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Evaluation of follow-up strategies for women with epithelial ovarian cancer following completion of primary treatment (Review)

Zachou G, El-Khouly F, Dilley J

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[Intervention Review]

Evaluation of follow-up strategies for women with epithelial ovarian cancer following completion of primary treatment

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ABSTRACT

Background

This is an update of a previous Cochrane Review, last updated in 2014. Ovarian cancer is the eighth most common cancer and seventh most common cause of death due to cancer in women worldwide. Traditionally, most women who have been treated for cancer undergo long-term follow-up in secondary care. However, it has been suggested that the use of routine review may not be effective in improving survival, or health-related quality of life (HRQOL), or relieving anxiety. In addition, traditional follow-up may not be cost-effective.

Objectives

To compare the potential effects of different strategies of follow-up in women with epithelial ovarian cancer, following completion of primary treatment.

Search methods

For this update, we searched the Cochrane Gynaecological Cancer Group Trials Register, CENTRAL 2022, Issue 11, MEDLINE, and Embase from August 2013 to November 2022. We also searched review articles and contacted experts in the field.

Selection criteria

All randomised controlled trials (RCTs) that evaluated follow-up strategies for women with epithelial ovarian cancer following completion of primary treatment.

Data collection and analysis

We followed standard Cochrane methodology. Two review authors independently selected potentially relevant trials, extracted data, and assessed risk of bias. They compared results, and resolved disagreements by discussion. We assessed the certainty of evidence, using the GRADE approach, for the outcomes of interest: overall survival (OS), health-related quality of life (HRQOL), psychological effects, and cost analysis.

Main results

For this update, we included one new RCT, including 112 women with ovarian, fallopian tube, or peritoneal cancer, who had completed primary treatment by surgery, with or without chemotherapy. This study reported the effect of individualised, i.e. individually tailored, nurse-led follow-up versus conventional medical follow-up on HRQOL, psychological outcomes, and cost-analysis.

Individualised follow-up improved HRQOL in one of the two scales, with a decrease in mean difference (MD) in the QLQ-C30 discomfort scale following 12 months of individualised treatment compared to 12 months of conventional treatment (MD -5.76 points, 95% confidence interval (CI) -10.92 to -0.60; 1 study, 112 participants; low-certainty evidence; minimal important difference 4 to 10 points). There may be little or no difference in the other HRQOL scale (QLQ-Ov28, MD -0.97 points, 95% CI -2.57 to 0.63; 1 study, 112 participants: low-certainty evidence); psychological outcome, measured with the hospital anxiety and depression scale (HADS; MD 0.10 point, 95% CI -0.81 to 1.02; 1 study, 112 participants: low-certainty evidence), or cost analysis (MD -GBP 695.00, 95% CI -1467.23 to 77.23; 1 study, 112 participants: moderate-certainty evidence).

Our previous review included one RCT, with 529 women in a confirmed remission, with normal CA125 concentration and no radiological evidence of disease, after surgery and first-line chemotherapy for ovarian cancer. This study evaluated immediate treatment of ovarian cancer relapse following a rise of serum CA125 levels versus delaying treatment until symptoms developed for OS, and HRQOL.

There was little or no difference in OS between the immediate and delayed arms after a median follow-up of 56.9 months (unadjusted hazard ratio (HR) 0.98, 95% CI 0.80 to 1.20; 1 study, 529 participants; moderate-certainty evidence). Time from randomisation to first deterioration in global health score or death was shorter in the immediate treatment group than in the delayed treatment group (HR 0.71, 95% CI 0.58 to 0.88).

Authors' conclusions

Limited evidence from one trial suggests that routine surveillance with CA125 in asymptomatic women and treatment at CA125-defined relapse does not seem to offer survival advantage when compared to treatment at symptomatic relapse. However, this study pre-dates the use of PARPi maintenance treatment and the increased use of secondary cytoreductive surgery, so the results may be limited in their applicability to current practice.

Limited evidence from one trial suggests that individualised nurse-led follow-up may improve HRQOL in women with ovarian cancer following completion of primary treatment.

Large RCTs are needed to compare different types of follow-up, looking at survival, HRQOL, psychological effects, and cost as outcomes.

PLAIN LANGUAGE SUMMARY

Evaluation of follow-up strategies for women with epithelial ovarian cancer following completion of primary treatment

Key messages

Early chemotherapy for recurrences of ovarian cancer may not prolong life and may reduce quality of life. Note that this trial took place prior to current treatment, so may not apply for women being treated for ovarian cancer today.

Individualised nurse-led follow-up after treatment may improve quality of life more than regular medical follow-up, but may not make much difference for anxiety, depression, or cost.

What did we want to find out?

Ovarian cancer is the eighth most common cancer, and seventh most common cause of cancer death in women worldwide. Traditionally, women were followed up after their treatment in hospital outpatient departments. We wanted to evaluate the evidence for different types of follow-up for women who had completed treatment for the most common type of ovarian cancer.

What did we do?

We searched the medical literature for studies that evaluated different types of follow-up for women who had undergone treatment for ovarian cancer. We assessed their limitations, summarised their results, and assessed how certain we were in the evidence for: overall survival, health-related quality of life, psychological effects (for example, anxiety, depression), and cost-effectiveness.

What did we find?

We found two randomised studies, in which women who had completed their treatment for ovarian cancer were randomly assigned to one of two follow-up groups. Each study examined two different types of follow-up, so we had to examine each study separately, rather than pooling their results.

Limited evidence from one study suggests that regardless of whether women receive chemotherapy immediately after discovering their cancer has recurred (identified by the increase of a tumour marker in the blood, called CA125), or delay treatment until they develop symptoms, there is no real difference in how long they survive. Early treatment of recurrence with chemotherapy may reduce overall quality of life.

Limited evidence from one study suggests that women who receive individualised nurse-led follow-up report better health-related quality of life outcomes compared to those who receive conventional medical follow-up. Psychological effects (anxiety and depression) and costs were similar in both groups of women.

What are the limitations of the evidence?

There is limited evidence from these two trials regarding the appropriate follow-up for women with ovarian cancer. The certainty of the evidence ranges from low to moderate, due to risk of bias and imprecision. Also, these trials pre-date other studies that demonstrate a benefit to maintenance treatment (medicines to reduce tumour growth that are continued after routine chemotherapy is finished), and studies that demonstrate a benefit to further surgery at the time of relapse for some women with low volume disease, who may not be symptomatic. Whether the results of the follow-up studies would apply now, with these new treatment options available at relapse, is uncertain.

How up to date is this evidence?

November 2022

Summary of findings 1. Immediate versus delayed treatment for women with epithelial ovarian cancer following completion of primary treatment

Outcome	Anticipated absolute effects[a] (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty	What happens
	Risk with delayed treatment	Risk with immediate treatment				
Overall survival	Study Population		HR 0.98 (0.80 to 1.20) [Overall survival]	529 (1 RCT)	⊕⊕⊕ Moderate[b]	Delayed treatment in women with increased CA125 after completion of primary treatment for ovarian cancer likely results in little to no difference in overall survival.
	697 per 1000	701 per 1000 (624 to 775)				
Health-related quality of life assessed wih EORTC QLQ-C30	Time from randomisation to first deterioration		HR 0.71 (0.58 to 0.88)	529 (1 RCT)	⊕⊕◯◯ Low[c]	Time from randomisation to first deterioration in global health score (defined as more than 10% decrease from pre-randomisation score or death), or death was shorter in the immediate treatment group than in the delayed treatment group.
	3.2 months	5.8 months				
Psychological effects	-	-	-	-	-	Outcome not assessed
Cost analysis	-	-	-	-	-	Outcome not assessed

GRADE Working Group definitions

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect

Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect

CI: confidence interval; EORTC QLQ-C: European Organisation for Research and Treatment of Cancer Core Quality of Life; HR: hazard ratio; RCT: randomised controlled trial

[a]Absolute risk for death was calculated using the formula proposed by Tierney 2007 per 1000 = 1000 - (exp[ln(1 - proportion of women with event) x HR]) x 1000.
[b]Downgraded by one level for imprecision due to wide confidence interval and single study.
[c]Downgraded by two levels for risk of bias (lack of blinding in outcome assessment) and imprecision (single study).

Summary of findings 2. Individualised nurse-led follow-up versus conventional medical follow-up for women with epithelial ovarian cancer following completion of primary treatment

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty	What happens
	Risk with conventional medical follow-up	Risk with individualised nurse-led follow-up				
Overall survival	-	-	-	-	-	Outcome not assessed
HRQOL assessed with QLQ-C30 *(assessed at 12 months)*		MD 5.76 points lower (10.92 lower to 0.60 lower)	-	112 (1 RCT)	⊕⊕◯◯ Low[a,b]	Individualised follow-up may improve HRQOL, but the evidence is uncertain. Musoro 2020 reported that the marginally important difference for women with ovarian cancer ranged from 4 to 10 points.
HRQOL assessed with QLQ-Ov28 *(assessed at 12 months)*		MD 0.972 points lower (2.57 lower to 0.63 higher)	-	112 (1 RCT)	⊕⊕◯◯ Low[a,b]	Individualised follow-up may have little or no effect on HRQOL, but the evidence is uncertain.
Psychological effect assessed with the HAD *(assessed at 12 months)*		MD 0.1 points higher (0.81 lower to 1.02 higher)	-	112 (1 RCT)	⊕⊕◯◯ Low[a,b]	Individualised follow-up may have little or no effect on the HAD score at 12 months, but the evidence is uncertain.
Cost analysis assessed in British pounds		MD 695 British pounds lower (1467 lower to 77 higher)	-	112 (1 RCT)	⊕⊕⊕◯ Moderate[b]	Individualised follow-up probably has little or no effect on cost.

GRADE Working Group definitions

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect

Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect

CI: confidence interval; HAD: hospital anxiety and depression; HRQOL: health-related quality of life; MD: mean difference; RCT: randomised controlled trial

[a]Downgraded by one level for risk of bias, due to unblinded study design, which may have had an impact on some outcomes and unclear risk for attrition and other biases.
[b]Downgraded by one level for imprecision due to small study sample and single study.

BACKGROUND

Description of the condition

Ovarian cancer is the eighth most common, and the seventh deadliest cancer amongst women (GLOBOCAN 2020). Worldwide, there are more than 300,000 new cases of ovarian cancer diagnosed each year, accounting for around 3.5% of all cancers diagnosed in women. A woman's risk of developing cancer of the ovaries by the age of 75 varies between countries, and ranges from 0.2% to 1.7% (IARC 2021). This corresponds to an age-standardised rate of ovarian cancer of between 2 and 15 cases per 100,000 women under 75 years of age per year. Globally, the estimated lifetime risk for a woman developing ovarian cancer is 1 in 85 women (GLOBOCAN 2020). In Europe, 33% to 42% of women with ovarian cancer are alive five years after diagnosis (CRUK 2022; EUROCARE 2015). The poor survival associated with ovarian cancer is largely because most women are diagnosed when the cancer is at an advanced stage (Siegel 2023).

Description of the intervention

Traditionally, most people who have been treated for cancer undergo long-term, even life-long, follow-up in secondary care (Kew 2006; Leeson 2013; Schneider 2020). The rationale is that if a recurrence of cancer is picked up early, i.e. before the onset of symptoms, it is more likely to be amenable to treatment and therefore, survival rates will be improved (Harter 2021). Furthermore, it is proposed that this routine review provides other opportunities, including management of symptoms – either from the disease itself, or from side effects of treatment – and access to supportive and palliative care. Women may also be reassured that the cancer has not returned, which maintains their psychological well-being; these appointments also allow for the collection of outcome data, and provide positive feedback for the clinicians involved in the person's care (Kerr-Wilson 1995; Sandell 2022).

It has been suggested that the use of routine review may not be effective in achieving the aims listed above. Detection of recurrence may even be delayed, as some women will not present with symptoms until their next routine appointment (Olaitan 2001). Evidence from endometrial, cervical, and vulval cancers has called into question the benefit of detecting recurrence at an asymptomatic stage, as in most cases, detection of recurrent disease at an asymptomatic stage did not appear to confer any survival benefit (Kew 2005). However, it appears that studies investigating gynaecological cancers are hampered by retrospective design and poor methodological quality (Kew 2005). A meta-analysis of randomised controlled trials (RCTs) of follow-up after bowel cancer suggested that intensive follow-up provides a benefit that is not conferred by little or no follow-up. The effect was most pronounced in trials that used computed tomography (CT) and frequent measurements of serum carcinoembryonic antigen (CEA (Renehan 2002)). There was an absolute reduction in all-cause five-year mortality of 10%. However, salvage surgery offered a second chance of cure in a small number of cases (2% to 5%), and the additional gain in survival might have been attributable to other factors. These factors included increased psychological well-being, or altered lifestyle, or improved treatment of coincidental disease through regular medical contact, or a combination of all three, which may have contributed to the improved survival (Renehan 2005).

How the intervention might work

Qualitative work in gynaecological cancer, with women who were treated for early-stage disease, including those who were treated for ovarian cancer, showed that the over-riding reason that women want continued follow-up is fear of recurrence. In one survey, 95% of women attributed their lack of cancer recurrence to close medical follow-up (Costanzo 2005). Women find routine visits to the hospital reassuring, especially if they are already under hospital follow-up (Fidjeland 2018). However, for some, feelings of anxiety and apprehension are severe (Greimel 2011), and may actually deter them from attending (Bradley 2000). A study suggested that living with the risk of cancer recurrence is a life-long social and psychological challenge, affecting women and their families; women's approaches to managing that risk affected their perception of the future (Roberts 2009).

The use of other follow-up strategies, such as the use of nurse-led follow-up (in lung and breast cancer (Beaver 2009; Moore 2002)), or primary care follow-up (in breast cancer (Grunfeld 1996)), or patient-initiated follow-up (in early stage endometrial cancer (Jeppesen 2018)) have been shown to be as effective as the traditional secondary care model. However, their impact on health-related quality of life (HRQOL) issues has not been assessed.

Why it is important to do this review

The objectives of follow-up for epithelial ovarian cancer include psychological support, treatment of symptoms due to side effects of treatment, audit, and treatment of recurrence of the cancer. Treatment of recurrent ovarian cancer represents a challenge, with poor long-term prognosis. Whilst there is no curative salvage treatment for recurrent ovarian disease in those who previously responded to platinum-based chemotherapy, for some women, surgery with or without chemotherapy may offer an opportunity to produce significant periods of disease remission after recurrence (Bristow 2009). The follow-up of asymptomatic women generally includes a complete clinical history, a serum CA125 sample, a physical examination, and may also include imaging, such as a CT scan, although this is usually performed when symptoms or signs appear.

It is difficult to extrapolate management of other malignancies to ovarian cancer, since it has a different natural history to both non-gynaecological and other gynaecological cancers. The use of CA125 for early detection of recurrence has been greatly reduced over the years in the UK (Coleman 2020; Leeson 2013), as its impact on the timing of chemotherapy has yet to be determined (Goonewardene 2007). However, a recent study found that secondary (further) cytoreductive surgery followed by chemotherapy, in women with recurrent ovarian cancer, seems to improve overall survival (OS) compared with chemotherapy alone, for highly selected women who have resectable disease at relapse, with lower CA125 levels and reduced ascites (Harter 2021). Therefore, detection prior to development of symptoms may be beneficial, as it may increase access to secondary cytoreductive surgery. Also, the development and use of poly (ADP-ribose) polymerase (PARP) inhibitors, as maintenance therapy after routine chemotherapy, may impact the applicability of the studies evaluating follow-up strategies, as these studies pre-date the trials evaluating the use of PARP inhibitors in ovarian cancer (Tattersall 2022).

This is an update of an earlier review that identified one RCT (Clarke 2014). This review set out to systematically evaluate the evidence available for the role of follow-up after the primary treatment of ovarian cancer, and the optimal use of investigations.

OBJECTIVES

To compare the potential effects of different strategies of follow-up in women with epithelial ovarian cancer, following completion of primary treatment.

METHODS

Criteria for considering studies for this review

Types of studies

- Randomised controlled trials (RCTs)

Types of participants

- Women of any age, diagnosed with primary ovarian cancer of epithelial histological subtype, who have completed primary treatment

Types of interventions

We considered any of the following comparisons:

- Medical follow-up using various interventions, including symptomatology, physical examination, serum tumour markers, and radiological investigations;
- Nurse-led follow-up;
- Primary care follow-up;
- Patient-directed follow-up.

Types of outcome measures

Primary outcomes

- Overall survival (OS): survival until death from all causes (survival from the time when women were randomised)

Secondary outcomes

- Health-related quality of life (HRQOL), measured using a scale that has been validated through reporting of norms in a peer-reviewed publication
- Psychological effects, measured using a scale that has been validated through reporting of norms in a peer-reviewed publication
- Cost analysis

Search methods for identification of studies

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

Electronic searches

The search strategy from our original Cochrane Review, that aimed to identify RCTs that compared follow-up strategies in women with epithelial ovarian cancer, was searched from inception to 2013, and adopted for CENTRAL, MEDLINE, and Embase.

For this update, we searched the following electronic databases up to November 2022:

- The Cochrane Central Register of Controlled Trials (CENTRAL, Issue 11, 2022);
- MEDLINE (August 2013 to November 18, 2022);
- Embase (August 2013 to 2022 week 46).

These strategies are presented in Appendix 1, Appendix 2, and Appendix 3.

Searching other resources

Unpublished and Grey literature

We searched the following trial registries for ongoing trials, to November 2022: clinicaltrials.gov; www.who.int/clinical-trials-registry-platform/the-ictrp-search-portal; and www.isrctn.com.

We also searched the following grey literature database to November 2022, for relevant sources: www.opengrey.eu.

Handsearching

We handsearched the reference lists of included studies and previous systematic reviews, identified during the literature search.

Data collection and analysis

Selection of studies

We downloaded all titles and abstracts retrieved by the electronic searches into a reference management database (Covidence). We removed duplicates, and two review authors (GZ and JD) independently examined the remaining references. We excluded those studies that clearly did not meet the inclusion criteria. Two review authors independently examined the full-text copies of potentially relevant studies, and assessed them for of eligibility.

Data extraction and management

Data extraction

We extracted data as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022). Two review authors (GZ and JD) independently extracted the following data for the included studies:

- author, year of publication and journal citation (including language);
- country;
- setting;
- inclusion and exclusion criteria;
- study design, methodology;
- participant characteristics (age, stage, and postoperative residuum of malignancy);
- numbers of participants in each arm of the trial;
- type of intervention and control (follow-up by different professional groups, use of investigations, timing of follow-up visits, and decision to give further treatment);
- data relating to risk of bias in trial - see below;
- duration of follow-up;
- outcomes – OS, HRQOL, psychological effects, and cost-effectiveness:
  - for each outcome: outcome definition (with diagnostic criteria if relevant);
  - unit of measurement (if relevant);

- for scales: upper and lower limits, and whether high or low score is good;
- results: number of participants allocated to each intervention group;
- for each outcome of interest: sample size; missing participants.

Data management

We used Review Manager 5 to collate and enter the data for the original review, and RevMan Web for this and subsequent updates (RevMan 2020; RevMan Web 2023).

For time-to-event data (e.g. OS), 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 from Parmar 1998.

For continuous data (i.e. HRQOL, psychological effects, and cost), we expressed the treatment effect as a mean difference (MD) with 95% confidence interval (CI) to reflect the uncertainty of the summary estimates.

We extracted both unadjusted and adjusted statistics, where reported.

Where possible, we extracted all data concerning intention-to-treat analysis, in which participants were analysed in groups to which they were assigned.

We noted the time points at which outcomes were collected and reported.

Assessment of risk of bias in included studies

The risk of bias in the included RCTs was assessed using Cochrane's RoB 1 tool and the criteria specified in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). This included assessment of:

- sequence generation;
- allocation concealment;
- blinding (of participants, healthcare providers, and outcome assessors);
- incomplete outcome data:
  - low risk, if fewer than 20% of women were lost to follow-up and reasons for loss were similar in both treatment arms;
  - high risk, if more than 20% of women were lost to follow-up, or reasons for loss differed between treatment arms;
  - unclear, if loss to follow-up was not reported;
- selective reporting of outcomes;
- other possible sources of bias.

Two review authors (GZ and JD) applied the criteria independently, and we resolved differences through discussion.

Measures of treatment effect

For time-to-event outcomes, we used the hazard ratio (HR).

We used mean difference (MD) for HRQOL, psychological effect scores, and for the economic analysis derived from Cox's regression analysis.

Unit of analysis issues

We did not expect any unit of analysis issues.

Dealing with missing data

We did not impute missing outcome data for any of the outcomes in the review. We attempted to contact authors for missing data, where possible.

Assessment of heterogeneity

The two RCTs included in this study had different interventions; due to this discrepancy, we did not conduct a meta-analysis.

Assessment of reporting biases

We did not produce funnel plots to assess the potential for small study effects, as there were fewer than 10 studies in the analysis (Higgins 2022).

Data synthesis

We identified two included studies, assessing different outcomes, so it was not possible to perform a meta-analysis. Therefore, it was not appropriate 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.

Subgroup analysis and investigation of heterogeneity

We did not investigate heterogeneity, as a meta-analysis was not possible.

Sensitivity analysis

We did not perform any sensitivity analyses, as the two included studies assess different outcomes.

Summary of findings and assessment of the certainty of the evidence

We assessed the overall certainty of the evidence for each outcome according to the GRADE approach. This accounts for issues related to internal validity (risk of bias, inconsistency, imprecision, publication bias), and external validity, such as directness of results (Langendam 2013). We developed summary of findings tables, based on the methods described in Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2022), and using GRADEpro GDT software (GRADEpro GDT). We used the GRADE checklist and GRADE Working Group certainty of evidence definitions (Meader 2014). We downgraded the evidence from high certainty by one level for serious (or by two for very serious) concerns for each limitation.

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

Due to the heterogeneity in intervention approaches between the two studies, we created separate summary of findings tables, using guidance from the *Cochrane Handbook of Systematic Reviews of Interventions* (Schünemann 2022). The summary of findings tables reported on the following outcomes, listed in order of priority: OS, HRQOL, psychological effects, and cost analysis (Summary of findings 1; Summary of findings 2).

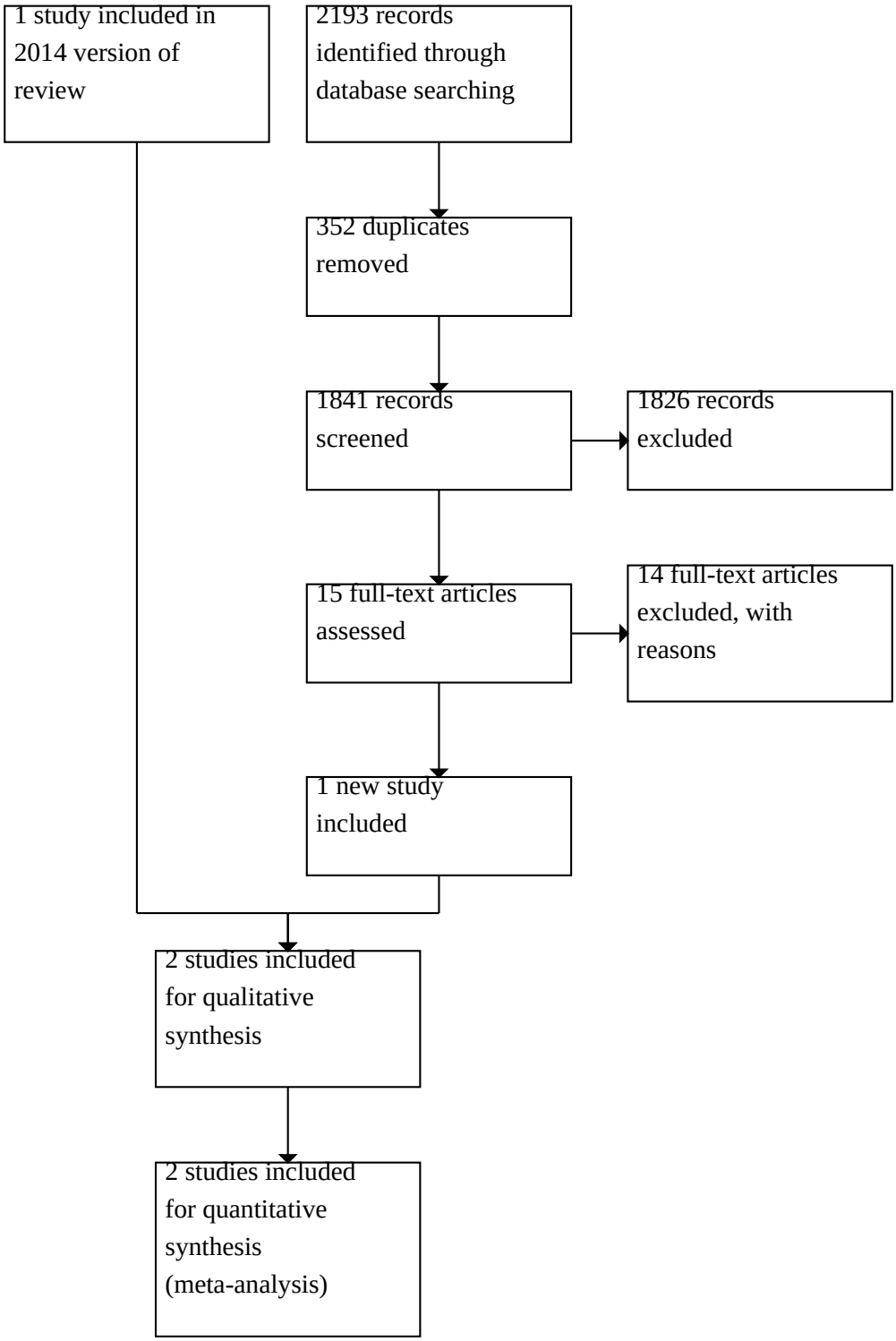
RESULTS

Description of studies

Results of the search

For this update, the search identified 1841 unique references (Figure 1). The review authors read their titles and abstracts, and excluded articles that obviously did not meet the inclusion criteria. The review authors retrieved the full text of 15 articles, translated articles into English where appropriate, and identified updated versions of relevant studies. After the full-text screening, we excluded 14 articles, for the reasons described in Characteristics of excluded studies. In this update, we identified only one completed randomised controlled trial (RCT) that met our inclusion criteria (Lanceley 2017).

Figure 1. PRISMA study selection flow chart



The updated search in 2013 identified 532 references, 13 of which were deemed possibly relevant, but were all excluded after full text review. In the original Cochrane Review (Kew 2011), 1107 references were identified, 7 of which were possibly relevant; only one RCT met all the inclusion criteria (Rustin 2010).

Both included RCTs are described in Characteristics of included studies.

Included studies

In this update of the review, we identified one completed randomised controlled trial (RCT (Lanceley 2017)). The original Cochrane Review identified another completed RCT (Rustin 2010).

Lanceley 2017

This RCT was conducted in three UK gynaecologic cancer centres, and compared individually tailored follow-up, led by a gynaecologic Clinical Nurse Specialist (CNS) versus conventional medical follow-up. The trial enroled 113 women, with a follow-up period of two years. The women had a clinical diagnosis of ovarian, fallopian tube, or peritoneal cancer; had completed primary treatment by surgery, with or without chemotherapy, regardless of remission status; and had an expected survival of more than three months. All were at least 18 years old, and were willing and able to participate in the trial. The primary outcomes were cost, and effects on health-related quality of life (HRQOL) and mood. HRQOL was reported using the European Organisation for Research and Treatment of Cancer 14 Core Quality of Life Questionnaire (EORTC) QLQ-C30 score (Aaronson 1993), and the EORTC QLQ-Ov28 score (Greimel 2003). Mood was reported using the hospital anxiety and depression scale (HADS (Zigmond 1983)).

Women were randomly allocated to receive either individualised follow-up (N = 57) or conventional follow-up (N = 56). One of the women randomised to conventional follow-up was ineligible, and was excluded from the study, leaving 112 women for analysis. There were no differences in clinical or demographic characteristics. Mean age in the intervention arm was 62 years (range = 23 to 92 years) compared to 61 years (range = 21 to 85 years) in the conventional arm. At baseline, there was no significant treatment effect on the global EORTC QLQ-C30 score (P = 0.3), global QLQ-Ov28 score (P = 0.34), or global HADS score (P = 0.3).

Rustin 2010

This was a randomised controlled, multi-centred trial in ovarian cancer, of immediate treatment of disease relapse, based on CA125 level alone versus delayed treatment, based on conventional clinical indicators (MRC OV05/EORTC 55955 trials). The trial registered 1442 participants: 529 of these women showed an increase in CA125 levels, and were randomly assigned to treatment groups and included in the analysis; all 529 were assessed at the end of the trial (265 in the immediate treatment group, and 264 in the delayed treatment group). At the start of the trial, all the women had confirmation of remission, with normal CA125 concentration, and no radiological evidence of disease after surgery and first-line chemotherapy. The primary outcome measure was overall survival (OS), calculated from the date of randomisation to the date of the last follow-up or death from any cause.

Women assigned to immediate treatment started chemotherapy 4.8 months earlier (95% confidence interval (CI) 3.6 to 5.3 months) than those allocated to delayed treatment. The median length of follow-up was 56.9 months (interquartile range (IQR) 37.4 to 81.8 months from randomisation); there were a total of 370 deaths in the trial (186 in the immediate treatment group and 184 in the delayed treatment group). Median age at registration was 61 years (range = 53 to 68); 81% were International Federation of Gynecology and Obstetrics (FIGO) stages III/IV. Chemotherapy treatment was given according to local institutional protocols. Predominant histologies were serous (53% of randomised women), and endometrioid (17% of randomised women). Median follow-up from randomisation was 49 months.

Median survival from randomisation was 25.7 months (95% CI 23.0 to 27.9) for women receiving immediate treatment, and 27.1 months (95% CI 22.8 to 30.9) for those receiving delayed treatment, with a median follow-up of 56.9 months (IQR 37.4 to 81.8) from randomisation.

Median time spent with a good global health score was 7.2 months (95% CI 5.3 to 9.3) for women assigned to immediate treatment, and 9.2 months (95% CI 6.4 to 10.5) for those assigned to delayed treatment.

The trial reported OS as the primary outcome measure, and provided unadjusted and several adjusted estimates of the hazard ratio (HR). The trialists used these stratification factors to adjust the HR for OS: age; FIGO stage; first-line chemotherapy; time from completion of first-line chemotherapy to doubling of CA125 concentration; and country. A second adjusted HR used these prognostic factors: histology; World Health Organization (WHO) performance status; and time from doubling of CA125 concentration to randomisation. The trialists also reported an HR adjusted for both stratification and prognostic factors. A sensitivity analysis of non-curtailed data (all follow-up data received, not curtailed at five years for MRC OV05 and three years for EORTC 55955) was also performed for OS.

The trial also reported time to second-line chemotherapy (calculated from the date of randomisation to the date of initiation of second-line chemotherapy, for women who did not receive second-line chemotherapy censored at the date of last contact), and time to third-line treatment or death, but these outcomes were not of interest to this review.

Health-related quality of life (HRQOL) was reported by calculating the time to first deterioration in HRQOL score or death, using the EORTC QLQ-C30 questionnaire.

The trialists also performed subgroup analyses of individual components of the QLQ-C30 subscales, and reported these functional HRQOL components: physical; role; emotional; cognitive; and social. Some of these were subdivided into symptom HRQOL components. There were inconsistencies in HRs and their 95% CIs for most components in the paper's Table 4, and the reported significance probabilities, and it was not clear what adjustment(s) had been made on the estimates.

Excluded studies

We excluded 14 references after reviewing the full text, for the following reasons:

- not an RCT (Esselen 2016; Le 2016; Rustin 2011);
- primary or secondary outcomes not assessed (Juraskova 2017);

- incorrect participants (Frangou 2021; Lindeman 2015; Morrison 2018; Ngu 2020);
- duplicate (Esselen 2017; ISRCTN45565436; Morrison 2017; NCT00002895; NCT02298855; NCT03838861).

For further details of all the excluded studies see Characteristics of excluded studies.

Risk of bias in included studies

Two review authors independently assessed the risk of bias for the two included studies (see Figure 2 and Figure 3).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study

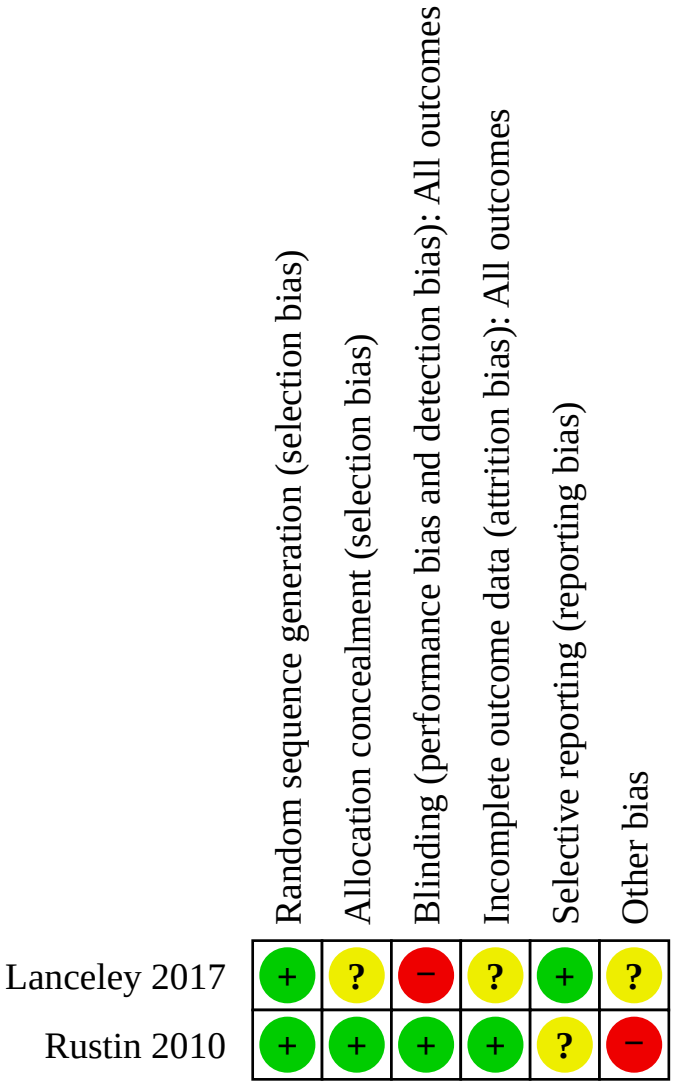
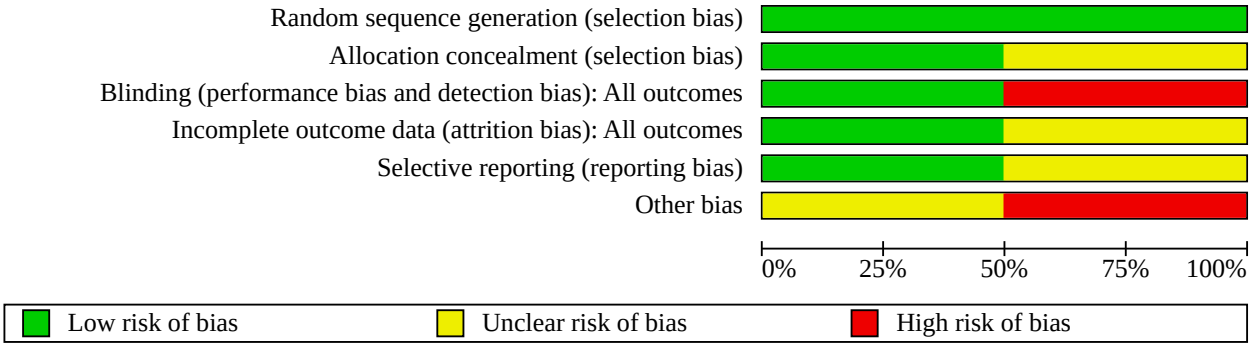


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item across studies



Allocation

Rustin 2010 reported the method of generation of the sequence of random numbers used to allocate women to treatment arms and concealed this allocation sequence from participants and healthcare professionals involved in the trial. All women had CA125 levels monitored, and those whose CA125 levels rose to more than two times the upper limit of normal were randomised to one of two treatment arms.

Lanceley 2017 was deemed low risk for allocation bias. A web-based random sequence generation was used to allocate participants into the two intervention groups (1:1 ratio) using randomness derived from atmospheric noise. No details were provided for the allocation sequence concealment.

Blinding

In Rustin 2010, study participants and clinicians were blinded to monitored CA125 levels. Clinicians of women randomised to the immediate treatment arm were informed that CA125 levels had risen, a confirmatory test was performed, and women were treated according to local protocols. Clinicians and women in the delayed treatment group remained unaware of the monitoring CA125 levels; if symptoms developed, CA125 was performed locally to monitor response to treatment, and women were treated according to standard local practice.

Lanceley 2017 was an open-label study, and the outcome was likely influenced by the lack of blinding. This is likely to influence self-reported outcomes, such as HRQOL and mood, so it was deemed to be at high risk for detection and performance bias; it was unlikely to have introduced any bias to an objective outcome, i.e. the cost analysis.

Incomplete outcome data

In Rustin 2010, all women who were randomised were analysed by intention-to-treat, so it was judged to be at low risk for attrition bias.

In Lanceley 2017, the potential for attrition bias was deemed unclear, as the proportion of missing data due to non-compliance varied during the follow-up period (range = 2% to 23%). However, there were no significant differences in the proportion of missing outcome data in the groups. In the economic analysis outcome, missing data were imputed by the authors for all participants, independently of the intervention group, using appropriate imputation methods.

Selective reporting

Rustin 2010 was at unclear risk of reporting bias, as insufficient information was available to enable judgement on whether outcomes were selectively reported.

Lanceley 2017 was at low risk for reporting bias, as the protocol was followed, and all outcomes were published.

Other potential sources of bias

In Rustin 2010, point estimates and 95% confidence intervals did not tally with corresponding P values for time-to-first deterioration in quality of life score or death for many of the individual subscales of the EORTC QLQ-C30 questionnaire (Table 4, Rustin 2010), so we scored the 'free of other bias' item in the assessment at high risk of bias.

Lanceley 2017 reported that despite the commitment to enrol consecutive participants, more were deemed unsuitable for inclusion by their consultant than were anticipated, and some were simply judged too sick, with multiple comorbidities. We were also concerned that nurses trained to deliver the individualised follow-up were likely to be invested in its success, and thus, they may have been more attentive, and fulfilled the women's expectations of continuity and responsiveness to their difficulties. Therefore, we judged it to be at unclear risk for other bias.

Effects of interventions

See: **Summary of findings 1** Immediate versus delayed treatment for women with epithelial ovarian cancer following completion of primary treatment; **Summary of findings 2** Individualised nurse-led follow-up versus conventional medical follow-up for women with epithelial ovarian cancer following completion of primary treatment

Immediate versus delayed treatment in women with increased CA125 levels

We found one study, which included 529 women, and met our inclusion criteria (Rustin 2010). This study reported data on immediate versus delayed treatment in women who had confirmation of remission (defined as normal CA125 concentration

and no radiological evidence of disease) after surgery and first-line chemotherapy.

Primary outcomes

Overall survival (OS)

There may be little difference in a meaningful reduction in survival between women who received immediate treatment and those who received delayed treatment after a median follow-up of 56.9 months (unadjusted HR 0.98, 95% CI 0.80 to 1.20; P = 0.85; 1 study, 529 participants; moderate-certainty evidence; Analysis 1.1). The confidence interval spans possible outcomes that include both a 20% improvement and a 20% reduction in survival. The unadjusted estimate was robust to estimates that were adjusted for stratification factors (age, FIGO stage, first-line chemotherapy, time from completion of first-line chemotherapy to doubling of CA125 concentration, and country: HR 0.99; 95% CI 0.80 to 1.22), prognostic factors (histology, WHO performance status, and time from doubling of CA125 concentration to randomisation: HR 0.98; 95% CI 0.79 to 1.21), and the adjustment of both stratification and prognostic factors (HR 1.01, 95% CI 0.82 to 1.25). The trial authors also carried out a sensitivity analysis of non-curtailed data (all follow-up data received, not curtailed at five years for MRC OV05 and three years for EORTC 55955: HR 1.01; 95% CI 0.82 to 1.23).

Secondary outcomes

Health-related quality of life (HRQOL)

Rustin 2010 used the EORTC QLQ-C30 questionnaire to measure HRQOL. Time from randomisation to first deterioration in global health score or death was shorter in the immediate treatment group (median 3.2 months, 95% CI 2.4 to 4.3) than in the delayed treatment group (5.8 months, 95% CI 4.4 to 8.5), with an HR of 0.71 (95% CI 0.58 to 0.88; P = 0.002). The trial authors stated that subgroup analyses of individual components of the QLQ-C30 subscales showed deterioration in the score sooner in the immediate group than in the delayed group for almost all subscales, and there was evidence of significant disadvantages for role, emotional, social, and fatigue subscales with immediate treatment. However, this was not consistent with the 95% CIs stated in table 4 in the trial report, and it was not clear what adjustments were made on the estimates.

The trial report also mentioned that since the QLQ-C30 questionnaire only asks about symptoms in the previous week, and the forms were completed just before each course of chemotherapy, this method could underestimate any reduction in quality of life due to chemotherapy.

Psychological effects

This outcome was not assessed.

Cost analysis

This outcome was not assessed.

Individualised nurse-led follow-up versus conventional medical follow-up

We found one study, assessing 112 women, which reported outcomes for individualised nurse-led follow-up versus conventional medical follow-up (Lanceley 2017).

Primary outcome

Overall survival

This outcome was not assessed.

Secondary outcomes

QLQ-C30 score

Women in the individualised follow-up group reported 5.76 points less discomfort, measured on the QLQ-C30 discomfort scale, following 12 months of individualised care compared to women in the conventional group (95% CI -10.92 to -0.60; 1 study, 112 participants; low-certainty evidence; Analysis 2.1). That corresponds to an improved quality of life of 0.016 points per day. These estimates were derived from a mixed-effects regression model, adjusting for tumour stage and age. Musoro 2020 reported that the marginally important difference in EORTC QLQ-C30 scale for women with ovarian cancer ranged from 4 to 10 points.

QLQ-Ov28 score

No benefit was reported in HRQOL when the QLQ-Ov28 was used. The trial found that there may be little or no difference in the HRQOL between the interventions (mean difference (MD) -0.97, 95% CI -2.57 to 0.63; 1 study, 112 participants: low-certainty evidence; Analysis 2.2; adjusted for tumour stage and age at randomisation).

Psychological effects

Psychological effects, assessed by the HADS, were found to be similar between the individualised and the conventional follow-up (MD 0.10, 95% CI -0.81 to 1.02; 1 study, 112 participants; low-certainty evidence; Analysis 2.3; adjusted for tumour stage and age at randomisation).

Cost analysis

There may be little difference in cost between the interventions in the adjusted analysis, although the confidence intervals are wide and span no difference (MD GBP -695, 95% CI -1467 to 77; 1 study, 112 participants; moderate-certainty evidence; Analysis 2.4; adjusted for age at baseline, disease stage at baseline, disease grade at baseline, and study site). The cost was calculated per person in British pounds; the difference excludes general practitioner and practise nurse visits, as the data on primary care contacts were imputed, using appropriate methods.

DISCUSSION

Summary of main results

We found two randomised controlled trials (RCTs) that met our inclusion criteria.

Rustin 2010, which included 529 women, reported data on immediate treatment of recurrence versus delayed treatment in women who, at the time of recruitment to the trial, had confirmation of remission with normal CA125 concentration and no radiological evidence of disease after surgery and first-line chemotherapy. Overall, it showed that there may be no survival advantage from immediate treatment following a raised serum marker level alone (Summary of findings 1).

Women treated in the immediate treatment arm (treated on the basis of a CA125 rise alone) appeared to show deterioration sooner on the health-related quality of life (HRQOL) scale, QLQ-C30.

Lanceley 2017, including 112 participants, compared individualised, nurse-led follow-up with conventional medical follow-up on HRQOL, psychological effect, and cost analysis. The trial reported decreased discomfort, calculated on the HRQOL scale, QLQ-C30. However, there was little or no difference in the HRQOL scale, QLQ-Ov28, in the psychological scale and in the cost analysis between the two arms (Summary of findings 2).

Overall completeness and applicability of evidence

This update includes one more RCT, which compares individualised nurse-led follow-up with conventional medical follow-up (Lanceley 2017). Rustin 2010 compared immediate treatment of relapse, based on CA125 level alone, versus delayed treatment, based on conventional clinical indicators.

In Rustin 2010, outcomes were incompletely reported, as separate comprehensive reporting of HRQOL and psychological effects were not carried out and cost analysis was not assessed. Lanceley 2017 reported the impact of interventions on HRQOL, psychological effects, and cost analysis.

We acknowledge that Rustin 2010 predates Poveda 2021 and Harter 2021. For women with relapsed ovarian cancer and BRCA1/2 mutation, Poveda 2021 showed that maintenance therapy with olaparib, a poly (ADP-ribose) polymerase (PARP) inhibitor, may improve overall survival (OS; as reviewed in the meta-analysis by Tattersall 2022). In Harter 2021, secondary cytoreductive surgery followed by chemotherapy resulted in increased OS in selected women with recurrent epithelial ovarian cancer. The applicability of Rustin 2010 may be limited in view of these findings.

Quality of the evidence

This review evaluated the current evidence for the evaluation of follow-up strategies for women with epithelial ovarian cancer following completion of primary treatment.
The certainty of evidence for overall survival was moderate, as it was downgraded due to imprecision caused by a wide confidence interval. The certainty of HRQOL and psychological outcomes was low. The main reasons were the risk of bias, due to the unblinded study design, which may have had an impact on some outcomes, and the unclear risk for attrition and other biases. The certainty was also affected by imprecision due to the small study sample. For the cost analysis, the certainty of evidence was moderate, mainly due to imprecision caused by the small study size.

Potential biases in the review process

A comprehensive literature search was performed, and all studies were screened and data extracted by at least two reviewers, independently. The review was restricted to RCTs, as these provide the strongest level of evidence. Hence, we made every attempt to minimise bias in the review process. To our knowledge, there were no bias in the review process.

Agreements and disagreements with other studies or reviews

One previous review, which pre-dates our included studies, suggested that there is uncertainty about whether the early detection of recurrence is beneficial in terms of survival; the review did not demonstrate a clinical advantage of an intensive follow-up programme (Gaducci 2007). The authors concluded that the definition of specific guidelines for the surveillance of women with this malignancy was still controversial. Moreover, retrospective analyses assessing the value of postoperative surveillance programmes have some potential bias (lead time, length time bias).

Apart from Rustin 2010, all other studies on follow-up strategies use the detection of recurrence as the primary end point. This is problematic, since the data from Rustin 2010 demonstrate that time to detection of recurrence is not an adequate surrogate marker for overall survival, and may have an adverse effect on the women. The two may diverge, depending on treatments available at relapse. Detection of recurrence without subsequent information about survival risks the introduction of lead-time bias. In other words, tests that detect recurrence earlier may simply increase the length of time that the recurrence is known about, rather than making any difference to the overall time period from diagnosis to death. There is also the concern of length of time bias, whereby more indolent (slow growing) tumours have a longer pre-clinical course, and therefore, are more likely to be detected by periodic tests. Women with more indolent tumours are likely to have better survival rates.

Whilst recognising that detection of recurrence is not an endpoint of this review, there are many sources that investigated follow-up strategies after treatment for epithelial ovarian cancer, which permits consideration of these strategies for future studies.

Lanceley 2017 used relapse-free time as one of the outcomes. They also used HRQOL, psychological effects, and cost-analysis, which are the secondary outcomes specified in the original protocol.

We also identified five sets of national/international guidelines.

British Gynaecological Cancer Society: recommendations and guidance on patient-initiated follow-up (PIFU)

This guideline was created in an attempt to provide stratified pathways of PIFU in gynaecological malignancies, adapting them to women's needs (Newton 2020). Although it acknowledges the results of Rustin 2010, it recognises that it might be difficult to translate them to the modern era, as the trial was undertaken outside the possibility of secondary cytoreduction for recurrent disease, and before the establishment of targeted and maintenance agents. It recommends that younger women with stage 1A (grade 1 and 2) and stage 1C (grade 1) disease who have undergone fertility-preserving surgery, which includes a unilateral salpingo-oophorectomy and full surgical staging, have similar recurrence rates and overall survival to those undergoing conventional treatment. However, these women should have regular hospital follow-up and ultrasound scans of the contralateral ovary, and so are excluded from PIFU. Women with stages 1A/B ovarian cancer (of any grade) who have been adequately staged, with pelvic and para-aortic lymphadenectomy and peritoneal biopsies, should be offered PIFU after the completion of treatment, as they have low risk of recurrence (< 10%). If PIFU is declined, telephone follow-up, with or without blood tests, can also be offered for two years after the end of treatment. For women with stage 1C-4 disease, clinic-based follow-up is recommended for the first three years after completing treatment, as this is the most common time period in which recurrent disease develops. Each visit should include symptom assessment, physical examination, and CA125 measurement. In years four and five, women can be offered

telephone follow-up with CA125 serial measurement, if deemed suitable by their clinician.

British Gynaecological Cancer Society: epithelial ovarian/ fallopian tube/primary peritoneal cancer guidelines: recommendations for practice

This guideline recognises that there is limited evidence regarding follow-up strategies in ovarian cancer (Fotopoulou 2017). The follow-up schedule can differ according to local protocols but by convention, the most common one is every three months for the first two years, and then every six months up to five years after the end of treatment. At each visit, it is essential to complete a careful history, assessment of new and potentially tumour-related symptoms, and a clinical examination. Based on Rustin 2010 findings, the guideline endorses that CA125 measurement is not mandatory, but it can herald progressive disease and surgically-resectable disease recurrence. The results from ongoing randomised trials may change the follow-up recommendations, if secondary cytoreductive surgery is proven to be associated with increased survival. The recommendations may also change with the establishment of new targeted maintenance therapy, such as immunotherapy.

European Society of Medical Oncology: newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO clinical practice guidelines for diagnosis, treatment, and follow-up

This guideline also recognises the limited evidence on follow-up strategies for ovarian cancer. It recommends follow-up every three months for two years, every four months during the third year, and every six months during years four and five, or until progression is documented (Ledermann 2013). Each visit should include clinical evaluation, with or without pelvic examination and measurement of CA125. This guideline acknowledges the findings of Rustin 2010, and notes that some clinicians do not measure CA125 as part of follow-up, while others do, as there is a possibility of missing surgically resectable recurrence if CA125 is not measured. Data from ongoing trials will hopefully determine if surgery for relapse improves survival. It notes that follow-up strategies are based on local protocols and women's wishes, as some may want the reassurance provided by a normal CA125 reading. A CT scan is recommended if there is clinical or CA125 evidence for progressive disease. A PET-CT scan can show disease deposits that are not visible on CT scan, and can facilitate the selection of women for secondary debulking surgery, whose disease is amenable to cytoreduction.

Journal of the American College of Radiology: ACR appropriateness criteria on staging and follow-up of ovarian cancer

This guideline provided no recommendations for follow-up (Javitt 2007).

National Institute for Health: consensus conference on ovarian cancer: screening, treatment, and follow-up

This guideline, formed at a consensus meeting, acknowledged that the ideal follow-up after ovarian cancer was unclear at that time (Trimble 1994). However, the contributors recommended three- or four-monthly follow-up for the first two years after completion of primary therapy, with frequency reducing after this time. The guideline recommended that each visit should include a complete history, physical examination - including rectal and vaginal examination - and CA125 measurement; it also recommended that radiological investigations should be individualised.

Early detection of recurrence

See table in Appendix 4.

Physical examination

Physical examination alone is a poor tool for detecting recurrence and has a sensitivity of only 14% (Feinberg 2022). Chan reported on a sample of 80 women with recurrent ovarian cancer; all women who had abnormal findings on examination (51%) had either suspicious symptoms, a raised CA125, or both (Chan 2008).

CA125

CA125 can accurately predict recurrence of disease (Kaesemann 1986; Tuxen 2002; Vinokurov 1992). A doubling of the CA125 level is significant. A rise of CA125 occurs one to nine months before clinical and radiological relapse (Bruzzone 1990; Crombach 1985; Hising 1991; Kaesemann 1986; Palmer 2006; Parker 2006; Rustin 1996a; Tuxen 2002). However, a recently reported randomised study of 529 women who had completed first-line platinum-based chemotherapy showed no survival advantage from immediate treatment at the time of CA125 relapse, when compared with treatment at symptomatic relapse (Rustin 2010). Second-line chemotherapy was given, on average, five months earlier in the immediate treatment arm. Knowledge of the CA125 result has been shown to be associated with depression and anxiety (Parker 2006; Reid 2011). Some anxiety can be reduced by having the CA125 result available at the clinic visit, rather than waiting until the clinic to take the blood and then receiving the result at a later stage (Palmer 2006).

Other tumour markers

A number of other tumour markers have been investigated, either alone or in combination with CA125, to improve detection of recurrence; none have provided evidence of benefit in terms of survival if recurrence is detected earlier.

Investigations of carcinogenic embryonic antigen have been reported in several papers. This marker is raised in 65% of women with ovarian cancer (Khoo 1979), and it is more likely to be elevated in mucinous tumours, so may be of use for women with these tumours when the CA125 level is normal at diagnosis (Lenehan 1986).

Human epididymis protein 4 may be a valuable marker in the detection of ovarian cancer recurrence, but larger studies are needed to evaluate its role (Capriglione 2017).

Imaging

A number of papers have looked at different methods of imaging to try to detect recurrence.

Ultrasound has been shown to be more sensitive than clinical examination alone in detecting recurrence, and has an overall accuracy of 98% when compared to findings with laparotomy (Khan 1986). In women with no clinical or biochemical signs of relapse, ultrasound has been shown to have a positive predictive value of 100%, with only one false negative (i.e. cancer present, but not identified as being present) out of

275 cases (Testa 2005). However, the use of a combination of CA125 level and clinical examination can identify 98% of recurrences (Fehm 2005). Computed tomography (CT), or where that is inconclusive, magnetic resonance imaging (MRI), are more useful than ultrasound for proving macroscopic disease recurrence (Prayer 1993; Testa 2005). Ultrasound may have a role in the detection of extraperitoneal lesions (Okai 1992).

Women in whom recurrence is suspected on the basis of CA125 level and clinical review require imaging to plan treatment (Fehm 2005). CT or MRI remain the imaging of choice. Both have good sensitivity and specificity for the detection of recurrence (Gritzmann 1986; Kubik 2000; Low 1999). There is no role for additional CT of the chest (Sella 2001), over and above CT of the abdomen and pelvis, unless there are respiratory symptoms (Dachman 2001). The roles of RIS/positron emission tomography (PET) and PET CT have yet to be fully established. In one report, PET seemed to have no benefit when compared to MRI or CT (Kubik 2000). However, initial data in a small series seems to suggest that its role is likely to be in the diagnosis of recurrence when initial CT or MRI has been inconclusive (Barzen 1990; García 2003; Grabiec 2006; Hauth 2005; Kim 2007; Mangili 2007; Nakamoto 2001; Thrall 2007; Torizuka 2002; Zhu 2002; Zimny 2001). It may also have an additional role in determining the mode of treatment for the recurrence, in particular, the place of surgery and prediction of resectability (whether the tumour can be removed (Kitajima 2008; Lenhard 2008)). However, it is probably inferior to the CA125 level for evaluating prognosis in women during follow-up. In the case of central pelvic masses, there may be a role for transvaginal colour Doppler ultrasound in discriminating between malignant and non-malignant causes (Testa 2002).

Peritoneal cytology

One large series of 577 aspirations of the Pouch of Douglas in 110 women during follow-up after ovarian cancer showed a sensitivity of 60% (Engblom 1995). It was the first or only indication of recurrence in nine women (33%). Accuracy of the technique is not improved by performing the technique under ultrasound guidance (VillaSanta 1980; Vuento 2007).

In another series of 31 women, a reservoir was implanted in the peritoneal cavity at the time of debulking surgery and used for monitoring (Sugiyama 1996). Six women had positive cytology as the only sign of recurrence. Sensitivity and specificity were not reported.

Other methods

One small case series looked at gynaegnost (lactate dehydrogenase on vaginal tampons), but did not draw any significant conclusions (Cerejeira 1989).

Laparoscopy

Von Georgi found no benefit from early detection of recurrence (Von Georgi 2004). Laparoscopy reduced the false negative rate in comparison to CA125, but required an invasive procedure without evidence of additional benefit (Shinozuka 1994).

AUTHORS' CONCLUSIONS

Implications for practice

The main evidence in this review come from two randomised controlled trials.

Rustin 2010 demonstrated a lack of evidence that routine surveillance of CA125 levels in asymptomatic women, thus permitting immediate treatment at relapse, offers any survival advantage when compared to delaying treatment until symptomatic relapse. In the absence of symptoms and with a normal CA125 result, clinical examination is not mandatory. The additional surveillance of other tumour markers does not offer significant advantage for detecting recurrence when compared with CA125 alone. Routine radiological examination has not shown to be of benefit in asymptomatic women. Immediate treatment with chemotherapy also appears to have a negative impact on quality of life; this maybe attributable to additional cycles of chemotherapy, resulting in additional toxicity.

Lanceley 2017 showed that nurse-led follow-up may improve health-related quality of life in women who had completed primary treatment for ovarian cancer. Psychological impact and cost seemed to be similar with conventional medical follow-up.

Implications for research

Current routine cancer follow-up strategies are costly and need to be justified in order to derive maximal benefit from the available healthcare resources. Further research into follow-up strategies is needed; this should be directed towards quality of life issues and psychological impact, in addition to investigating survival outcomes and cost-effectiveness.

One of the studies identified in this review concentrated on women, most of whom had already been treated with chemotherapy at time of relapse (Rustin 2010). Recent evidence showed that second-line cytoreductive surgery followed by chemotherapy is beneficial for women with recurrent ovarian cancer compared to chemotherapy alone (Harter 2021).

Larger prospective trials should assess follow-up pathways for women with epithelial ovarian cancer after completion of primary therapy. These should include a move away from traditional models of hospital-based routine follow-up towards other strategies, such as nurse-led, telephone and patient-initiated follow-up. Individual women's needs and choice require further investigation, as part of a long-term survivorship assessment.

There is increasing interest in the role of circulating tumour cells and circulating cell-free DNA, as they seem to have diagnostic and predictive value in different types of cancer, including ovarian (Giannopoulou 2017). These newer techniques can potentially facilitate early detection of recurrence, but further studies are necessary before the implementation of these techniques in clinical practise.

We need to appreciate that epithelial ovarian cancer is a heterogeneous disease, and follow-up strategies should be tailored to staging as well as germline and somatic mutations. There is also an increasing need for the development of a risk scoring system, which can tailor individual follow-up. However, alterations in practice would need prospective evaluation, and the role of follow-

up may change with the development of new treatments. That emphasises the need of re-evaluation of the follow-up strategies in an ongoing basis.

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CHARACTERISTICS OF STUDIES

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

Lanceley 2017

Study characteristics	
Methods	A randomised controlled, multi-centre trial of individually tailored follow-up (synonymously termed individualised or intervention treatment) led by a gynaecologic clinical nurse specialist versus conventional follow-up. Cost, effects on QoL (using QLQ-C30 and QLQ-Ov28 questionnaire), mood (using HADS scale), and patient satisfaction were compared.
Participants	Eligible participants were women with the clinical diagnosis of ovarian cancer or fallopian tube or peritoneal cancer who had completed primary treatment by surgery alone or with chemotherapy irrespective of outcome with regard to remission, were expected to have a survival of more than 3 months, aged 18 years or older, and willing and able to participate. After randomisation, clinical or demographic characteristics of participants in the groups were similar and these included: stage at diagnosis, Eastern Cooperative Oncology Group performance status, coexisting diseases, ethnicity, marital and employment status and highest education level. Mean age of participants in the intervention arm was 62 years (range: 23 to 92 years), whereas in the conventional arm, the mean was 61 years (range: 21 to 85 years). At baseline, there was no significant treatment effect on the global QLQ-C30 score (P = 0.3), global QLQ-Ov28 score (P = 0.34), or global HADS score (P = 0.3).
Interventions	• **Individually tailored follow-up led by a gynaecologic cancer nurse:** women selected for individualised follow-up were allocated to one of several gynaecologic cancer nurse specialists. They met with the nurse immediately after their end of treatment appointment to negotiate follow-up to suit their individual situation. Contact was flexible, primarily by telephone at pre-arranged mutually convenient times, although some women opted for face-to-face appointments, usually at the regular gynaecologic cancer clinic. In addition, contact with the nurse was made when necessary in the regular gynaecologic oncology clinic or by telephone without prearranged appointment. Women were assessed using a holistic guide to identify signs of disease progression, symptoms warranting intervention, and psychological issues. Unless the woman had worsening symptoms needing further treatment, the nurse was responsible for the care of women receiving individualised follow-up. • **Conventional medical follow-up:** consisted of 1 posttreatment outpatient appointment with further appointments at 3 monthly intervals including complete clinical history and CA-125 and radiological imaging when symptoms or signs appeared.
Outcomes	**Global QLQ-C30 score** • Outcome type: continuous outcome • Direction: lower is better • Scale: 0- to 100-point scale **Global QLQ-Ov28 score** • Outcome type: continuous outcome • Direction: lower is better • Scale: 0- to 100-point scale **Global HADS score** • Outcome type: continuous outcome • Direction: lower is better • Scale: 0- to 100-point scale **Cost analysis**

Lanceley 2017 *(Continued)*

- Outcome type: continuous outcome
- Direction: lower is better

Identification	**Sponsorship source:** The work was partly funded by The Eve Appeal Gynaecological Cancer Charity and undertaken at UCLH/UCL within the NIHR UCLH/UCL Comprehensive Biomedical Research Center, supported by the Department of Health. The research activity of C.B. was partially supported by the FP7-305280 MIMOmics European Collaborative Project, as part of the HEALTH-2012-INNOVATION scheme. **Country:** United Kingdom **Authors name:** Dr. Anne Lanceley **Institution:** Department of Women's Cancer, The UCL Elizabeth Garrett Anderson Institute for Women's Health, University College London **Email:** a.lanceley@ucl.ac.uk **Address:** 74 Huntley St, London WC1E 6AU
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random sequence generation was assured by using randomness derived from atmospheric noise through www.random.org
Allocation concealment (selection bias)	Unclear risk	Web-based method of allocation was used, but no details were provided for the allocation sequence concealment.
Blinding (performance bias and detection bias) All outcomes	High risk	Participants and personnel were not blinded and the quality of life and psychological effect outcomes are likely to be influenced by lack of blinding. However, blinding would not be possible. Participants met with the nurse immediately after their end of treatment appointment to negotiate follow-up to suit their individual situation. Knowledge of the assigned intervention is likely to influence patient-reported outcomes, such as QoL and mood. However, the cost analysis outcome is unlikely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The proportion of missing data due to non-compliance varied during the follow-up period (range: 2% to 23%). However, there were no significant differences in the proportion of missing outcome data in the groups. Missing data in economic analysis outcome were imputed for all participants, independently of the intervention group, using appropriate methods.
Selective reporting (reporting bias)	Low risk	The study followed the prespecified protocol and is deemed to be low risk for reporting bias.
Other bias	Unclear risk	Despite the commitment to enrol consecutive women, more women than anticipated were deemed unsuitable for inclusion by their consultant, and some were simply judged too sick, with multiple comorbidity. Also, nurses trained to deliver the individualised follow-up were likely to be invested in its success, and thus, they may have been more attentive and fulfilled women's expectations of continuity and responsiveness to their difficulties.

Rustin 2010

Study characteristics	
Methods	A randomised controlled, multi-centre trial in ovarian cancer of immediate treatment of relapse based on CA125 level alone versus delayed treatment based on conventional clinical indicators (MRC OV05/ EORTC 55955 trials) OV05/55955 was designed to determine whether there were benefits from immediate treatment based on a confirmed elevation of CA125 levels versus delaying treatment until clinically indicated Women whose CA125 levels rose to more than two times the upper limit of normal were randomised to one of two treatment arms that received immediate or delayed treatment Randomisation to the immediate or delayed treatment groups used a 1:1 ratio and was done independently by each co-ordinating centre From 1996 to 2005, 1442 participants registered from 59 sites in 10 countries (centres across the UK, Spain, Norway, the Netherlands, France, Russia, Belgium, Ireland, Austria, and South Africa). Randomisation closed on 31 March 2008 when the targeted number of events (deaths) was reached, with 529 participants randomised (265 to the immediate treatment group and 264 to the delayed treatment group)
Participants	Eligible participants were women with ovarian cancer who were in complete clinical remission following first-line platinum-based chemotherapy and establishment of a normal CA125 level Women with the following histologies were included: epithelial ovarian cancers, fallopian tube cancers or primary serous peritoneal carcinoma After randomisation, baseline characteristics were well-balanced between the groups. Median age at registration was 61 years (range: 53 to 68); 81% were FIGO stage III/IV Second-line chemotherapy began a median of 5 months earlier in the immediate arm. Predominant histologies were serous and endometrioid, involving 53% and 17%, respectively, among randomised participants
Interventions	Women whose serum CA125 levels exceeded twice the upper limit of normal were randomised to either: • **Arm I:** the clinician was informed of the initial rise in CA125 level. A confirmatory test was performed immediately. Within 4 weeks of the initial CA125 elevation, women with a second confirmed elevation received treatment for recurrent disease according to standard local practice. Women with a normal CA125 on the confirmatory test received no treatment until clinically indicated • **Arm II:** the clinician was blinded to the CA125 results. Women underwent normal monitoring. When clinically indicated, women commenced treatment according to standard local practice. Relapses, regardless of modality of detection, were treated according to local standard practice by the gynaecological oncologist
Outcomes	**Primary outcome** Overall survival calculated from date of randomisation to date of last follow-up or death from any cause. At the time of analysis, survivors were censored at the date they were last known to be alive **Secondary outcomes** • Time to second-line chemotherapy (calculated from date of randomisation to date of initiation of second-line chemotherapy, women who did not receive second-line chemotherapy were censored at the date of last contact) • Time to third-line treatment or death (calculated from date of randomisation to date of starting third-line treatment or death, whichever occurred first, survivors without treatment censored at the last contact)

Rustin 2010 *(Continued)*

- QoL with duration of good QoL in the global health score (defined as improved or no more than a 10% decrease from pre-randomisation score)
  - Time of first global health-related deterioration (defined as more than 10% decrease from pre-randomisation score or death)

Identification	Funding UK Medical Research Council and the European Organisation for Research and Treatment of Cancer.
Notes	Intention-to-treat analysis Median follow-up from randomisation was 56.9 (IQR 37.4 to 81.8) months The primary outcome measurement was overall survival and the trial was designed to detect a 10% improvement in 2-year overall survival in the immediate treatment arm with at least 85% power and 5% significance level Median survival from randomisation was 25.7 months (95% CI 23.0 to 27.9) for women on immediate treatment and 27.1 months (95% CI 22.8 to 30.9) for those on delayed treatment, with a median follow-up of 56.9 months (IQR 37.4 to 81.8) from randomisation and 370 deaths (186 immediate, 184 delayed) Median time spent with good global health score was 7.2 months (95% CI 5.3 to 9.3) for women assigned to immediate and 9.2 months (95% CI 6.4 to10.5) for those assigned to delayed treatment QoL assessed at baseline, at each follow-up visit, and, if treatment was instituted, before each chemotherapy course Participants were followed-up every 3 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The method of minimisation was used with the stratification factors: International Federation of Gynecology and Obstetrics (FIGO) stage (I versus II versus III versus IV); first-line chemotherapy (single agent platinum versus platinum combination without taxane versus platinum taxane combination versus other); time from completion of first-line chemotherapy to raised CA125 concentration (< 6 versus 6 to 11 versus 12 to 24 versus > 24 months); age (MRC OV05 at randomisation, EORTC 55955 at registration; < 30 versus 30 to 55 versus 56 to 65 versus > 65 years); and site".
Allocation concealment (selection bias)	Low risk	"CA125 results were masked to sites and women until randomisation to early treatment or until clinical recurrence for those in the delayed treatment group".
Blinding (performance bias and detection bias) All outcomes	Low risk	"Serum CA-125 was measured every three months but women and investigators were blinded to the results, which were only available to the trials units". Women and investigators were not blinded when HRQOL outcome was measured from randomisation to first deterioration.
Incomplete outcome data (attrition bias) All outcomes	Low risk	100% analysed: 529/529 for primary outcome, and overall survival analysed using appropriate statistical techniques that accounted for censoring 21 (4%) women were lost to follow-up
Selective reporting (reporting bias)	Unclear risk	Insufficient information available to permit judgement

Rustin 2010 *(Continued)*

Other bias	High risk	Point estimates and 95% CIs did not tally with corresponding P values for time to first deterioration in QoL score or death for many of the individual subscales of EORTC QLQ-C30 questionnaire (Table 4 in trial report). For example, for the emotional subscale in the functional QoL category the upper 95% CI was 1.02 and the P value was 0.02. Similarly, significant subscale factors appeared to have a vastly decreased P value from that which might be expected given the point and CI estimates It was also unclear for what the HRs in Table 4 were adjusted

Abbreviations
CI = confidence interval
FIGO = International Federation of Gynecology and Obstetrics
HR = hazard ratio
IQR = interquartile range
QoL = quality of life

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

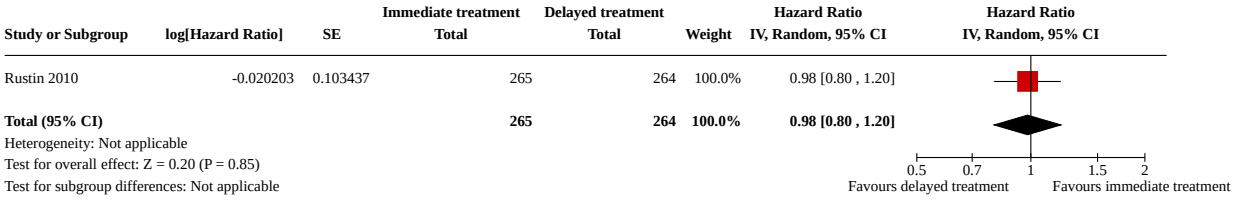
Study	Reason for exclusion
Esselen 2016	Not a randomised controlled trial
Esselen 2017	Duplicate
Frangou 2021	Wrong intervention and population
ISRCTN45565436	Duplicate
Juraskova 2017	Primary or secondary outcomes not assessed, wrong intervention
Le 2016	Not a randomised controlled trial
Lindeman 2015	Wrong population
Morrison 2017	Duplicate
Morrison 2018	Wrong population
NCT00002895	Duplicate
NCT02298855	Duplicate
NCT03838861	Wrong population
Ngu 2020	Wrong population
Rustin 2011	Not a randomised control trial

DATA AND ANALYSES

Comparison 1. Immediate versus delayed treatment in women with increased CA125 levels

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Overall survival	1	529	Hazard Ratio (IV, Random, 95% CI)	0.98 [0.80, 1.20]

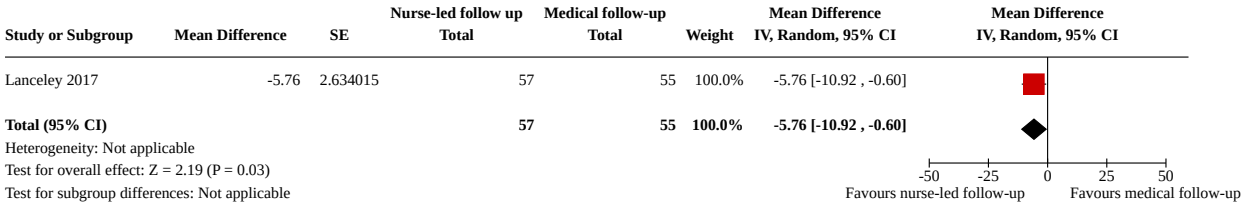
Analysis 1.1. Comparison 1: Immediate versus delayed treatment in women with increased CA125 levels, Outcome 1: Overall survival



Comparison 2. Individualised nurse-led follow-up versus conventional medical follow-up

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Quality of life (QLQ-C30 score)	1	112	Mean Difference (IV, Random, 95% CI)	-5.76 [-10.92, -0.60]
2.2 Quality of life (QLQ-Ov28 score)	1	112	Mean Difference (IV, Random, 95% CI)	-0.97 [-2.57, 0.63]
2.3 Psychological effects (HADS)	1	112	Mean Difference (IV, Random, 95% CI)	0.10 [-0.81, 1.02]
2.4 Cost analysis	1	112	Mean Difference (IV, Random, 95% CI)	-695.00 [-1467.23, 77.23]

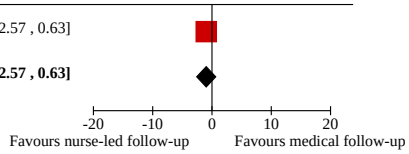
Analysis 2.1. Comparison 2: Individualised nurse-led follow-up versus conventional medical follow-up, Outcome 1: Quality of life (QLQ-C30 score)



Analysis 2.2. Comparison 2: Individualised nurse-led follow-up versus conventional medical follow-up, Outcome 2: Quality of life (QLQ-Ov28 score)

Study or Subgroup	Mean Difference	SE	Nurse-led follow-up Total	Medical follow-up Total	Weight	Mean Difference IV, Random, 95% CI
Lanceley 2017	-0.972	0.817453	57	55	100.0%	-0.97 [-2.57 , 0.63]
Total (95% CI)			**57**	**55**	**100.0%**	**-0.97 [-2.57 , 0.63]**

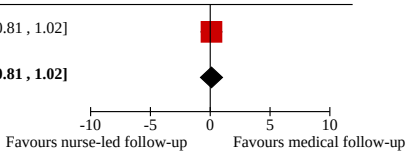
Heterogeneity: Not applicable
Test for overall effect: Z = 1.19 (P = 0.23)
Test for subgroup differences: Not applicable



Analysis 2.3. Comparison 2: Individualised nurse-led follow-up versus conventional medical follow-up, Outcome 3: Psychological effects (HADS)

Study or Subgroup	Mean Difference	SE	Nurse-led follow-up Total	Medical follow-up Total	Weight	Mean Difference IV, Random, 95% CI
Lanceley 2017	0.1044	0.468	57	55	100.0%	0.10 [-0.81 , 1.02]
Total (95% CI)			**57**	**55**	**100.0%**	**0.10 [-0.81 , 1.02]**

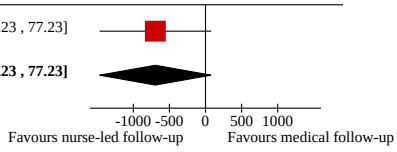
Heterogeneity: Not applicable
Test for overall effect: Z = 0.22 (P = 0.82)
Test for subgroup differences: Not applicable



Analysis 2.4. Comparison 2: Individualised nurse-led follow-up versus conventional medical follow-up, Outcome 4: Cost analysis

Study or Subgroup	Mean Difference	SE	Nurse-led follow-up Total	Medical follow-up Total	Weight	Mean Difference IV, Random, 95% CI
Lanceley 2017	-695	394	57	55	100.0%	-695.00 [-1467.23 , 77.23]
Total (95% CI)			**57**	**55**	**100.0%**	**-695.00 [-1467.23 , 77.23]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.76 (P = 0.08)
Test for subgroup differences: Not applicable



APPENDICES

Appendix 1. CENTRAL search strategy

1. MeSH descriptor Ovarian Neoplasms explode all trees
2. ovar* near/5 (cancer* or tumor* or tumour* or neoplas* or malignan* or carcinoma*)
3. (#1 OR #2)
4. MeSH descriptor Follow-Up Studies explode all trees
5. (follow up) or follow-up
6. MeSH descriptor Aftercare explode all trees
7. aftercare or (after care) or after-care
8. surveillance
9. (#4 OR #5 OR #6 OR #7 OR #8)
10. (#3 AND #9)

Appendix 2. MEDLINE search strategy

1. exp Ovarian Neoplasms/
2. (ovar* adj5 (cancer* or tumor* or tumour* or neoplas* or malignan* or carcinoma*)).mp.
3. 1 or 2
4. Follow-Up Studies/

5. (follow up or follow-up).mp.
6. surveillance.mp.
7. Aftercare/
8. (aftercare or after care or after-care).mp.
9. 4 or 5 or 6 or 7 or 8
10. 3 and 9
11. randomized controlled trial.pt.
12. controlled clinical trial.pt.
13. 13 randomized.ab.
14. 14 placebo.ab.
15. 15 clinical trials as topic.sh.
16. 16 randomly.ab.
17. 17 trial.ab.
18. 18 11 or 12 or 13 or 14 or 15 or 16 or 17
19. 19 10 and 18

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

Appendix 3. Embase search strategy

1. exp ovary tumor/
2. (ovar* adj5 (cancer* or tumor* or tumour* or neoplas* or malignan* or carcinoma*)).mp.
3. 1 or 2
4. follow up/
5. (follow up or follow-up).mp.
6. surveillance.mp.
7. aftercare/
8. (aftercare or after care of after-care).mp.
9. 4 or 5 or 6 or 7 or 8
10. 3 and 9
11. random*.mp.
12. factorial*.mp.
13. (crossover* or cross over* or cross-over*).mp.
14. placebo*.mp.
15. (doubl* adj blind*).mp.
16. (singl* adj blind*).mp.
17. assign*.mp.
18. allocat*.mp.
19. volunteer*.mp.
20. crossover procedure/
21. double blind procedure/
22. randomized controlled trial/
23. single blind procedure/
24. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25. 10 and 24

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

Appendix 4. Tumour markers

Tumour marker	Paper	Summary
IGF-1	Rohr 2016	No correlations with clinical and pathological prognostic factors

(Continued)

CA125 + b2m	Hernádi 1992	b2m has low specificity for detection of ovarian cancer; CA125 performs better
CA72.4	Fayed 1998	When added to CA125, it improves sensitivity and specificity for detecting recurrence, especially in mucinous tumours
CEA	Khoo 1974	Persistently low levels are consistent with a good prognosis
	Khoo 1979 Lenehan 1986	Serial samples were useful in predicting relapse in a small number of women; clinical role is limited to a small subset of women
CA72.4, CA19.9	Fioretti 1992	Useful for detecting recurrence in women with normal CA125 at diagnosis
PLAP-A, PLAP-C	Fisken 1989	No correlation with disease
Anti-p53	Gadducci 1998	Not clinically useful
CYFRA 21-1	Gadducci 2001	Not prognostic of survival
D-dimer	Gadducci 1995	Not clinically useful
Urinary neopterine	Hetzel 1983	
TPA	Inoue 1985	Lacks tumour specificity
SLX	Iwanari 1989	May be of benefit in combination with CA125
CA125 + CA15.3 + CA72.4 + SCC + 90K	Garzetti 1991	Includes all gynaecological malignancies. CA125 plus 90K identified 86% of recurrences
CA125 + CEA + ferritin + TPA	Lahousen 1987	If normal can avoid second look laparotomy
CA125 + CASA	Oehler 1999	CASA less sensitive than CA125, CASA may be useful when CA125 inconclusive
Sialyl Le(x)-i	Kobayashi 1989	Up to 96% showed rise in levels with tumour progression
OPN	Schorge 2004	Inferior to CA125 in determining response to treatment, but showed an earlier rise in recurrent disease
CA125 + TPS	Sliutz 1995	Improved detection of recurrence when compared to CA125 alone
IAP	Shimizu 1986	May have a role in early detection of recurrence
TPS	Tempfer 1998	TPS is useful, but cannot replace CA125
	Zakrzewska 2000	TPS may rise before CA125 rises in women with recurrence

WHAT'S NEW

Date	Event	Description
31 August 2023	New search has been performed	Searches updated

Date	Event	Description
31 August 2023	New citation required and conclusions have changed	Lanceley 2017 included; outcomes added to the conclusions; text amended; authorship updated

HISTORY

Protocol first published: Issue 3, 2006
Review first published: Issue 6, 2011

Date	Event	Description
12 September 2018	Amended	Eleven references added to 'Classification pending' after a horizon scanning literature search in August 2018.
1 September 2014	New citation required but conclusions have not changed	Text amended, author list updated
31 July 2013	New search has been performed	No new studies were identified during this update

CONTRIBUTIONS OF AUTHORS

Georgia Zachou and James Dilley updated the content for the current review (2022), with the contribution of Fatima El-Khouly.

DECLARATIONS OF INTEREST

Georgia Zachou: none known
James Dilley: none known
Fatima El-Khouly: none known

SOURCES OF SUPPORT

Internal sources

- none, Other

  The review update was undertaken without formal internal support.

External sources

- Department of Health, UK

  NHS Cochrane Collaboration Programme. Grant Scheme CPG-506

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The search strategy was amended and run on MEDLINE, rather than dialogue data star. Two authors from the protocol (Nagindra Das and Katherine Deane) did not contribute to the main review. One new author joined the group for the main review. None of the previous authors contributed to this update. Disease free survival was removed as an outcome, because time to detection of recurrence is not an adequate surrogate marker for overall survival (OS). The two may diverge, depending on treatments available at relapse. Furthermore, detection of recurrence without subsequent information about survival risks the introduction of lead-time bias. There is also the concern of length-time bias, whereby more indolent tumours have a longer pre-clinical course and are therefore, more likely to be detected by periodic tests. The cost-effectiveness outcome was amended to cost analysis for clarity.

INDEX TERMS

Medical Subject Headings (MeSH)

Carcinoma, Ovarian Epithelial [therapy]; Follow-Up Studies; *Neoplasm Recurrence, Local; *Ovarian Neoplasms [therapy]

MeSH check words

Female; Humans