with advanced epithelial ovarian cancer.

What are the conclusions?

Use of platinum agents, doxorubicin or paclitaxel used as maintenance chemotherapy has not proved effective to prolong the life time of women with epithelial ovarian cancer. Further investigations regarding the effect of paclitaxel used as maintenance chemotherapy are required.

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Summary of findings 1. Maintenance chemotherapy versus observation

Maintenance chemotherapy vs. observation

Patient or population: patients with epithelial ovarian cancer
Intervention: maintenance chemotherapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Maintenance chemotherapy				
3-year PFS Follow-up: median 43.5 months	**Study population**		**RR 1.07** (0.91 to 1.25)	541 (4 studies)	⊕⊕⊕⊝ **moderate**[1]	There was no statistically significant difference in the three-, five- and 10-year PFS or OS. For the five-year PFS the combined risk ratio (RR) was 1.06 (95% confidence interval (CI) 0.97 to 1.17) and for five-year OS, the combined RR was 1.03 (95% CI, 0.96 to 1.10) .
	521 per 1000	**557 per 1000** (474 to 651)				
5-year PFS Follow-up: mean 88.5 months	**Study population**		**RR 1.06** (0.97 to 1.17)	761 (3 studies[1])	⊕⊕⊕⊝ **moderate**[1]	
	664 per 1000	**704 per 1000** (644 to 777)				
10-year PFS Follow-up: median 96.7 months	**Study population**		**RR 0.96** (0.65 to 1.41)	219 (2 studies)	⊕⊕⊕⊝ **moderate**[1]	
	327 per 1000	**314 per 1000** (213 to 461)				
3-year OS Follow-up: median 43.5 months	**Study population**		**RR 1.00** (0.92 to 1.08)	679 (5 studies)	⊕⊕⊕⊝ **moderate**[1]	
	795 per 1000	**795 per 1000** (731 to 858)				
5-year OS Follow-up: median 6.7 years	**Study population**		**RR 1.03** (0.96 to 1.10)	899 (4 studies)	⊕⊕⊕⊝ **moderate**[1]	
	746 per 1000	**768 per 1000** (716 to 821)				
10-year OS Follow-up: median 96.7 months	**Study population**		**RR 1.08** (0.78 to 1.49)	219 (2 studies)	⊕⊕⊕⊝ **moderate**[1]	
	383 per 1000	**414 per 1000**				

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	(299 to 571)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OS:** overall survival; **PFS:** progression-free survival; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Downgraded as allocation concealment is unclear

Summary of findings 2. Platin-based maintenance chemotherapy versus observation

Platin-based maintenance chemotherapy for epithelial ovarian cancer

Patient or population: patients with epithelial ovarian cancer
Intervention: platin-based maintenance chemotherapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Platin-based maintenance chemotherapy				
3-year PFS Follow-up: median 96.7 months	**Study population**		**RR 1.04** (0.86 to 1.24)	341 (3 studies)	⊕⊕⊕⊖ **moderate**[1]	There was no consistent effect in the three-, five- and 10-year PFS or OS. For the five-year PFS the combined risk ratio (RR) was 1.18 (95% confidence interval (CI) 0.88 to 1.58) and for five-year OS, the combined RR was 1.07 (95% CI, 0.88 to 1.31) .
	571 per 1000	**594 per 1000** (491 to 709)				
5-year PFS Follow-up: median 96.7 months	**Study population**		**RR 1.18** (0.88 to 1.58)	219 (2 studies)	⊕⊕⊕⊖ **moderate**[1]	
	411 per 1000	**485 per 1000** (362 to 650)				
10-year PFS Follow-up: median 96.7 months	**Study population**		**RR 0.96** (0.65 to 1.41)	219 (2 studies)	⊕⊕⊕⊖ **moderate**[1]	
	327 per 1000	**314 per 1000** (213 to 461)				

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3-year OS Follow-up: median 96.7 months	**Study population**		**RR 1.06** (0.94 to 1.18)	341 (3 studies)	⊕⊕⊕⊖ **moderate**[1]
	762 per 1000	**808 per 1000** (716 to 899)			
5-year OS Follow-up: median 96.7 months	**Study population**		**RR 1.07** (0.88 to 1.31)	219 (2 studies)	⊕⊕⊕⊖ **moderate**[1]
	617 per 1000	**660 per 1000** (543 to 808)			
10-year OS Follow-up: median 96.7 months	**Study population**		**RR 1.08** (0.78 to 1.49)	219 (2 studies)	⊕⊕⊕⊖ **moderate**[1]
	383 per 1000	**414 per 1000** (299 to 571)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OS:** overall survival; **PFS:** progression-free survival; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Downgraded as allocation concealment is unclear

Summary of findings 3. Doxorubicin-based maintenance chemotherapy versus observation

Doxorubicin-based maintenance chemotherapy for epithelial ovarian cancer

Patient or population: patients with epithelial ovarian cancer
Intervention: Doxorubicin-based maintenance chemotherapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Doxorubicin-based maintenance chemotherapy				

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3-year OS Follow-up: median 40 months	**Study population**		**RR 1.00** (0.86 to 1.15)	204 (2 studies)	⊕⊕⊕⊖ **moderate**[1]	There was no consistent effect for doxorubicin-based maintenance chemotherapy. Overall survival for three and five years RR was 1.00 (95% CI 0.86 to 1.15 and 0.79 to 1.27, respectively)
	781 per 1000	**781 per 1000** (672 to 898)				
5-year OS Follow-up: median 40 months	**Study population**		**RR 1.00** (0.79 to 1.27)	204 (2 studies)	⊕⊕⊕⊖ **moderate**[1]	
	571 per 1000	**571 per 1000** (451 to 726)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OS:** overall survival; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Downgraded as allocation concealment is unclear

Summary of findings 4. Maintenance chemotherapy compared to maintenance radiotherapy for epithelial ovarian cancer

Maintenance chemotherapy compared to maintenance radiotherapy for epithelial ovarian cancer

Patient or population: epithelial ovarian cancer
Intervention: maintenance chemotherapy
Comparison: maintenance radiotherapy

Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Maintenance radiotherapy	**Maintenance chemotherapy**				
3-year PFS	**Study population**		**RR 1.07** (0.75 to 1.54)	141 (1 study)	⊕⊕⊖⊖ **low**[1,2]	The results showed no statistical difference between chemotherapy and radiotherapy groups.The 5-
	420 per 1000	**450 per 1000** (315 to 647)				

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	Moderate				
5-year PFS	**Study population**		**RR 0.86** (0.55 to 1.37)	141 (1 study)	⊕⊕⊝⊝ **low**[1,2]
	348 per 1000	**299 per 1000** (191 to 477)			
	Moderate				
10-year PFS	**Study population**		**RR 0.89** (0.51 to 1.55)	141 (1 study)	⊕⊕⊝⊝ **low**[1,2]
	261 per 1000	**232 per 1000** (133 to 404)			
	Moderate				
3-year OS	**Study population**		**RR 1.06** (0.85 to 1.32)	141 (1 study)	⊕⊕⊝⊝ **low**[1,2]
	652 per 1000	**691 per 1000** (554 to 861)			
	Moderate				
5-year OS	**Study population**		**RR 0.97** (0.70 to 1.35)	141 (1 study)	⊕⊕⊝⊝ **low**[1,2]
	493 per 1000	**478 per 1000** (345 to 665)			
	Moderate				
10-year OS	**Study population**		**RR 0.94** (0.58 to 1.52)	141 (1 study)	⊕⊕⊝⊝ **low**[1,2]
	304 per 1000	**286 per 1000**			

year OS RR was 0.97 (95% CI 0.70 to 1.35).

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		(177 to 463)		
Moderate				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OS:** overall survival; **PFS:** progression-free survival; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Downgraded as allocation concealment is unclear
[2] Downgraded as the baseline is imbalanced

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BACKGROUND

This review is an update of a previously published Cochrane review (Mei 2010; Mei 2013).

Description of the condition

Worldwide, approximately 238,719 women are diagnosed with ovarian cancer and about 151,917 die from this disease each year. Ovarian cancer is the seventh most common cancer among women. (GLOBOCAN 2012). A woman's cumulative risk of developing ovarian cancer by age 65 years is 0.5%: 0.4% in less developed countries and 0.7% in more developed countries. It is less common in women under the age of 35 years, and its incidence increases with age (GLOBOCAN 2002).

Of all the malignant gynaecological tumours, ovarian cancer has the highest mortality rate because ovarian cancer often does not cause symptoms until it has become widespread (Poveda 2003). Despite, however, good responses to chemotherapy, there is a high recurrence rate (Ozols 2006). Epithelial ovarian cancer accounts for about 90% of all cases of ovarian cancer (Thigpen 2004). Debulking surgery and six courses of platinum-based chemotherapy results in complete clinical remission (CCR) in up to 75% of cases (Thigpen 2004). However, 75% of the responders will relapse within the median time of 18 to 28 months (Stuart 2003) and only 20% to 40% women will survive beyond five years (Kikuchi 2005). Studies have shown that more than six courses of induction chemotherapy does not improve progression-free survival (PFS) or overall survival (OS) but increases toxicity (Bertelsen 1993; Hakes 1992; Lambert 1997). Women receiving prolonged courses of chemotherapy therefore may gain little survival benefit while suffering from more adverse effects.

Description of the intervention

It has been suggested that maintenance or consolidation chemotherapy may be administered for epithelial ovarian cancer. Maintenance chemotherapy refers to chemotherapy given after women have achieved CCR or pathological complete remission (PCR), after initial surgery and induction chemotherapy.

How the intervention might work

The aim of the intervention is to prolong the interval of remission and improve the OS. Some clinicians differentiate maintenance chemotherapy from consolidation chemotherapy, as high-dose or relatively short-term chemotherapy given after CCR or PCR (Ozols 2004). The aim in this setting is to prevent recurrence rather than delay recurrence. Currently there are no specific definitions for these concepts, so we will consider consolidation and maintenance chemotherapy as the same, as long as it is applied after the women have achieved CCR or PCR and it will be referred to as maintenance chemotherapy in this review.

CCR is defined as a patient with a normal CA-125 blood test according to the local laboratory parameters, having no cancer-related symptoms, a normal physical examination and a negative CT scan of the abdomen and/or pelvis and chest x-ray (Markman 2003). PCR is defined as a patient with CCR confirmed as tumour-negative by the second-look surgery (Varia 2003).

Why it is important to do this review

Some studies have indicated that maintenance chemotherapy can improve PFS (Markman 2003), while others did not show any effect. To date, there have not been any published systematic reviews on the impact of maintenance chemotherapy for epithelial ovarian cancer.

OBJECTIVES

To assess the effectiveness and toxicity of maintenance chemotherapy for epithelial ovarian cancer and to evaluate the impact on quality of life (QoL) of maintenance chemotherapy.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs).

Types of participants

Women with epithelial ovarian cancer who have achieved CCR or PCR after initial surgery and chemotherapy.

Types of interventions

- Maintenance chemotherapy versus no further intervention
- Maintenance chemotherapy versus maintenance radiotherapy
- Maintenance chemotherapy versus other maintenance therapy except chemotherapy and radiotherapy (e.g. biotherapy, immunotherapy)

Types of outcome measures

Primary outcomes

- PFS and OS rates

Secondary outcomes

- Adverse effect events (nausea-vomiting, diarrhoea, ileus, bone marrow toxicity, neurotoxicity, mucositis, renal toxicity, hepatic toxicity, bladder toxicity etc) and
- QoL (if a validated scale had been used)

Search methods for identification of studies

Electronic searches

For the original review we searched the following databases, The Cochrane Gynaecological Cancer Review Group Specialised Register, The Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Library, 2009, Issue 1, MEDLINE (from 1950 to May 2009), Embase (from 1966 to May 2009), PubMed (May 2009), CBMdisc (1978 to May 2009), CNKI (1979 to May 2009) and VIP (1989 to May 2009). For the first update the searches were extended to October 2012.

For this update we extended the search to: CENTRAL Issue 2, 2017, MEDLINE (January Week 4, 2017), Embase (week 6, 2017), PubMed (to March 2017),CNKI (to March 2017), CBMdisc (to March 2017) and VIP (to March 2017).

For MEDLINE, the subject search used a combination of vocabulary (MeSH terms) and free text terms (Appendix 1). We adapted

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the search strategy accordingly for CENTRAL, Embase, PubMed, CBMdisc,CNKI and VIP. The search strategies can be found in Appendix 2, Appendix 3, Appendix 4.

For MEDLINE, Embase and PubMed, there were no language restrictions placed on the search.

The search strategies used were developed and executed by the author team.

Searching other resources

- We checked the reference lists of obtained articles to check for other related published and unpublished studies.
- We searched relevant web sites for ongoing trials:
  - http://www.nccn.org
  - http://www.clinicaltrials.gov/ct
  - http://www.gog.org
  - http://www.cancer.gov/clinicaltrials
  - http://www.eortc.be/
  - http://www.swog.org/
- Personal communication: In addition, we contacted authors of included RCTs to identify any additional published and unpublished materials.

Data collection and analysis

Selection of studies

Two review authors (ML and WDM) scanned the titles and abstracts from the initial search in order to exclude those that did not meet the inclusion criteria. The full text of potentially relevant studies were obtained for independent assessment of eligibility by two review authors (ML and CH). Any disagreements were resolved through discussion with a third review author (FF) if necessary.

Data extraction and management

Two review authors (XHY and WX) independently extracted data using a previously specified form listing the following:

- study characteristics (randomisation process, allocation concealment, blinding, attrition bias and intention-to-treat (ITT) analysis);
- basic information of the participants (number of the women, mean age, age range);
- base-line data of the participants (FIGO stages, histological type, pathological grade and response to the first-line treatment);
- intervention (drug, dose and courses); and
- outcome (OS after three, five and 10 years, PFS after three, five and 10 years, the incidence and severity of toxicity such as nausea-vomiting, mucositis, leucopenia, thrombocytopenia, neutropenia, neurotoxicity, hepatic toxicity and renal toxicity and QoL score).

We resolved any disagreements by referring to the trial report or by consulting a third review author (FF). We contacted the trial authors for additional information if data from the trial reports were insufficient or missing.

Assessment of risk of bias in included studies

We assessed and reported the methodological risk of bias of included studies in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), which recommends the explicit reporting of the following individual elements for RCTs.

- Selection bias: random sequence generation and allocation concealment
- Performance bias: blinding of participants and personnel (i.e. treatment providers) [blinding may only be applicable to outcome assessors, see point below]
- Detection bias: blinding of outcome assessment
- Attrition bias: incomplete outcome data
- Reporting bias: selective reporting of outcomes
- other possible sources of bias (e.g. baseline imbalance)

Two review authors (ML and WDM) independently applied the 'Risk of bias' tool and resolved differences by discussion or by appeal to a third review author (FF). We judged each item as being at high, low or unclear risk of bias as set out in the criteria provided by Higgins 2011, and provide a quote from the study report or a statement as justification for the judgement for each item in the risk of bias table or both. We summarised results in both a 'Risk of bias' graph and a risk of bias summary. When interpreting treatment effects and meta-analyses, we took into account the 'Risk of bias' for the studies that contribute to that outcome.

Measures of treatment effect

When sufficient, clinically similar trials were available, we pooled the results in meta-analyses. For dichotomous outcomes, we calculated the risk ratio (RR) for each study and pooled them. For continuous outcomes, we planned to pool the mean differences (or standardised mean differences) between the treatment arms at the end of follow-up.

Dealing with missing data

Whenever possible, we contacted the original investigators to request missing data.

Data synthesis

When sufficient, clinically similar trials were available, we pooled their results in meta-analyses. We analysed the data using Review Manager 5. We used RR and its 95% confidence interval (CI) to estimate the combined effect of OS, PFS and certain adverse effect rate. If the effect could not be combined, we described the outcome separately. If QoL had been reported by continuous data, we would have pooled the mean differences between the treatment arms.

We presented the overall quality of the evidence for each outcome according to the GRADE approach, which takes into account issues not only related to internal validity (risk of bias, inconsistency, imprecision, publication bias) but also to external validity such as directness of results (Langendam 2013). We created 'Summary of findings' tables based on the methods described the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and using GRADEpro GDT. We used the GRADE checklist and GRADE Working Group quality of evidence definitions (Meader 2014). We downgraded the evidence from 'high' quality by one level for serious (or by two for very serious) concerns for each limitation.

- **High quality:** We are very confident that the true effect lies close to that of the estimate of the effect.

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

Subgroup analysis and investigation of heterogeneity

We performed subgroup analysis by type of regimen, such as platinum-based chemotherapy and doxorubicin-based chemotherapy. We tested heterogeneity using both the Chi^2 test and the I^2 test. A significance level of less than 0.10 of Chi^2 was interpreted as evidence of heterogeneity. I^2 was used to estimate total variation across studies, where less than 30% is considered as low level of heterogeneity and higher than 50% as high level (Higgins 2002). If there was evidence of substantial heterogeneity, we investigated and reported the possible reasons for this.

Sensitivity analysis

We intended that if the eligibility of some studies in the meta-analysis had been dubious, sensitivity analysis might involve undertaking the meta-analysis twice: firstly including all studies and secondly only excluding studies that were of high risk of bias and had unadjusted results. We planned to report the sensitivity analyses in a summary table.

RESULTS

Description of studies

Results of the search

Since the last version of this review no new studies were identified for inclusion. In the last version search identified 718 citations and initially 559 were excluded through title and abstract screening. We then obtained full-text articles for the remaining 159 trials for further scrutiny. For this update, we identified an additional 722 citations trials but none of them were identified for inclusion. The flow chart on how the selection of studies was made can be found in Figure 1.

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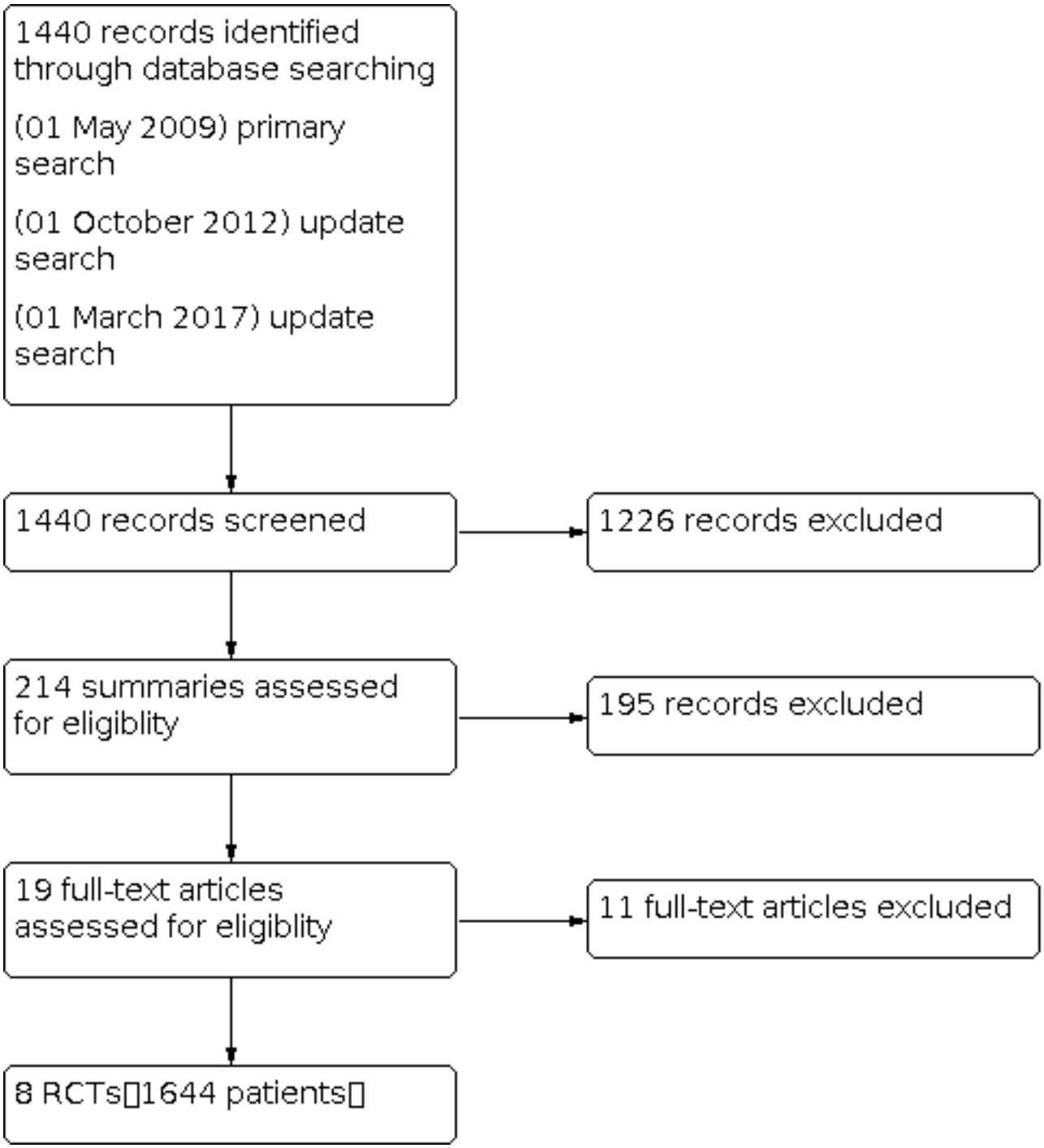
Figure 1. Studies Selection



Included studies

We identified eight RCTs and included data from 1644 women in this review. Seven trials compared maintenance chemotherapy with no further treatment (Bolis 2006; Cheng 2006; Mannel 2011; Nicoletto 2004; Pecorelli 2009; Piccart 2003; Placido 2004).

One study (Sorbe 2003) was a three-arm study comparing maintenance chemotherapy, maintenance radiotherapy and no further treatment. A total of 172 women were included, 98 with pathological complete remission (PCR) and 74 with complete clinical remission (CCR). The included women had endometrial ovarian cancer ranging from stage Ⅰc to stage Ⅳ. Women with stage Ⅲ to Ⅳ accounted for 89.9% of the total number of women included.

In addition, Piccart 2003 included women with non-epithelial cancer, but we included it because the percentage of participants with non-epithelial cancer was very small and there was no significant heterogeneity when compared with the other studies.

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Excluded studies

Eleven trials were initially identified as potentially eligible for inclusion but were subsequently found to be ineligible and therefore excluded (Abaid 2010; Cure 2001; Lesnock 2011; Mannel 2010; Markman 2003; Markman 2009; Scarfone 2002Bois 2014; Gordon 2011; Lee 2006; Suidan 2014). Reasons for exclusions are listed in the table of Characteristics of excluded studies.

Risk of bias in included studies

We summarised the risk of bias in included studies in Figure 2 and Figure 3.

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

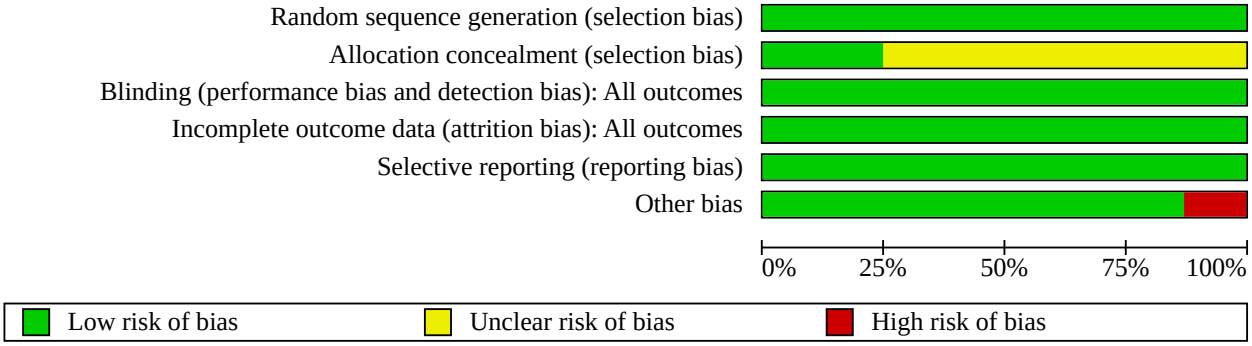

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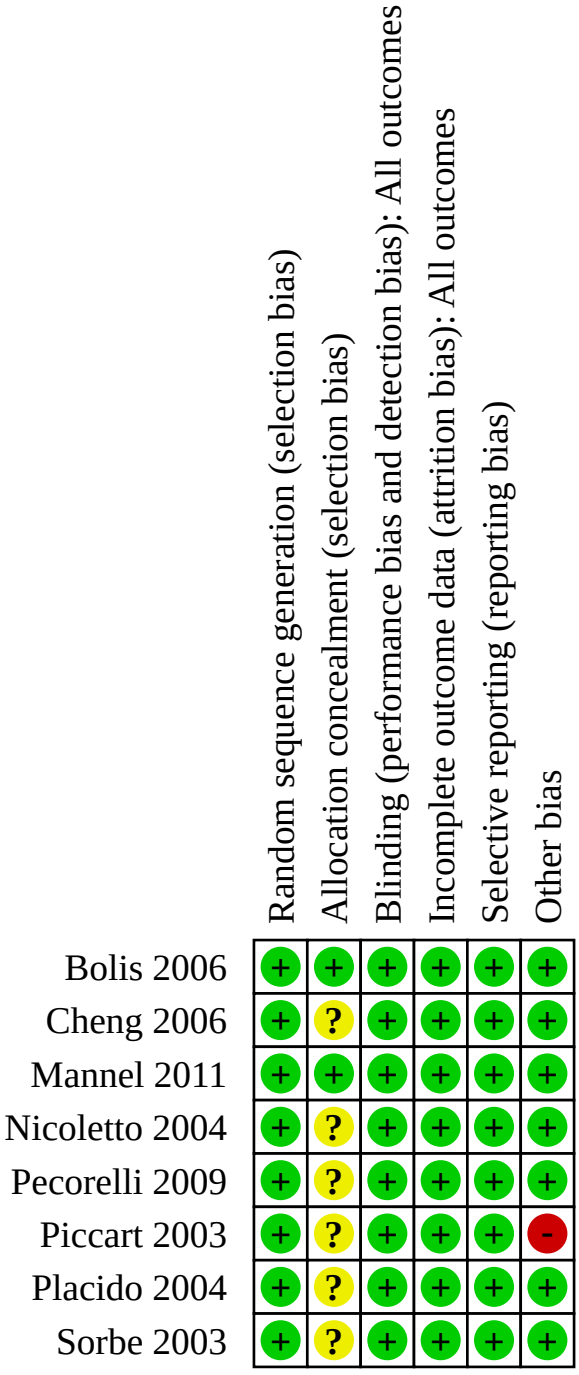
Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

All eight studies used randomised allocation, but only four described the randomisation method (Bolis 2006; Mannel 2011; Pecorelli 2009; Placido 2004) and two (Bolis 2006; Mannel 2011) had adequate allocation concealment. According to the assessment criteria, all could be judged with low risk of bias for sequence generation and unclear risk of bias for allocation concealment.

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Blinding

None of the included studies used blinding, but this is not likely to have influenced the results as the outcomes were overall survival (OS) and progression-free survival (PFS). We therefore judged the studies as having low risk of bias for blinding.

Incomplete outcome data

Two studies lost one patient to follow-up (Nicoletto 2004; Piccart 2003), but both used intention-to-treat (ITT) analysis and for OS and PFS the proportion of missing outcomes compared with observed event risk was not enough to have a clinically relevant impact on the intervention effect. One study had 32 patients who withdrew during the follow-up (Mannel 2011), but it was balanced between the treatment and the control arms, therefore, they were graded with low risk of bias.

Selective reporting

All expected outcomes were reported. There was no selective reporting identified for any of the studies.

Other potential sources of bias

Piccart 2003 had a high risk of bias as "the study was closed prematurely in view of a disappointing recruitment rate. …". The remaining studies appeared to be free of other sources of bias.

Effects of interventions

See: **Summary of findings 1** Maintenance chemotherapy versus observation; **Summary of findings 2** Platin-based maintenance chemotherapy versus observation; **Summary of findings 3** Doxorubicin-based maintenance chemotherapy versus observation; **Summary of findings 4** Maintenance chemotherapy compared to maintenance radiotherapy for epithelial ovarian cancer

Maintenance chemotherapy versus observation

Data were available on 1221 women from six of the included trials (Bolis 2006; Mannel 2011; Nicoletto 2004; Pecorelli 2009; Piccart 2003; Sorbe 2003). One trial used cisplatin alone (Piccart 2003), another studied epidoxorubicin (Bolis 2006), a third cisplatin-based combination chemotherapy (Nicoletto 2004), another trial used the regimen of cisplatin and doxorubicin (Sorbe 2003) and another two studies used paclitaxel (Mannel 2011; Pecorelli 2009). The intended number of courses ranged from three to six. Except for Mannel 2011, the other included studies had maintenance chemotherapy scheduled to start after the women had achieved PCR or CCR. There was no significant heterogeneity within each category of drugs. In addition, there was no difference in the three-, five- and 10-year PFS or OS. For the five-year PFS the combined risk ratio (RR) was 1.06 (95% confidence interval (CI) 0.97 to 1.17; 3 studies; 761 participants; moderate-certainty evidence) (Analysis 1.2) and for five-year OS, the combined RR was 1.03 (95% CI, 0.96 to 1.10; 4 studies, 899 participants; moderate-certainly evidence) (Analysis 1.5) (Summary of findings 1)

Two trials (Mannel 2011; Pecorelli 2009) that used paclitaxel were not combined in the analysis because there was significant heterogeneity between the stage of disease. Mannel 2011 included high-risk early-staged disease (stage I-A or B (grade 3 or clear cell), all I-C or II epithelial ovarian cancer) whereas, Pecorelli 2009 mainly included advanced staged disease. In addition, the regimens used in each study were different; Mannel 2011 used weekly low-dose paclitaxel (40 mg/m^2) and Pecorelli 2009 used six courses of paclitaxel (175 mg/m^2) at three-week intervals. Neither study indicated if paclitaxel could decrease the recurrence rate or increase the OS rate.

One trial (Cheng 2006) used a regimen of cisplatin and cyclophosphamide or taxol was also not included in the meta-analysis as it used different outcomes. The results indicated maintenance chemotherapy could prolong the time of progression-free interval (P = 0.033), while it had little effect on prolonging survival time (P = 0.22).

Another trial (Placido 2004) used topotecan and was not included in the meta-analysis because the follow-up duration was shorter and the outcomes could not be combined with other studies. It indicated that the one-year PFS was 60.4% and 65.4% in the topotecan and control arms, respectively and there was no significant difference between the arms.

Trials using cisplatin-based regimens

We analysed three studies including 341 women (Nicoletto 2004; Piccart 2003; Sorbe 2003) comparing cisplatin alone or combined with other drugs with no further treatment. Results were not conclusive and the 95% CI for absolute difference in OS was consistent with a 12% detriment to a 31% benefit of chemotherapy at five years. Similarly, the 95% CI for absolute difference in PFS is consistent with a 12% detriment to a 58% benefit at five years (Summary of findings 2).

Trials using doxorubicin-based regimens

We undertook a subgroup analysis of two studies including 204 women (Bolis 2006; Sorbe 2003) comparing doxorubicin-based maintenance chemotherapy with observation. Overall survival for three and five years was RR 1.00 (95% CI 0.86 to 1.15 and 0.79 to 1.27 respectively; 2 studies, 204 participants; moderate-certainty evidence) (Analysis 3.1; Analysis 3.2; Summary of findings 3).

Maintenance chemotherapy versus maintenance radiotherapy

One trial (Sorbe 2003) randomised 141 women into the chemotherapy and whole abdominal radiotherapy group. Sixty-seven women achieved PCR and the other 74 women CCR. There was considerable diversity of results across the two subgroups. The test for heterogeneity was significant for the combined RR for three- and 10-year PFS and 10-year OS. Ten-year PFS in the PCR group was in favour of whole abdominal radiotherapy (RR 0.51, 95% CI 0.27 to 1.00; low-certainty evidence) (Analysis 4.3) (Summary of findings 4). The other results showed no statistical difference between chemotherapy and radiotherapy in either group.

Maintenance chemotherapy versus other maintenance therapy

We found no eligible RCTs for this comparison.

Toxicity of maintenance chemotherapy

Seven trials described the toxicities of maintenance chemotherapy (Bolis 2006; Mannel 2011; Nicoletto 2004; Pecorelli 2009; Piccart 2003; Placido 2004; Sorbe 2003), but only one (Mannel 2011) made comparison between intervention and control groups. It reported that the incidence of grade 2 or worse peripheral neuropathy, infection or fever, and dermatologic events was significantly higher among patients treated on the maintenance weekly paclitaxel

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regimen (P < 0.001). There was also a slight incidence of grade 2 or worse cardiovascular events (P = 0.044) among those on the maintenance regimen. Grade 3 or 4 peripheral neuropathy was reported in 0.7% of the observation group compared to 4.4% of the maintenance paclitaxel group (P = 0.012).

One trial (Piccart 2003) used intraperitoneal cisplatin and reported that the main side effect was bowel obstruction due to intraperitoneal catheters. The most common toxicities of cisplatin were vomiting (82% grade 2) and renal toxicity (45% grade 2).

Another trial (Bolis 2006) using epidoxorubicin reported neutropenia, anaemia and thrombocytopenia and 41.9% of women had severe grade 4 neutropenia .

In the trial that used topotecan (Placido 2004), data were available for 112 out of 117 women in the experimental arm. Grade 3 to 4 neutropenia was recorded in 58% of women and 21% had grade 3 thrombocytopenia. Nausea and vomiting were the most frequent non-haematologic toxicities.

When comparing chemotherapy with radiotherapy, more side effects were recorded in the radiotherapy group, notably adverse gastro-intestinal effects. In the radiotherapy arm,14.5% of women had severe diarrhoea, bloody stools or bowel obstruction compared to 4.2% of women in the chemotherapy arm (P = 0.034).

DISCUSSION

Summary of main results

To date, there are no data which adequately support the use of platinum, doxorubicin or paclitaxel as maintenance chemotherapy for ovarian cancer.

When comparing maintenance chemotherapy with maintenance radiotherapy, the number of included women was too small to give an accurate results. However, from the subgroup analysis we may speculate that maintenance chemotherapy is more appropriate for women in complete clinical remission (CCR), while women in pathological complete remission (PCR) will benefit from maintenance radiotherapy.

The toxicity from platin was tolerable but the clinical application of doxorubicin and topotecan may be limited due to the severe bone marrow toxicity induced.

Overall completeness and applicability of evidence

This review was unable to address the issue of impact on quality of life (QoL) of maintenance chemotherapy due to a lack of trials reporting data relating to QoL. Therefore, it could not be addressed in the meta-analysis.

This review was unable to report on the results of meta-analysis of toxicity of maintenance chemotherapy as only one of the included trials (Mannel 2011) made comparison between the chemotherapy and observed groups. It was only possible to describe the observed toxicities during treatment.

This review was also unable to address the issue of whether maintenance chemotherapy is more effective than other maintenance therapy, especially biologic therapy because so far no RCT has focused on this topic.

Quality of the evidence

This meta-analysis is based on data from 1644 women, from eight RCTs that compared platinum-, doxorubicin- or paclitaxel-based maintenance chemotherapy with no further treatment in epithelial ovarian cancer. We employed a number of methods to try to identify all trials and included both published and unpublished data in this review; thereby minimising the influence of publication bias. Most of the included trials were downgraded as allocation concealment was unclear, therefore we downgraded the evidence to moderate quality. Although the number of included women is small, this meta-analysis currently provides a reliable assessment of the average treatment effect of platinum and doxorubicin among women with advanced epithelial ovarian cancer. For the comparison of maintenance chemotherapy with maintenance radiotherapy, the baseline is imbalanced so we downgraded the evidence to low quality. Further researches may change the estimate results..

Potential biases in the review process

Current practice prescribes that maintenance therapy begins after a woman achieves PCR or CCR but does not define how long the woman must be in remission before maintenance therapy is commenced. None of the trials included in this review described the exact start time of maintenance chemotherapy. It is widely accepted that the remission phase of platin-sensitive cases usually lasts more than six months. Therefore, if maintenance chemotherapy was started earlier than this, some platin non-sensitive cases may be included, which may introduce bias into the review.

Agreements and disagreements with other studies or reviews

The meta-analysis indicated that there has not been sufficient evidence to prove that maintenance chemotherapy using platin or doxorubicin for advanced epithelial ovarian cancer can improve the progression-free survival (PFS) or overall survival (OS). According to Markman 2003, 12 courses of paclitaxel can significantly prolong PFS rather than three courses. However, the control arm used three courses of maintenance chemotherapy but not observation and the trial was closed prematurely. So far, only one trial (Pecorelli 2009), studied paclitaxel as maintenance chemotherapy for advanced epithelial ovarian cancer but the results showed no survival benefit. One ongoing trial using paclitaxel as maintenance chemotherapy may provide new evidence (NCT00108745).

AUTHORS' CONCLUSIONS

Implications for practice

Since the last version of this review no new studies have been found, so there is still insufficient evidence to support the use of platin, doxorubicin or paclitaxel used as maintenance chemotherapy and is more effective than observation alone.

Implications for research

Considering the wide use of paclitaxel and its effectiveness during the induction phase of chemotherapy for advanced epithelial ovarian cancer, further studies on the effect of paclitaxel as maintenance chemotherapy should be investigated.

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Larger treatment effects are needed before there is convincing evidence that maintenance chemotherapy is beneficial. Any future high-quality trials should include QoL as this is an important consideration when prescribing maintenance chemotherapy.

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CHARACTERISTICS OF STUDIES

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

Bolis 2006

Study characteristics		
Methods	RCT	
Participants	138 women with epithelial ovarian cancer achieved PCR or CCR Stage 2c, 3 and 4 Mean age was 55.6 years old Median follow-up time was 40 months	
Interventions	Epidoxorubicin versus observation	
Outcomes	3-year OS and 5-year OS; toxic events	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated list
Allocation concealment (selection bias)	Low risk	Quote: "..according to a computer-generated list, by phone at the coordinating center" Comment: Probably done.
Blinding (performance bias and detection bias) All outcomes	Low risk	No blinding, but the outcome and the outcome measurement are not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported

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Bolis 2006 *(Continued)*

Other bias	Low risk	The study appears to be free of other sources of bias

Cheng 2006

Study characteristics		
Methods	RCT	
Participants	44 women with epithelial ovarian cancer achieved CCR Stage 3 and 4 Mean age was 53.8 years old in maintenance chemotherapy group and 53.7 in observation group Mean follow-up time was 39.6 months in maintenance chemotherapy group and 33.2 months in observation group	
Interventions	Platin + CTX/Taxel versus observation	
Outcomes	Recurrence rate, disease-free survival	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: " patients were randomly allocated" Comment: Probably done
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding (performance bias and detection bias) All outcomes	Low risk	No blinding, but the outcome and the outcome measurement are not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Mannel 2011

Study characteristics	
Methods	RCT
Participants	542 women with early stage of epithelial ovarian cancer.

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Mannel 2011 *(Continued)*

	stage IA or B grade 3 or clear cell subtype, or any stage IC, or stage II disease. Mean age was 55.1 years old in maintenance chemotherapy group and 56 in observation group Mean follow-up time was 6.7 years
Interventions	Weekly paclitaxel 40 mg/m² × 24 weeks versus observation
Outcomes	OS, PFS
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "treatment was randomly assigned through the GOG Statistical and Data Center prior to receiving any chemotherapy." Comment: Probably done
Allocation concealment (selection bias)	Low risk	Quote: "The treatment assignment was not revealed until after the patient was successfully registered onto the study" Comment: Probably done
Blinding (performance bias and detection bias) All outcomes	Low risk	No blinding, but the outcome and the outcome measurement are not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "18 patients randomized to the additional 24 weeks of paclitaxel withdrew during the follow-up,14 patients of the control group withdrew during the follow-up." Comment: It is balanced between the two groups
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Nicoletto 2004

Study characteristics

Methods	RCT
Participants	122 women with epithelial ovarian cancer achieved PCR Stage 1c, 2b, 2c, 3 and 4 Mean age was 55 years old Median follow-up time was not reported
Interventions	5-Fu + cisplatin versus observation

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Nicoletto 2004 *(Continued)*

Outcomes	3-year OS and 3-year PFS; toxic events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "…at time of randomization" Comment: Probably done
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding (performance bias and detection bias) All outcomes	Low risk	No blinding, but the outcome and the outcome measurement are not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "one patient refused treatment entirely after randomization and is therefore not evaluable" Comment: For OS and PFS, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate.
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Pecorelli 2009

Study characteristics

Methods	RCT
Participants	200 women with epithelial ovarian cancer Stage IIB–IV with PCR or CCR Mean age was 59 years old in maintenance chemotherapy group and 58 in observation group Median follow-up time was 43.5 months
Interventions	6 cycles of paclitaxel 175 mg/m^2 every 3 weeks versus observation
Outcomes	OS and PFS
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A system of random permuted blocks within strata was used."

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Pecorelli 2009 *(Continued)*

		Comment: Comment: Probably done
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding (performance bias and detection bias) All outcomes	Low risk	No blinding, but the outcome and the outcome measurement are not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "6% never started treatment, and a total of 17% stopped treatment early because of toxicity (9%), progression/death (3%), patient refusal (3%), or other reasons (2%)." Comment: For OS and PFS, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate.
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Piccart 2003

Study characteristics	
Methods	RCT
Participants	153 women with ovarian cancer achieved PCR Stage 2b, 2c, 3 and 4 Mean age was 55 years old Median follow-up time was 96.7 months
Interventions	Cisplatin versus observation
Outcomes	3-, 5-, 8-, 10-year OS and PFS; toxic events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "randomization took place…" Comment: Probably done
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding (performance bias and detection bias) All outcomes	Low risk	No blinding, but the outcome and the outcome measurement are not likely to be influenced by lack of blinding.

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Piccart 2003 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "one patient no follow-up forms. No statistically significant difference between the two groups"
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	High risk	Quote: "the study was closed prematurely in view of a disappointing recruitment rate…"

Placido 2004

Study characteristics		
Methods	RCT	
Participants	273 women with epithelial ovarian cancer achieved CCR or partial clinical remission Stage 1c, 2, 3 and 4 Mean age was 55 years old in maintenance chemotherapy group and 56 in observation group Median follow-up time was 28 months	
Interventions	Topotecan versus observation; toxic events	
Outcomes	1-year PFS	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "…by means of a computer-driven minimization procedure" Comment: Probably done
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding (performance bias and detection bias) All outcomes	Low risk	No blinding, but the outcome and the outcome measurement are not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

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Sorbe 2003

Study characteristics	
Methods	RCT
Participants	172 women with epithelial ovarian cancer achieved PCR and CCR Stage 3 and 4 Mean age was 55 years old Median follow-up time was not reported
Interventions	Cisplatin + doxorubicin/epidoxorubicin versus observation
Outcomes	3-, 5-, 10-year OS and PFS; toxic events
Notes	This study is a 3-arm study comparing maintenance chemotherapy, maintenance radiotherapy and no further treatment. The total partIcipants were 172 women with 98 of PCR and 74 of CCR. The women with PCR were divided into chemotherapy, radiotherapy and observation groups while the women with CCR were divided into chemotherapy and radiotherapy groups.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Patients…were entered in a prospective, randomized, multicenter trial" Comment: Probably done
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding (performance bias and detection bias) All outcomes	Low risk	No blinding, but the outcome and the outcome measurement are not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

CCR: complete clinical remission
GOG: Gynecologic Oncology Group
OS: overall survival
PCR: pathological complete remission
PFS: progression-free survival
RCT: randomised controlled trial

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

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Study	Reason for exclusion
Abaid 2010	The follow-up of Markman 2003 and the results were of high potential bias
Bois 2014	It compared pazopanib and placebo but pazopanib is not a chemotherapy drug.
Cure 2001	It compared high-dose chemotherapy combined with PBSC versus normal dose maintenance chemotherapy
Gordon 2011	The randomisation was before induced chemotherapy and maintenance therapy was prescribed based on the intention of patients.
Lee 2006	Not RCT
Lesnock 2011	A cost-effect analysis of three GOG studies
Mannel 2010	The same trial with the Mannel 2011 but not the final result
Markman 2003	It compared short- versus long-duration maintenance chemotherapy
Markman 2009	The follow-up of Markman 2003 and the results were of high potential bias
Scarfone 2002	The original article or data are unavailable
Suidan 2014	Retrospective study of GOG172, not a RCT.

GOG: Gynecologic Oncology Group
PBSC: peripheral blood stem cell
RCT: randomised controlled trial

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

NCT00108745

Study name	Paclitaxel or polyglutamate paclitaxel or observation in treating women with stage III or stage IV ovarian epithelial or peritoneal cancer
Methods	RCT
Participants	Women with advanced ovarian or primary peritoneal cancer who achieve a complete clinical response to primary platinum/taxane chemotherapy
Interventions	• Arm I: women receive polyglutamate paclitaxel IV over 10-20 minutes on day 1. • Arm II: women receive paclitaxel IV over 3 hours on day 1. • Arm III: women receive no further anticancer treatment until evidence of disease progression. In arms I and II, treatment repeats every 28 days for up to 12 courses in the absence of disease progression or unacceptable toxicity
Outcomes	Primary outcome measures: overall survival Secondary outcome measures: Peripheral neuropathy by Gynecologic Oncology Group (GOG) NTX4 at 6 months after study enrolment General quality of life by Functional Assessment of Cancer Therapy-Ovarian-Trial Outcome Index (FACT-O-TOI) at 6 months after study enrolment Exploratory assessment of several tissue and serum angiogenic markers for prognosis by immunohistochemistry and antibody array prior to treatment in courses 1 and 2

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NCT00108745 *(Continued)*	
	Exploratory time-dependent assessment of quality of life and peripheral neuropathy by FACT-O-TOI and GOG-NTX4 monthly during year 1 and then every 3 months for 2 years
Starting date	March 2005
Contact information	Study Chair: Maurie Markman, MD; M.D. Anderson Cancer Center
Notes	

IV: intravenous
RCT: randomised controlled trial

DATA AND ANALYSES

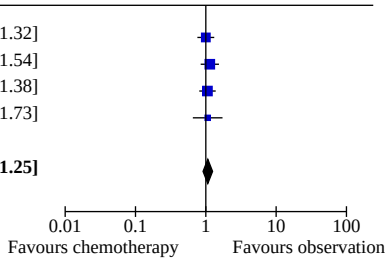
Comparison 1. Maintenance chemotherapy versus observation

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.1 3-year PFS	4	541	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.91, 1.25]
1.2 5-year PFS	3	761	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.97, 1.17]
1.3 10-year PFS	2	219	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.65, 1.41]
1.4 3-year OS	5	679	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.92, 1.08]
1.5 5-year OS	4	899	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.96, 1.10]
1.6 10-year OS	2	219	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.78, 1.49]

Analysis 1.1. Comparison 1: Maintenance chemotherapy versus observation, Outcome 1: 3-year PFS

Study or Subgroup	Maintenance chemotherapy Events	Total	Observation Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Nicoletto 2004	38	61	38	61	27.0%	1.00 [0.76 , 1.32]
Pecorelli 2009	50	101	43	99	30.9%	1.14 [0.85 , 1.54]
Piccart 2003	46	77	43	76	30.8%	1.06 [0.81 , 1.38]
Sorbe 2003	18	35	15	31	11.3%	1.06 [0.65 , 1.73]
Total (95% CI)		**274**		**267**	**100.0%**	**1.07 [0.91 , 1.25]**
Total events:	152		139			

Heterogeneity: Chi² = 0.41, df = 3 (P = 0.94); I² = 0%
Test for overall effect: Z = 0.82 (P = 0.41)
Test for subgroup differences: Not applicable



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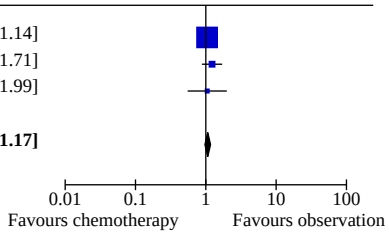
Analysis 1.2. Comparison 1: Maintenance chemotherapy versus observation, Outcome 2: 5-year PFS

Study or Subgroup	Maintenance chemotherapy Events	Total	Observation Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Mannel 2011	218	274	205	268	82.2%	1.04 [0.95 , 1.14]
Piccart 2003	41	77	33	76	13.2%	1.23 [0.88 , 1.71]
Sorbe 2003	13	35	11	31	4.6%	1.05 [0.55 , 1.99]
Total (95% CI)		**386**		**375**	**100.0%**	**1.06 [0.97 , 1.17]**
Total events:	272		249			

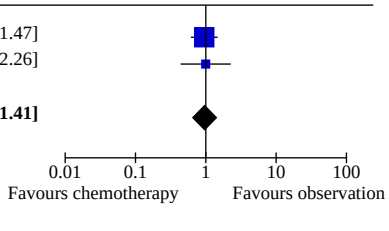
Heterogeneity: Chi² = 0.97, df = 2 (P = 0.62); I² = 0%
Test for overall effect: Z = 1.35 (P = 0.18)
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1: Maintenance chemotherapy versus observation, Outcome 3: 10-year PFS

Study or Subgroup	Maintenance chemotherapy Events	Total	Observation Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Piccart 2003	26	77	27	76	76.2%	0.95 [0.61 , 1.47]
Sorbe 2003	9	35	8	31	23.8%	1.00 [0.44 , 2.26]
Total (95% CI)		**112**		**107**	**100.0%**	**0.96 [0.65 , 1.41]**
Total events:	35		35			

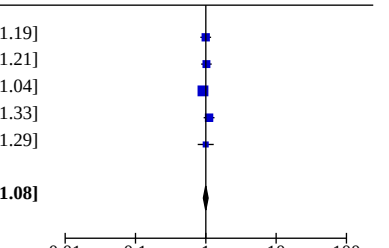
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.92); I² = 0%
Test for overall effect: Z = 0.20 (P = 0.84)
Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1: Maintenance chemotherapy versus observation, Outcome 4: 3-year OS

Study or Subgroup	Maintenance chemotherapy Events	Total	Observation Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bolis 2006	50	64	58	74	20.0%	1.00 [0.84 , 1.19]
Nicoletto 2004	50	61	49	61	18.2%	1.02 [0.86 , 1.21]
Pecorelli 2009	79	101	85	99	31.9%	0.91 [0.80 , 1.04]
Piccart 2003	62	77	55	76	20.5%	1.11 [0.93 , 1.33]
Sorbe 2003	27	35	24	31	9.4%	1.00 [0.77 , 1.29]
Total (95% CI)		**338**		**341**	**100.0%**	**1.00 [0.92 , 1.08]**
Total events:	268		271			

Heterogeneity: Chi² = 3.39, df = 4 (P = 0.49); I² = 0%
Test for overall effect: Z = 0.06 (P = 0.95)
Test for subgroup differences: Not applicable



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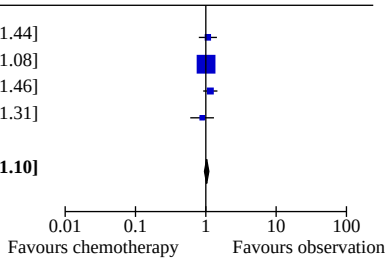
Analysis 1.5. Comparison 1: Maintenance chemotherapy versus observation, Outcome 5: 5-year OS

Study or Subgroup	Maintenance chemotherapy Events	Total	Observation Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bolis 2006	37	64	40	74	11.0%	1.07 [0.80 , 1.44]
Mannel 2011	236	274	229	268	68.9%	1.01 [0.94 , 1.08]
Piccart 2003	54	77	46	76	13.8%	1.16 [0.92 , 1.46]
Sorbe 2003	20	35	20	31	6.3%	0.89 [0.60 , 1.31]
Total (95% CI)		**450**		**449**	**100.0%**	**1.03 [0.96 , 1.10]**
Total events:	347		335			

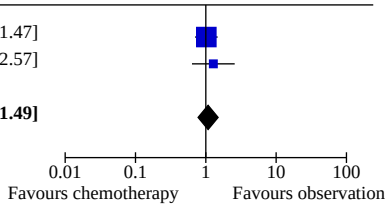
Heterogeneity: Chi² = 1.96, df = 3 (P = 0.58); I² = 0%
Test for overall effect: Z = 0.76 (P = 0.45)
Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1: Maintenance chemotherapy versus observation, Outcome 6: 10-year OS

Study or Subgroup	Maintenance chemotherapy Events	Total	Observation Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Piccart 2003	33	77	32	76	77.1%	1.02 [0.70 , 1.47]
Sorbe 2003	13	35	9	31	22.9%	1.28 [0.64 , 2.57]
Total (95% CI)		**112**		**107**	**100.0%**	**1.08 [0.78 , 1.49]**
Total events:	46		41			

Heterogeneity: Chi² = 0.32, df = 1 (P = 0.57); I² = 0%
Test for overall effect: Z = 0.45 (P = 0.65)
Test for subgroup differences: Not applicable



Comparison 2. Platin-based maintenance chemotherapy versus observation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 3-year PFS	3	341	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.86, 1.24]
2.2 5-year PFS	2	219	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.88, 1.58]
2.3 10-year PFS	2	219	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.65, 1.41]
2.4 3-year OS	3	341	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.94, 1.18]
2.5 5-year OS	2	219	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.88, 1.31]
2.6 10-year OS	2	219	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.78, 1.49]

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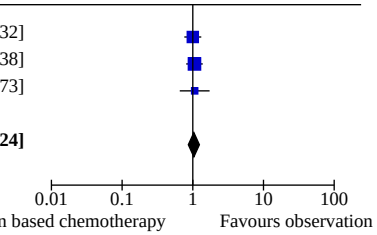
Analysis 2.1. Comparison 2: Platin-based maintenance chemotherapy versus observation, Outcome 1: 3-year PFS

Study or Subgroup	Platin based chemotherapy Events	Total	Observation Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Nicoletto 2004	38	61	38	61	39.1%	1.00 [0.76 , 1.32]
Piccart 2003	46	77	43	76	44.5%	1.06 [0.81 , 1.38]
Sorbe 2003	18	35	15	31	16.4%	1.06 [0.65 , 1.73]
Total (95% CI)		**173**		**168**	**100.0%**	**1.04 [0.86 , 1.24]**
Total events:	102		96			

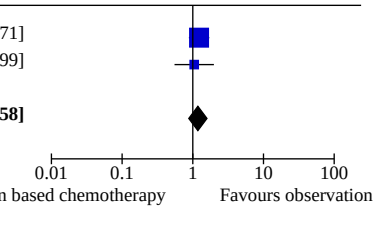
Heterogeneity: Chi² = 0.09, df = 2 (P = 0.95); I² = 0%
Test for overall effect: Z = 0.38 (P = 0.71)
Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2: Platin-based maintenance chemotherapy versus observation, Outcome 2: 5-year PFS

Study or Subgroup	Platin based chemotherapy Events	Total	Observation Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Piccart 2003	41	77	33	76	74.0%	1.23 [0.88 , 1.71]
Sorbe 2003	13	35	11	31	26.0%	1.05 [0.55 , 1.99]
Total (95% CI)		**112**		**107**	**100.0%**	**1.18 [0.88 , 1.58]**
Total events:	54		44			

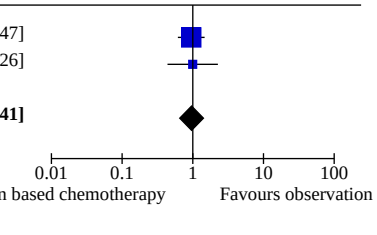
Heterogeneity: Chi² = 0.19, df = 1 (P = 0.67); I² = 0%
Test for overall effect: Z = 1.10 (P = 0.27)
Test for subgroup differences: Not applicable



Analysis 2.3. Comparison 2: Platin-based maintenance chemotherapy versus observation, Outcome 3: 10-year PFS

Study or Subgroup	Platin based chemotherapy Events	Total	Observation Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Piccart 2003	26	77	27	76	76.2%	0.95 [0.61 , 1.47]
Sorbe 2003	9	35	8	31	23.8%	1.00 [0.44 , 2.26]
Total (95% CI)		**112**		**107**	**100.0%**	**0.96 [0.65 , 1.41]**
Total events:	35		35			

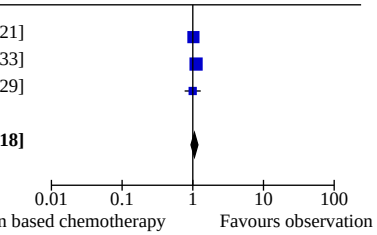
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.92); I² = 0%
Test for overall effect: Z = 0.20 (P = 0.84)
Test for subgroup differences: Not applicable



Analysis 2.4. Comparison 2: Platin-based maintenance chemotherapy versus observation, Outcome 4: 3-year OS

Study or Subgroup	Platin based chemotherapy Events	Total	Observation Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Nicoletto 2004	50	61	49	61	37.7%	1.02 [0.86 , 1.21]
Piccart 2003	62	77	55	76	42.6%	1.11 [0.93 , 1.33]
Sorbe 2003	27	35	24	31	19.6%	1.00 [0.77 , 1.29]
Total (95% CI)		**173**		**168**	**100.0%**	**1.06 [0.94 , 1.18]**
Total events:	139		128			

Heterogeneity: Chi² = 0.67, df = 2 (P = 0.71); I² = 0%
Test for overall effect: Z = 0.94 (P = 0.35)
Test for subgroup differences: Not applicable



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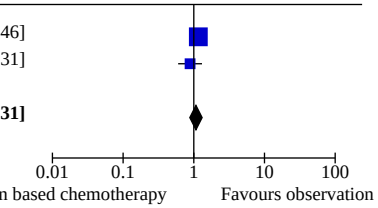
Analysis 2.5. Comparison 2: Platin-based maintenance chemotherapy versus observation, Outcome 5: 5-year OS

Study or Subgroup	Platin based chemotherapy Events	Total	Observation Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Piccart 2003	54	77	46	76	68.6%	1.16 [0.92 , 1.46]
Sorbe 2003	20	35	20	31	31.4%	0.89 [0.60 , 1.31]
Total (95% CI)		**112**		**107**	**100.0%**	**1.07 [0.88 , 1.31]**
Total events:	74		66			

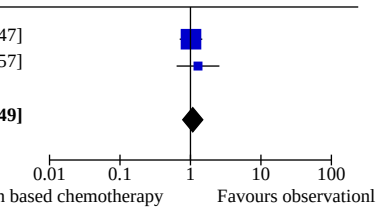
Heterogeneity: Chi² = 1.36, df = 1 (P = 0.24); I² = 26%
Test for overall effect: Z = 0.69 (P = 0.49)
Test for subgroup differences: Not applicable



Analysis 2.6. Comparison 2: Platin-based maintenance chemotherapy versus observation, Outcome 6: 10-year OS

Study or Subgroup	Platin based chemotherapy Events	Total	Observation Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Piccart 2003	33	77	32	76	77.1%	1.02 [0.70 , 1.47]
Sorbe 2003	13	35	9	31	22.9%	1.28 [0.64 , 2.57]
Total (95% CI)		**112**		**107**	**100.0%**	**1.08 [0.78 , 1.49]**
Total events:	46		41			

Heterogeneity: Chi² = 0.32, df = 1 (P = 0.57); I² = 0%
Test for overall effect: Z = 0.45 (P = 0.65)
Test for subgroup differences: Not applicable



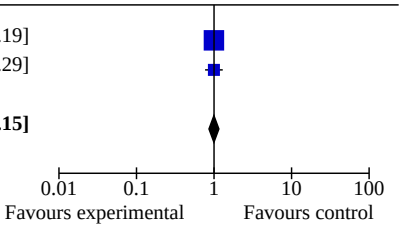
Comparison 3. Doxorubicin-based maintenance chemotherapy versus observation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 3-year OS	2	204	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.86, 1.15]
3.2 5-year OS	2	204	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.79, 1.27]

Analysis 3.1. Comparison 3: Doxorubicin-based maintenance chemotherapy versus observation, Outcome 1: 3-year OS

Study or Subgroup	Doxorubicin based Events	Total	Observation Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bolis 2006	50	64	58	74	67.9%	1.00 [0.84 , 1.19]
Sorbe 2003	27	35	24	31	32.1%	1.00 [0.77 , 1.29]
Total (95% CI)		**99**		**105**	**100.0%**	**1.00 [0.86 , 1.15]**
Total events:	77		82			

Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.04 (P = 0.96)
Test for subgroup differences: Not applicable



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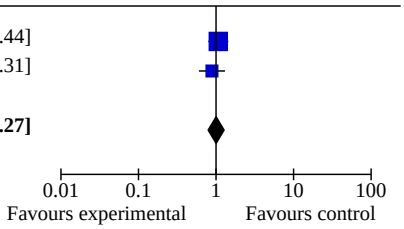
Analysis 3.2. Comparison 3: Doxorubicin-based maintenance chemotherapy versus observation, Outcome 2: 5-year OS

Study or Subgroup	Doxorubicin based Events	Total	Observation Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bolis 2006	37	64	40	74	63.6%	1.07 [0.80 , 1.44]
Sorbe 2003	20	35	20	31	36.4%	0.89 [0.60 , 1.31]
Total (95% CI)		**99**		**105**	**100.0%**	**1.00 [0.79 , 1.27]**
Total events:	57		60			

Heterogeneity: Chi² = 0.57, df = 1 (P = 0.45); I² = 0%
Test for overall effect: Z = 0.02 (P = 0.98)
Test for subgroup differences: Not applicable



Comparison 4. Maintenance chemotherapy versus maintenance radiotherapy

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
4.1 3-year PFS	1	141	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.75, 1.54]
4.1.1 PCR	1	67	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.50, 1.11]
4.1.2 CCR	1	74	Risk Ratio (M-H, Fixed, 95% CI)	2.14 [0.99, 4.64]
4.2 5-year PFS	1	141	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.55, 1.37]
4.2.1 PCR	1	67	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.39, 1.12]
4.2.2 CCR	1	74	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [0.59, 3.79]
4.3 10-year PFS	1	141	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.51, 1.55]
4.3.1 PCR	1	67	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.27, 1.00]
4.3.2 CCR	1	74	Risk Ratio (M-H, Fixed, 95% CI)	4.00 [0.91, 17.59]
4.4 3-year OS	1	141	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.85, 1.32]
4.4.1 PCR	1	67	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.72, 1.16]
4.4.2 CCR	1	74	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.84, 1.94]
4.5 5-year OS	1	141	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.70, 1.35]
4.5.1 PCR	1	67	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.57, 1.20]
4.5.2 CCR	1	74	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.68, 2.29]
4.6 10-year OS	1	141	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.58, 1.52]
4.6.1 PCR	1	67	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.41, 1.20]
4.6.2 CCR	1	74	Risk Ratio (M-H, Fixed, 95% CI)	2.00 [0.66, 6.07]

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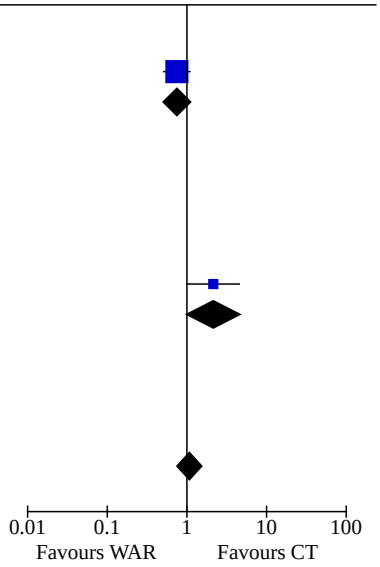
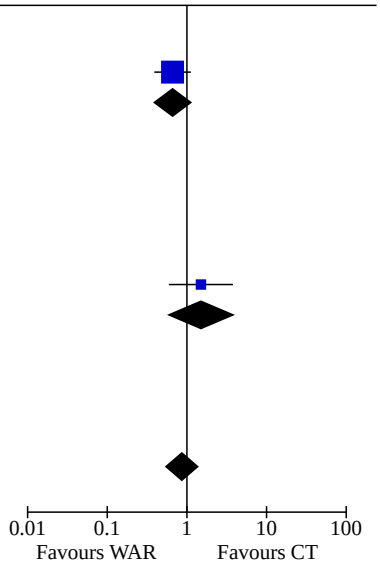
Analysis 4.1. Comparison 4: Maintenance chemotherapy versus maintenance radiotherapy, Outcome 1: 3-year PFS

Study or Subgroup	CT Events	CT Total	WAR Events	WAR Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.1.1 PCR						
Sorbe 2003	18	35	22	32	76.7%	0.75 [0.50 , 1.11]
Subtotal (95% CI)		**35**		**32**	**76.7%**	**0.75 [0.50 , 1.11]**
Total events:	18		22			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.43 (P = 0.15)						
4.1.2 CCR						
Sorbe 2003	15	37	7	37	23.3%	2.14 [0.99 , 4.64]
Subtotal (95% CI)		**37**		**37**	**23.3%**	**2.14 [0.99 , 4.64]**
Total events:	15		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.93 (P = 0.05)						
Total (95% CI)		**72**		**69**	**100.0%**	**1.07 [0.75 , 1.54]**
Total events:	33		29			
Heterogeneity: Chi² = 6.24, df = 1 (P = 0.01); I² = 84%						
Test for overall effect: Z = 0.39 (P = 0.70)						
Test for subgroup differences: Chi² = 5.63, df = 1 (P = 0.02), I² = 82.2%						



Analysis 4.2. Comparison 4: Maintenance chemotherapy versus maintenance radiotherapy, Outcome 2: 5-year PFS

Study or Subgroup	CT Events	CT Total	WAR Events	WAR Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.2.1 PCR						
Sorbe 2003	13	35	18	32	75.8%	0.66 [0.39 , 1.12]
Subtotal (95% CI)		**35**		**32**	**75.8%**	**0.66 [0.39 , 1.12]**
Total events:	13		18			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.54 (P = 0.12)						
4.2.2 CCR						
Sorbe 2003	9	37	6	37	24.2%	1.50 [0.59 , 3.79]
Subtotal (95% CI)		**37**		**37**	**24.2%**	**1.50 [0.59 , 3.79]**
Total events:	9		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.86 (P = 0.39)						
Total (95% CI)		**72**		**69**	**100.0%**	**0.86 [0.55 , 1.37]**
Total events:	22		24			
Heterogeneity: Chi² = 2.35, df = 1 (P = 0.13); I² = 58%						
Test for overall effect: Z = 0.63 (P = 0.53)						
Test for subgroup differences: Chi² = 2.27, df = 1 (P = 0.13), I² = 56.0%						



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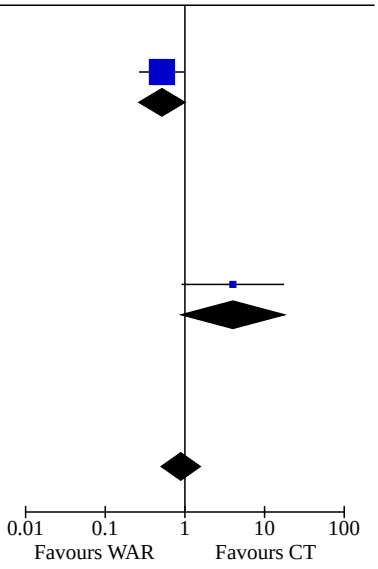
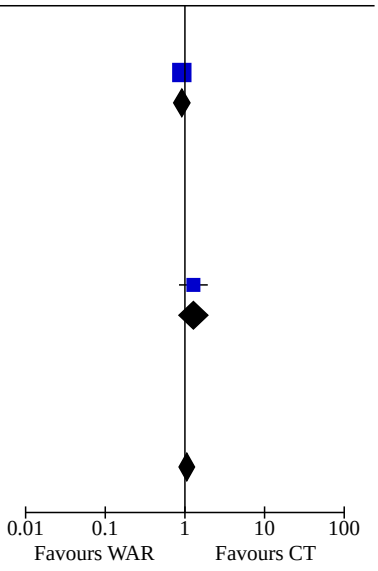
Analysis 4.3. Comparison 4: Maintenance chemotherapy versus maintenance radiotherapy, Outcome 3: 10-year PFS

Study or Subgroup	CT Events	CT Total	WAR Events	WAR Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.3.1 PCR						
Sorbe 2003	9	35	16	32	89.3%	0.51 [0.27 , 1.00]
Subtotal (95% CI)		**35**		**32**	**89.3%**	**0.51 [0.27 , 1.00]**
Total events:	9		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.97 (P = 0.05)						
4.3.2 CCR						
Sorbe 2003	8	37	2	37	10.7%	4.00 [0.91 , 17.59]
Subtotal (95% CI)		**37**		**37**	**10.7%**	**4.00 [0.91 , 17.59]**
Total events:	8		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.83 (P = 0.07)						
Total (95% CI)		**72**		**69**	**100.0%**	**0.89 [0.51 , 1.55]**
Total events:	17		18			
Heterogeneity: Chi² = 6.58, df = 1 (P = 0.01); I² = 85%						
Test for overall effect: Z = 0.42 (P = 0.67)						
Test for subgroup differences: Chi² = 6.15, df = 1 (P = 0.01), I² = 83.7%						



Analysis 4.4. Comparison 4: Maintenance chemotherapy versus maintenance radiotherapy, Outcome 4: 3-year OS

Study or Subgroup	CT Events	CT Total	WAR Events	WAR Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.4.1 PCR						
Sorbe 2003	27	35	27	32	61.0%	0.91 [0.72 , 1.16]
Subtotal (95% CI)		**35**		**32**	**61.0%**	**0.91 [0.72 , 1.16]**
Total events:	27		27			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.75 (P = 0.45)						
4.4.2 CCR						
Sorbe 2003	23	37	18	37	39.0%	1.28 [0.84 , 1.94]
Subtotal (95% CI)		**37**		**37**	**39.0%**	**1.28 [0.84 , 1.94]**
Total events:	23		18			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.16 (P = 0.25)						
Total (95% CI)		**72**		**69**	**100.0%**	**1.06 [0.85 , 1.32]**
Total events:	50		45			
Heterogeneity: Chi² = 2.26, df = 1 (P = 0.13); I² = 56%						
Test for overall effect: Z = 0.48 (P = 0.63)						
Test for subgroup differences: Chi² = 1.89, df = 1 (P = 0.17), I² = 47.1%						



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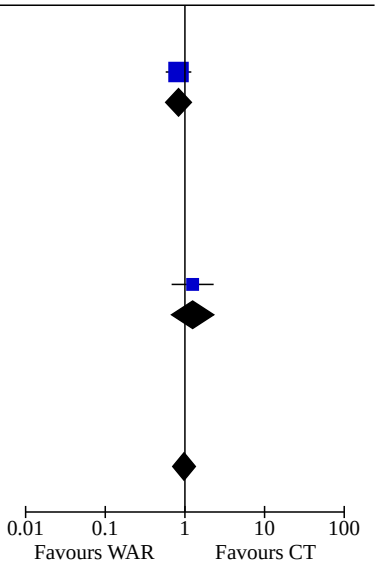
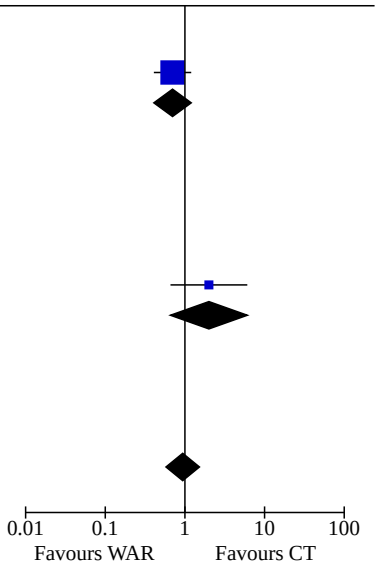
Analysis 4.5. Comparison 4: Maintenance chemotherapy versus maintenance radiotherapy, Outcome 5: 5-year OS

Study or Subgroup	CT Events	CT Total	WAR Events	WAR Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.5.1 PCR						
Sorbe 2003	20	35	22	32	65.7%	0.83 [0.57 , 1.20]
Subtotal (95% CI)		**35**		**32**	**65.7%**	**0.83 [0.57 , 1.20]**
Total events:	20		22			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.98 (P = 0.33)						
4.5.2 CCR						
Sorbe 2003	15	37	12	37	34.3%	1.25 [0.68 , 2.29]
Subtotal (95% CI)		**37**		**37**	**34.3%**	**1.25 [0.68 , 2.29]**
Total events:	15		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.72 (P = 0.47)						
Total (95% CI)		**72**		**69**	**100.0%**	**0.97 [0.70 , 1.35]**
Total events:	35		34			
Heterogeneity: Chi² = 1.36, df = 1 (P = 0.24); I² = 26%						
Test for overall effect: Z = 0.15 (P = 0.88)						
Test for subgroup differences: Chi² = 1.27, df = 1 (P = 0.26), I² = 21.0%						



Analysis 4.6. Comparison 4: Maintenance chemotherapy versus maintenance radiotherapy, Outcome 6: 10-year OS

Study or Subgroup	CT Events	CT Total	WAR Events	WAR Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.6.1 PCR						
Sorbe 2003	13	35	17	32	81.6%	0.70 [0.41 , 1.20]
Subtotal (95% CI)		**35**		**32**	**81.6%**	**0.70 [0.41 , 1.20]**
Total events:	13		17			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.30 (P = 0.19)						
4.6.2 CCR						
Sorbe 2003	8	37	4	37	18.4%	2.00 [0.66 , 6.07]
Subtotal (95% CI)		**37**		**37**	**18.4%**	**2.00 [0.66 , 6.07]**
Total events:	8		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.22 (P = 0.22)						
Total (95% CI)		**72**		**69**	**100.0%**	**0.94 [0.58 , 1.52]**
Total events:	21		21			
Heterogeneity: Chi² = 2.92, df = 1 (P = 0.09); I² = 66%						
Test for overall effect: Z = 0.26 (P = 0.80)						
Test for subgroup differences: Chi² = 2.78, df = 1 (P = 0.10), I² = 64.1%						



APPENDICES

Appendix 1. MEDLINE search strategy

#1 exp Ovarian Neoplasms/

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#2 (ovar* adj5 (cancer* or tumor* or tumour* or malignan* or neoplas* or carcinoma*)).mp.
#3 1 or 2
#4 drug therapy.fs.
#5 exp Antineoplastic Agents/
#6 Antineoplastic Combined Chemotherapy Protocols/
#7 chemotherap*.mp.
#8 4 or 5 or 6 or 7
#9 (maintain or maintenance or consolidat*).mp.
#10 3 and 8 and 9
#11 randomized controlled trial.pt.
#12 controlled clinical trial.pt.
#13 randomized.ab.
#14 placebo.ab.
#15 drug therapy.fs.
#16 randomly.ab.
#17 trial.ab.
#18 groups.ab.
#19 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
#20 10 and 19
key:
mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier
pt=publication type
fs=floating subheading
ab=abstract

Appendix 2. CENTRAL search strategy

#1 MeSH descriptor: [Ovarian Neoplasms] explode all trees
#2 ovar* near/5 (cancer* or tumor* or tumour* or malignan* or neoplas* or carcinoma*)
#3 #1 or #2
#4 Any MeSH descriptor with qualifier(s): [Drug therapy - DT] in all MeSH products
#5 MeSH descriptor: [Antineoplastic Agents] explode all trees
#6 MeSH descriptor: [Antineoplastic Combined Chemotherapy Protocols] this term only
#7 chemotherap*
#8 #4 or #5 or #6
#9 maintain or maintenance or consolidat*
#10 #3 and #8 and #9

Appendix 3. Embase search strategy

#1 exp ovary tumor/
#2 (ovar* adj5 (cancer* or tumor* or tumour* or malignan* or neoplas* or carcinoma*)).mp.
#3 1 or 2
#4 dt.fs.
#5 exp antineoplastic agent/
#6 chemotherap*.mp.
#7 4 or 5 or 6
#8 (maintain or maintenance or consolidat*).mp.
#9 3 and 7 and 8
#10 crossover procedure/
#11 double-blind procedure/
#12 randomized controlled trial/
#13 single-blind procedure/
#14 random*.mp.
#15 factorial*.mp.
#16 (crossover* or cross over* or cross-over*).mp.
#17 placebo*.mp.
#18 (double* adj blind*).mp.
#19 (singl* adj blind*).mp.
#20 assign*.mp.
#21 allocat*.mp.
#22 volunteer*.mp.

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#23 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
#24 9 and 23
key:
mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword

Appendix 4. CNKI,VIP and CBMdisc

#1 ovarian cancer
#2 ovarian tumor
#3 maintenance therapy
#4 maintenance chemotherapy
#5 maintenance radiotherapy
#6 consolidation therapy
#7 consolidation chemotherapy
#8 consolidation radiotherapy
#9 or/1 2
#10 or/3 8
#11 9 and 10

WHAT'S NEW

Date	Event	Description
12 January 2022	Amended	Author by-line corrected.
12 January 2022	Review declared as stable	This review will be superseded by updates of the following reviews: Angiogenesis inhibitors for the treatment of ovarian cancer [10.1002/14651858.CD007930.pub2] and Poly(ADP-ribose) polymerase (PARP) inhibitors for the treatment of ovarian cancer [10.1002/14651858.CD007929.pub3].

HISTORY

Protocol first published: Issue 4, 2008
Review first published: Issue 9, 2010

Date	Event	Description
6 November 2017	New citation required but conclusions have not changed	No new studies identified for inclusion. Text updated as required and summary of findings tables added.
7 February 2017	New search has been performed	New searches run.
5 June 2013	Amended	Minor amendment to PLS
29 May 2013	New citation required but conclusions have not changed	Two studies added but conclusions remain unchanged.
5 May 2013	New search has been performed	Review updated, new searches run and text revised.
5 August 2010	Amended	EMBASE search strategy added.

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CONTRIBUTIONS OF AUTHORS

Mei Ling and Chen Hui were responsible for searching for studies, quality assessment, data extraction, data analysis and review development. Fang Fang offered clinical expertise and took part in the development of this review. Wei Dongmei, Zou Juan and Han Xu undertook searching for studies and quality assessment. Feng Dan, Xie Huanyu, Wang Xun and Chen Hui participated in data extraction and analysis. Liu Guan Jian offered methodological expertise. For the update, Mei Ling and Wei Dongmei were responsible for searching for studies, quality assessment, data extraction and data analysis. Mei Ling was in charge of revising the text.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- West China Second Hospital, China

External sources

- No sources of support provided

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

For the assessment of risk of bias in included studies, we changed the original five criteria to six criteria according to the guidelines of *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011)

INDEX TERMS

Medical Subject Headings (MeSH)

Antineoplastic Agents [*therapeutic use]; Disease-Free Survival; Maintenance Chemotherapy [adverse effects] [*methods]; Ovarian Neoplasms [*drug therapy] [mortality] [radiotherapy]; Quality of Life; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans

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