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

Clarke T, Galaal K, Bryant A, Naik R

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

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

Tilean Clarke[1], Khadra Galaal[2], Andrew Bryant[3], Raj Naik[4]

[1]London Metropolitan University, London, UK. [2]Gynaecological Oncology, Princess Alexandra Wing, Royal Cornwall Hospital, Truro, UK. [3]Institute of Health & Society, Newcastle University, Newcastle upon Tyne, UK. [4]Gynaecological Oncology, Northern Gynaecological Oncology Centre, Gateshead, UK

Contact: Tilean Clarke, London Metropolitan University, 166-220 Holloway Rd, London, N7 8DB, UK. tilean_gordon@hotmail.com.

A B S T R A C T

Background

Ovarian cancer is the sixth most common cancer and seventh commonest cause of death in women worldwide. Traditionally, many people 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, quality of life (QoL), or relieving anxiety, or both. In addition, traditional follow-up may not be cost-effective.

Objectives

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

Search methods

For this update we searched the Cochrane Gynaecological Cancer Group Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL) Issue 7, 2013, MEDLINE and EMBASE from November 2010 to July 2013. We also searched reference lists of review articles and contacted experts in the field.

Selection criteria

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

Data collection and analysis

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

Main results

The authors did not identify any new studies that were eligible for inclusion in this update of the review. The search for the original review identified only one RCT that met the inclusion criteria, which included 529 women. This study reported data on immediate treatment of ovarian cancer relapse following rise of serum CA125 levels versus delaying treatment until symptoms developed. All the women participating had previous confirmation of remission, with normal CA125 concentration and no radiological evidence of disease, after surgery and first-line chemotherapy for ovarian cancer.

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

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

1

Overall survival between the immediate and delayed arms showed no difference after a median follow-up of 56.9 months (unadjusted hazard ratio (HR) 0.98, 95% confidence interval (CI) 0.80 to 1.20; P value 0.85). 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; P value < 0.01). The trial was at low risk of bias.

Authors' conclusions

Limited evidence from a single trial suggests that routine surveillance with CA125 in asymptomatic patients and treatment at CA125 relapse does not seem to offer survival advantage when compared to treatment at symptomatic relapse. RCTs are needed to compare different types of follow-up, looking at survival, QoL, cost and psychological effects as outcomes.

PLAIN LANGUAGE SUMMARY

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

Ovarian cancer is the sixth most common cancer and seventh commonest cause of cancer death in women worldwide. Traditionally, many people who have been treated for cancer undergo long-term follow-up in a hospital outpatient setting. However, it has been suggested that the use of routine review (check-ups) may not result in women with ovarian cancer living longer. We set out to review the evidence for different types of follow-up for women who have completed treatment for the commonest type of ovarian cancer. Only one randomised study was found, and it did not find that immediate treatment with chemotherapy for relapse (identified by a tumour marker - CA125 - blood test) produced a benefit compared to delaying treatment until the women developed symptoms. The limited evidence suggests that there may be no benefit from early detection of recurrence of ovarian cancer and starting chemotherapy before symptoms develop. In addition, early treatment of recurrence with chemotherapy may reduce overall quality of life.

Randomised controlled trials are needed to compare different types of follow-up, looking at survival and quality of life outcomes. If new treatments become available for relapsed ovarian cancer, the methods of follow-up may need to be re-assessed to see if earlier intervention improves survival.

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

2

BACKGROUND

Description of the condition

Ovarian cancer is the sixth most common cancer among women (GLOBOCAN 2008). Worldwide there are more than 200,000 new cases of ovarian cancer each year, accounting for around 4% 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 0.5% to 1.6% (IARC 2002). This corresponds to an age-standardised rate of ovarian cancer of between 5 to 14 cases per 100,000 women under 75 years of age per year. In Europe, 37% to 41% of women with ovarian cancer are alive five years after diagnosis (EUROCARE 2003). The poor survival associated with ovarian cancer is largely because most women are diagnosed when the cancer is at an advanced stage (Jemal 2008).

Description of the intervention

Traditionally, many people who have been treated for cancer undergo long-term, even life-long, follow-up in secondary care (Barnhill 1992; Kerr-Wilson 1995; Kew 2006). The rationale for this 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 (Kunkler 1991). 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. Patients may also be provided with reassurance that the cancer has not returned, which maintains their psychological well-being, and these appointments also allow for the collection of outcome data and provide positive feedback for the clinicians involved in patients' care (Kerr-Wilson 1995).

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 (Kew 2005), as, in most cases, detection of recurrent disease at an asymptomatic stage did not appear to confer any survival benefit. However, it would appear 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 has 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 on women who have been treated for early stage disease, including those who have been treated for ovarian cancer, has shown that the over-riding reason that women want continued follow-up is fear of recurrence. In one survey 82% of women attributed their lack of cancer recurrence to close medical follow-up (Stewart 2001). Women find routine visits to the hospital reassuring, especially if they are experiencing unexpected symptoms (Bradley 2000). However, for some, feelings of anxiety and apprehension are severe (Stewart 2001), 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, with the women's approaches to managing that risk affecting 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 cancer) (Moore 2002), or primary care follow-up (in breast cancer) (Grunfeld 1996), have been shown to be as effective as the traditional secondary care model. However, their impact on quality of life (QoL) 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, and audit, as well as 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, surgery with or without chemotherapy may offer an opportunity to produce significant periods of disease remission after recurrence in some women (Bristow 2009). The follow-up of asymptomatic women generally includes consideration of the complete clinical history, taking a serum CA125 sample, making 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 cancer and other gynaecological cancers. The use of CA125 for early detection of recurrence is widespread (Barnhill 1992; Kew 2006), but the impact of this on the timing of chemotherapy has yet to be determined (Goonewardene 2007: Vaidya 2003). This is an update, which previously identified one RCT (Rustin 2010). This review set out to evaluate systematically 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 benefits of different strategies of follow-up in patients with epithelial ovarian cancer following completion of primary treatment.

METHODS

Criteria for considering studies for this review

Types of studies

- Randomised controlled trials (RCTs)

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

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

3

Types of participants

Women of any age diagnosed with primary ovarian cancer of epithelial histological sub-type 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: survival until death from all causes (survival from the time when women were randomised).

Secondary outcomes

- Health-related quality of life (QoL), 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-effectiveness.

Search methods for identification of studies

We sought papers in all languages and performed translations when necessary.

Electronic searches

See: Cochrane Gynaecological Cancer Group methods used in reviews.
For this update we searched the following electronic databases:

- the Cochrane Gynaecological Cancer Review Group's Trial Register;
- the Cochrane Central Register of Controlled Trials (CENTRAL Issue 7, 2013);
- MEDLINE (November 2010 to July week 4 2013);
- EMBASE (November 2010 to 2013).

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 adopted for MEDLINE, EMBASE and CENTRAL and used to search from November 2010 onwards. These strategies are presented in Appendix 1, Appendix 2 and Appendix 3, respectively.

Databases were searched up to July 2013.

Searching other resources

The authors checked the reference lists of articles and other reviews on the subject in order to retrieve further information about published or unpublished trials, and contacted researchers involved in this area.

Data collection and analysis

Selection of studies

All titles and abstracts retrieved by electronic searching were downloaded to a reference management database (Endnote), duplicates were removed and the remaining references were examined by two review authors independently. The authors excluded those studies that clearly did not meet the inclusion criteria. Full text copies of potentially relevant studies were obtained for independent assessment of eligibility by both review authors.

Data extraction and management

A review author extracted data from the only eligible trial identified onto a pre-designed data extraction form. Data extracted included:

- 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 – overall survival, health-related QoL:
  - 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.

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

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.

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

4

Assessment of risk of bias in included studies

The risk of bias in the included RCT was assessed using the Cochrane Collaboration's tool for assessment of risk of bias and the criteria specified in Chapter 8 of the Cochrane Handbook 2011. This included assessment of:

- sequence generation;
- allocation concealment;
- blinding (of participants, healthcare providers and outcome assessors);
- incomplete outcome data:
  - we recorded the proportion of participants whose outcomes were not reported at the end of the study; we noted if loss to follow-up was not reported.
  - we coded whether the level of loss to follow-up for each outcome was satisfactory as follows:
    - 'yes', if fewer than 20% of patients were lost to follow-up and reasons for loss to follow-up were similar in both treatment arms;
    - 'no', if more than 20% of patients were lost to follow-up or reasons for loss to follow-up differed between treatment arms;
    - 'unclear' if loss to follow-up was not reported.
- selective reporting of outcomes;
- other possible sources of bias.

The 'Risk of bias' tool was applied independently by two review authors (AB, KG), who resolved differences through discussion. Results are presented in a 'Risk of bias' graph.

Measures of treatment effect

For time-to-event outcomes, we used the HR.

Dealing with missing data

We did not impute missing outcome data.

Data synthesis

We only identified one included study 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.

R E S U L T S

Description of studies

Results of the search

The updated search strategy identified 532 unique references. The authors read the titles and abstracts of these and excluded articles that obviously did not meet the inclusion criteria at this stage. The authors retrieved 13 articles in full, translated articles into English where appropriate, and identified updated versions of relevant studies. The full text screening of these 13 references led to an empty search since no studies met the inclusion criteria, for the reasons described in Characteristics of excluded studies. Only one completed RCT, that had been previously identified in the original Cochrane review (Kew 2011), met our inclusion criteria and is described in Characteristics of included studies.

Included studies

This update of the review did not identify any new RCTs. Only one prospective study met the inclusion criteria (Rustin 2010). This was a randomised controlled, multi-centre 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 level and were then randomly assigned to treatment groups and included in the analysis, with all 529 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, 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), and 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 FIGO stage III/IV. Second-line chemotherapy started a median of five months earlier in the immediate treatment arm. Chemotherapy treatment was given according to local institutional protocols. Predominant histologies were serous and endometrioid, involving 53% and 17%, respectively, among the randomised participants. 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 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 treatment, 184 delayed treatment).

Median time spent with 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 overall survival as the primary outcome measure and provided unadjusted and several adjusted estimates of the HR. The trialists used the following stratification factors to adjust the HR for overall survival; age; International Federation of Gynecology and Obstetrics stage; first-line chemotherapy; time from completion of first-line chemotherapy to doubling of CA125 concentration; and country. A second adjusted HR used the following prognostic factors: histology; World Health Organization (WHO) performance status; and time from doubling of CA125 concentration to randomisation. The trialists also reported a 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 overall survival.

The trial also reported time to second-line chemotherapy (calculated from the date of randomisation to the date of initiation of second-line chemotherapy, with 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 QoL was reported by calculating time to first deterioration in QoL score or death using the EORTC QLQ-C30 questionnaire.

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

Excluded studies

Thirteen references were excluded after obtaining the full text for the following reasons:

- not an RCT (Bapsy 2012; Geurts 2011; Hall 2011; Kitajima 2012; Lajtman 2011; Madry 2011; Pastalozzi 2011; Pignata 2011; Rustin 2011; van de Poll-Franse 2011);
- retrospective study (Fuso 2011);
- primary or secondary outcomes not assessed (Alexandre 2012);
- incorrect participants (Buys 2012).

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

Risk of bias in included studies

The one included trial was at low risk of bias as it satisfied four criteria used to assess risk of bias (Rustin 2010; see Figure 1).

Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.
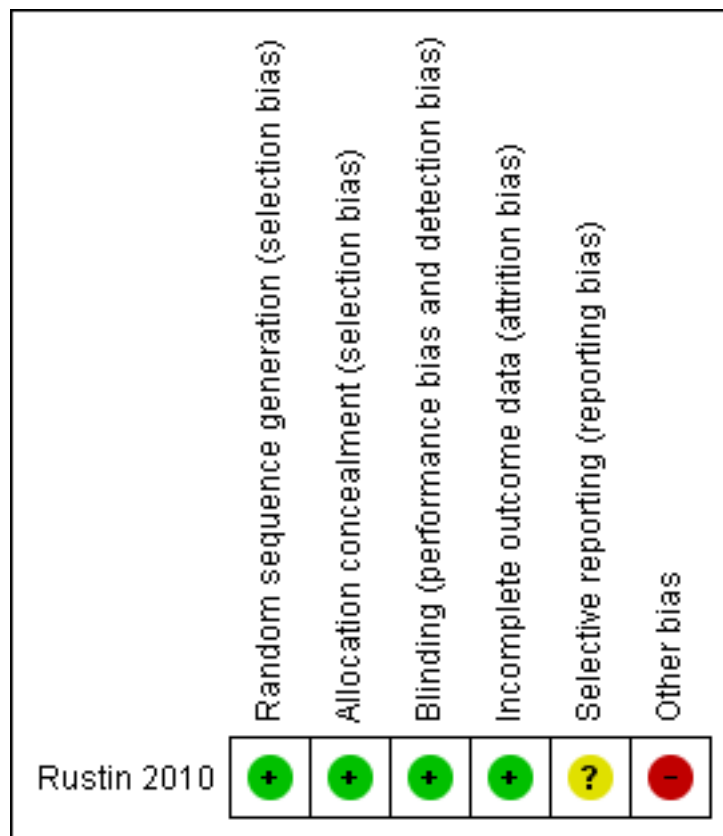
The trial reported the method of generation of the sequence of random numbers used to allocate women to treatment arms and concealed this allocation sequence from participants and healthcare professionals involved in the trial. All women had CA125 levels monitored and those whose CA125 levels rose to more than two times the upper limit of normal were randomised to one of two treatment arms. 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. All women who were randomised were analysed, but it was unclear whether outcomes had been selectively reported. 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 sub-scales of the EORTC QLQ-C30 questionnaire (Table 4, Rustin 2010), so we scored the 'free of other bias' item in the 'Risk of bias' assessment as being at high risk of bias.

Effects of interventions

Immediate versus delayed treatment in patients with increased CA125 levels

We found one study, which included 529 women, that 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.

Overall survival

(Analysis 1.1 - unadjusted estimate)

There was no statistically significant difference in the risk of death between women who received immediate treatment and those who received delayed treatment (unadjusted HR 0.98; 95% CI 0.80 to 1.20; P value 0.85). The unadjusted estimate was robust to estimates that were adjusted for stratification factors (age, International Federation of Gynecology and Obstetrics 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).

Quality of life

Time to first deterioration in quality of life score or death using EORTC QLQ-C30 questionnaire

Time from randomisation to first deterioration in global health score or death was shorter in the immediate group (median 3.2 months; 95% CI 2.4 to 4.3) than in the delayed group (5.8 months; 95% CI 4.4 to 8.5; HR 0.71; 95% CI 0.58 to 0.88; P value 0.002). The trial authors claimed that subgroup analyses of individual components of the QLQ-C30 sub-scales showed deterioration in score sooner in the immediate group than in the delayed group for almost all sub-scales, and there was evidence of significant disadvantages for role, emotional, social, and fatigue sub-scales with immediate treatment. However this was not consistent with the 95% confidence intervals stated in Table 4 in the trial report, and it was not clear what adjustment(s) had been made on the estimates.

The trial report also mentioned that since the QLQ-C30 questionnaire asks only 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.

DISCUSSION

Summary of main results

The authors did not identify any new randomised controlled trials (RCTs) that could be included in this update of the review. Only one previously identified randomised controlled trial (RCT), which included 529 women, met our inclusion criteria (Rustin 2010).

This trial 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. It showed that overall, there may be no survival advantage from immediate treatment following a raised serum marker level alone. There was a total of 370 deaths in the trial, and there was no evidence of a difference in overall survival between the immediate and delayed arms. Therefore, there may be no value in the routine measurement of CA125 in the follow-up of women with ovarian cancer who have a clinical complete remission following primary surgery and first-line platinum-based chemotherapy.

Women treated in the immediate treatment arm (treated on the basis of a CA125 rise alone) received 12 more total cycles of chemotherapy on average than women in the delayed treatment arm (30 months versus 18 months). Immediate treatment appeared to have a negative impact on quality of life (QoL). The decrease in QoL observed in the trial may have been attributable to additional cycles of chemotherapy resulting in additional toxicity (e.g. neuropathy (nerve damage), fatigue or hospital admissions secondary to neutropenia (a blood disorder)), and more time spent in hospital as an outpatient or inpatient. These data suggest that treatment may be safely delayed until there is evidence of clinical relapse.

There is a paucity of good quality data in this important area. We did not expect to identify a large number of RCTs, but the review was restricted to high quality evidence as retrospective case series are of inadequate quality and are at high risk of bias. The main limitation of this review is the fact that conclusions are based on single trial analyses.

Overall completeness and applicability of evidence

To date one RCT has compared immediate treatment of relapse, based on CA125 level alone, versus delayed treatment, based on conventional clinical indicators.

Overall, the quality of the evidence was moderate (GRADE Working Group); although the review comprised evidence from only one included trial, this trial was of a sufficient size. Outcomes were incompletely reported as separate comprehensive reporting of QoL and psychological effects was not carried out and cost-effectiveness was not assessed. Even though the trial was judged to have been at low risk of bias (Rustin 2010), the fact that there were no accompanying trials to support the evidence resulted in a downgrading of the evidence to reflect the uncertainty in the single trial analyses.

Quality of the evidence

The single included trial included a reasonably large number of women (529 participants) and was at low risk of bias, largely because it was a well conducted and reported trial. Outcomes were analysed using appropriate statistical techniques and a hazard ratio was used for time-to-event data, which is the best statistic for summarising the difference in risk in two treatment groups over the duration of a trial, when there is 'censoring', that is, when the time to death is unknown for some women as they were still alive at the end of the trial. The trial also performed sensitivity analyses to adjust for important stratification and prognostic

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

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

7

factors to test the robustness of unadjusted estimates. However, the confidence intervals and significance probabilities in subgroup analyses of individual components of the QLQ-C30 sub-scales were not consistent, and it was unclear whether these factors were statistically significant or not. This does not change the overall judgement regarding the quality of the evidence greatly, since the quality of the trial appears to be good, but the amount of evidence available does not allow robust conclusions to be reached in comparison of different follow-up strategies.

Potential biases in the review process

A comprehensive search was performed, and all studies were sifted and data extracted by at least two reviewers independently. The review was restricted to RCTs, as these provide the strongest level of evidence available. Hence we made every attempt to minimise bias in the review process.

The greatest threat to the validity of the review is likely to be the possibility of publication bias, that is studies that did not find the intervention to have been effective may not have been published. We were unable to assess this possibility as no new studies were identified.

Agreements and disagreements with other studies or reviews

One previous review, which pre-dates our only included study, suggested that there is uncertainty about whether the early detection of recurrence is beneficial in terms of survival, and that 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 patients 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 endpoint. 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 patient. 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. 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 time bias, whereby more indolent (slow growing) tumours have a longer pre-clinical course and are therefore 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 vast numbers of sources that have investigated follow-up strategies after treatment for epithelial ovarian cancer, which does permit consideration of these strategies for future studies

Authoritative guidelines

We identified three sets of national/international guidelines.

National Institute for Health (USA, 1994) Trimble 1994

This guideline, formed at a consensus meeting, acknowledged that the ideal follow-up after ovarian cancer was unclear at that time. 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 the complete history, physical examination - including rectal and vaginal examination - and CA125 measurement; it also recommended that radiological investigations should be individualised.

European Society of Medical Oncology (Europe, 2008 Annals of Oncology)

This guideline 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 (Aebi 2008). Each visit should include history and physical examination including pelvic examination. The guideline recommends that CA125 should be performed at each follow-up visit, and that a CT scan should be performed if there is clinical or CA125 evidence for progressive disease.

No evidence is provided to support any of these recommendations, other than that CA125 can accurately predict tumour recurrence.

ACR Appropriateness Criteria 2007

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

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 39.4% (Menczer 2006). 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 or 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. Furthermore, knowledge of the CA125 result has been shown to be associated with depression and anxiety (Parker 2006). 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).

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

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

8

Other tumour markers

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

Investigations of **c**arcinogenic **e**mbryonic **a**ntigen (CEA) 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 raised in mucinous tumours, so may be of use in women with these tumours when the CA125 level is normal at diagnosis (Lenehan 1986).

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 use of a combination of CA125 level and clinical examination can identify 98% of recurrences (Fehm 2005). 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 role of RIS/ PET and PET CT has 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 small series would seem to suggest that its role is likely to be in the diagnosis of recurrence where 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 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 patients (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 patients 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 (LDH) on vaginal tampons), but did not draw any significant conclusions (Cerejeira 1989).

Laparoscopy

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

AUTHORS' CONCLUSIONS

Implications for practice

The evidence in this review comes from a single, large trial. This trial provided no evidence that routine surveillance of CA125 levels in asymptomatic patients, 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 in terms of detecting recurrence when compared with CA125 alone. Routine radiological examination has not shown to be of benefit in asymptomatic women.

Immediate treatment with chemotherapy appears to have a negative impact on quality of life; this maybe attributable to additional cycles of chemotherapy resulting in additional toxicity.

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 (QoL) issues and psychological impact, in addition to investigating survival outcomes and cost-effectiveness.

The one study identified in this review concentrated on women, most of whom had already been treated with chemotherapy at time of relapse. Prospective trials on follow-up methods should also evaluate whether second-line debulking surgery is beneficial in women treated with surgery for recurrent ovarian cancer, since the effect of timing of surgical treatment on survival and QoL issues may be different to chemotherapy-only regimens.

Prospective trials are needed to evaluate interventions during follow-up that may help to reduce anxiety and promote return to normal functioning for asymptomatic women.

Interventions may 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 and the relative merits of these strategies should also be evaluated

in prospective studies. Individual patient needs and patient choice require further investigation, as part of a long-term survivorship assessment. However, alterations in practice would need prospective evaluation.

ACKNOWLEDGEMENTS

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

10

R E F E R E N C E S

References to studies included in this review

Rustin 2010 {published data only}

Rustin GJ, van der Burg ME, Griffin CL, Guthrie D, Lamont A, Jayson GC et al on behalf of MRC and EORTC collaborators. Early versus delayed treatment of relapsed ovarian cancer (MRC OV05/EORTC 55955): a randomised trial. *Lancet* 2010;**376 (9747)**:1155-63.

References to studies excluded from this review

Alexandre 2012 {published and unpublished data}

Alexandre J, Brown C, Coeffic D, Raban N, Pfistere J, Mäenpää J, et al. CA-125 can be part of the tumour evaluation criteria in ovarian cancer trials: experience of the GCIG CALYPSO trial. *British Journal of Cancer* 2012;**106**:633-7.

Bapsy 2012 {published and unpublished data}

Bapsy P. Ovarian cancer. *Journal of the Indian Medical Association* 2012;**110**(12):894-7.

Buys 2012 {published and unpublished data}

Buys S, Partridge E, Black A. Screening CA-125 and transvaginal ultrasound does not reduce ovarian cancer mortality. *Journal of the National Medical Association* 2012;**104**:116.

Fuso 2011 {published and unpublished data}

Fuso L, Evangelista A, Pagano E, Piovano E, Perotto S, Mazzola S. Variation in gynecological oncology follow-up practice: attributable to cancer centers or to patient characteristics? A Piedmont Regional Oncology Network Study.. *Tumori* 2011;**97**:551-8.

Geurts 2011 {published and unpublished data}

Geurts SME, van Altena AM, de Vegt F, Tjan-Heijnen VCG, Massuger LFAG, van Dijck JAAM, et al. No supportive evidence for clinical benefit of routine follow-up in ovarian cancer. A Dutch multicentre study. *International Journal of Gynecological Cancer* 2011;**21**(4):647-53.

Hall 2011 {published and unpublished data}

Hall M, Rustin G. Recurrent ovarian cancer: when and how to treat. *Current Oncology Reports* 2011;**13**:459-71.

Kitajima 2012 {published and unpublished data}

Kitajima K, Ueno Y, Suzuki K, Kita M, Ebina Y, Yamada H, et al. Low-dose non-enhanced CT versus full-dose contrast-enhanced CT in integrated PET/CT scans for diagnosing ovarian cancer recurrence. *European Journal of Radiology* 2012;**81**:3557-62.

Lajtman 2011 {published and unpublished data}

Lajtman E, Mlyncek M, Uharcek P, Matejka M. Follow-up after primary therapy of malignant epithelial ovarian tumours (review). *Bratislavske Lekarske Listy* 2011;**112**(10):579-85.

Madry 2011 {published and unpublished data}

Madry R, Adamczak-Ratajczak A. The Gordon Rustin revolution - the measurement of CA125 in the surveillance of patients

with ovarian cancer. *Family Medicine and Primary Care Review* 2011;**13**(2):189-91.

Pastalozzi 2011 {published and unpublished data}

Pastalozzi BC. Follow-up: what is evidence-based? Breast and gynecologic tumors. *Onkologie* 2011;**34**(6):14.

Pignata 2011 {published and unpublished data}

Pignata S, Cannella L, Leopardo D, Bruni GS, Facchini G, Pisano C. Follow-up with CA125 after primary therapy of advanced ovarian cancer: in favor of continuing to prescribe CA125 during follow-up. *Annals of Oncology* 2011;**22**(8):40-4.

Rustin 2011 {published and unpublished data}

Rustin GJS. Follow-up with CA125 after primary therapy of advanced ovarian cancer has major implications for treatment outcome and trial performances and should not be routinely performed. *Annals of Oncology* 2011;**22**(8):45-8.

van de Poll-Franse 2011 {published and unpublished data}

van de Poll-Franse LV, Nicolaije KAH, Vos MC, Pijnenborg JMA, Boll D, Husson O, et al. The impact of a cancer Survivorship Care Plan on gynecological cancer patient and health care provider reported outcomes (ROGY Care): study protocol for a pragmatic cluster randomized controlled trial. *Trials Journal* 2011;**12**(256).

References to ongoing studies

Lanceley {published data only}

Lanceley A. A randomised study comparing satisfaction with follow-up led by a trained cancer nurse versus conventional medical follow-up after primary treatment for ovarian cancer. [ISRCTN59149551]

Additional references

Aebi 2008

Aebi S, Castiglione M. Epithelial ovarian carcinoma: ESMO Clinical Recommendations for diagnosis, treatment and follow-up. *Annals of Oncology* 2008;**19**(Suppl 2):ii14-6.

Barnhill 1992

Barnhill D, O'Connor D, Farley J, Teneriello M, Armstrong D, Park R. Clinical surveillance of gynecologic cancer patients. *Gynecological Oncology* 1992;**46**(3):275-80.

Barzen 1990

Barzen G, Cordes M, Langer M, Friedman W, Mayr AC, Felix R. Value of radioimmunoscintigraphy compared to computed tomography in the diagnosis and follow-up of primary ovarian carcinoma. *RöFo:Fortschritte auf dem Gebiete der Röntgenstrahlen und derNuklearmedizin* 1990;**153**(1):85-91.

Bradley 2000

Bradley E, Pitts M, Redman C, Calvert E, Howells R, Wafai C. What are the factors associated with the follow-up preferences of women in long-term remission from gynaecological cancer?. *Journal of Obstetrics and Gynaecology* 2000;**20**(4):408-11.

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

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

11

Bristow 2009

Bristow RE, Puri I, Chi DS. Cytoreductive surgery for recurrent ovarian cancer: a meta-analysis. *Gynecologic Oncology* 2009;**112**(1):265-74.

Bruzzone 1990

Bruzzone M, Onetto M, Campora E, Chiara S, Oliva C, Guido T, et al. CA-125 monitoring in the management of ovarian cancer. *Anticancer research* 1990;**10**(5A):1353-9.

Cerejeira 1989

Cerejeira L, Pinto FMM, Otilia BMO, Moutinho J. Validity of gynaegnost in the follow-up of patients treated for ovarian cancer. *Revue Française de Gynécologie et d'Obstétrique* 1989;**84**(4):347-9.

Cochrane Handbook 2011

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Crombach 1985

Crombach G, Zippel HH, Würz H. Clinical significance of cancer antigen 125 CA 125 in ovarian cancer. *Cancer detection and prevention* 1985;**8**(1-2):135-9.

Dachman 2001

Dachman AH, Visweswaran A, Battula R, Jameel S, Waggoner SE. Role of chest CT in the follow-up of ovarian adenocarcinoma. *American Journal of Roentgenology* 2001;**176**(3):701-5.

Engblom 1995

Engblom PR, Grènman SE, Klemi PJ, Hirvonen TE, Rantanen VT, Salmi TA. The role of cul-de-sac aspiration cytology in the follow-up of ovarian cancer. *Acta Oncologica (Stockholm Sweden)* 1995;**34**(6):783-5.

EUROCARE 2003

Sant M, Aareleid T, Berrino F, Bielska Lasota M, Carli PM, Faivre J et al and the EUROCARE Working Group. EUROCARE-3: survival of cancer patients diagnosed 1990-94 - results and commentary. *Annals of Oncology* 2003;**14 (Supplement 5)**:v61-v118.

Fayed 1998

Fayed ST, Ahmad SM, Kassim SK, Khalifa A. The value of CA 125 and CA72-4 in management of patients with epithelial ovarian cancer. *Disease Markers* 1998;**14**(3):155-60.

Fehm 2005

Fehm T, Heller F, Krämer S, Jäger W, Gebauer G. Evaluation of CA125, physical and radiological findings in follow-up of ovarian cancer patients. *Anticancer Research* 2005;**25**(3A):1551-4.

Fioretti 1992

Fioretti P, Gadducci A, Ferdeghini M, Prontera C, Malagnino G, Facchini V, et al. The concomitant determination of different serum tumor markers in epithelial ovarian cancer: relevance for monitoring the response to chemotherapy and follow-up of patients. *Gynecologic Oncology* 1992;**44**(2):155-60.

Fisken 1989

Fisken J, Leonard RC, Shaw G, Bowman A, Roulston JE. Serum placental-like alkaline phosphatase PLAP: a novel combined enzyme linked immunoassay for monitoring ovarian cancer. *Journal of Clinical Pathology* 1989;**42**(1):40-5.

Gadducci 1995

Gadducci A, Marrai R, Baicchi U, Ferdeghini M, Fanucchi A, Facchini V, et al. The measurement of plasma D-dimer DD levels in the follow-up of patients with ovarian cancer. *Anticancer Research* 1995;**15**(6B):2683-6.

Gaducci 2007

Gadducci A, Cosio S, Zola P, Landoni F, Maggino T, Sartori E. Surveillance procedures for patients treated for epithelial ovarian cancer: a review of the literature. *International Journal of Cancer* 2007;**17**(1):21-31.

García 2003

García VMJ, Boán GJF, Villar LLM, Aramendía BJM, López GG, Richter EJA. F-18-FDG positron emission tomography in the diagnosis of ovarian recurrence. Comparison with CT scan and CA 125. *Revista Espanola de Medicina Nuclear* 2003;**22**(4):217-23.

Garzetti 1991

Garzetti GC, Di LRM, Ciavattini A, Pallotta MR, Marchegiani F, Valensise H, et al. Tumor markers in the early diagnosis of recurrence in gynecologic neoplasms: combined determination of CA-125, CA 15-3, CA 724, SCC, 90 K. *Annali di Ostetricia, Ginecologia, Medicina Perinatale* 1991;**112**(5):320-3.

GLOBOCAN 2008

Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C. GLOBOCAN 2012. Cancer incidence, mortality worldwide. IARC CancerBase No. 11, version 1.0. IARCPress, Lyon 2012.

Goonewardene 2007

Goonewardene TI, Hall MR, Rustin GJS. Management of asymptomatic patients on follow-up for ovarian cancer with rising CA-125 concentrations. *Lancet Oncology* 2007;**8(9)**:813-21.

Grabiec 2006

Grabiec M, Walentowicz M, Nowicki P. The value of FDG PET/CT, ultrasound and CT in diagnosing recurrent ovarian carcinoma. *Ginekologia Polska* 2006;**77**(10):746-52.

GRADE Working Group

GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ* 2004;**328**:1490-4.

Gritzmann 1986

Gritzmann N, Karnel F, Imhof H, Wagner G, Müller T E, Dittrich C. Abdominal computerized tomography in the after-care of ovarian cancers. *Digitale Bilddiagnostik* 1986;**6**(4):171-5.

Grunfeld 1996

Grunfeld E, Mant D, Yudkin P, Adewuyi-Dalton R, Cole D, Stewart J, et al. Routine follow up of breast cancer in primary care: randomised trial. *BMJ* 1996;**313**:665-9.

Hauth 2005

Hauth EAM, Antoch G, Stattaus J, Kuehl H, Veit P, Bockisch A, et al. Evaluation of integrated whole-body PET/CT in the detection of recurrent ovarian cancer. *European Journal of Radiology* 2005;**56**(2):263-8.

Hernádi 1992

Hernádi Z, Molnár V, Juhász B, Pólka R, Margitai B. Predictive value of the tumor marker combination CA-125 and beta-2-microglobulin in ovarian cancer. *Zentralblatt für Gynäkologie* 1992;**114**(1):6-9.

Hetzel 1983

Hetzel H, Bichler A, Fuchs D, Hausen A, Reibnegger G, Wachter H. Significance of urinary neopterine in gynecological oncology: follow-up of patients with ovarian cancer. *Cancer Detection and Prevention* 1983;**6**(1-2):263-6.

Hising 1991

Hising C, Anjegård IM, Einhorn N. Clinical relevance of the CA 125 assay in monitoring of ovarian cancer patients. *American Journal of Clinical Oncology* 1991;**14**(2):111-4.

IARC 2002

Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB. Cancer Incidence in Five Continents, Volume VIII. In: Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB editor(s). IARC Scientific Publication No 155. Lyon: IARC Scientific Publication, 2002.

Inoue 1985

Inoue M, Fujita Y, Abe Y, Inoue Y, Ueda G, Tanizawa O, et al. Tissue polypeptide antigen as a tumor marker for gynecologic malignancies. *Nippon Sanka Fujinka Gakkai Zasshi* 1985;**37**(9):1799-805.

Iwanari 1989

Iwanari O, Miyako J, Date Y, Moriyama M, Yoshino N, Kijima S, et al. Diagnosis and follow-up of ovarian cancer by a combination assay of serum sialyl SSEA-1 antigen and CA125 levels. *Nippon Gan Chiryo Gakkai Shi* 1989;**24**(6):1256-60.

Javitt 2007

Javitt MC. ACR Appropriateness Criteria on staging and follow-up of ovarian cancer. *Journal of the American College of Radiology* 2007;**4**(9):586-9.

Jemal 2008

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

Kaesemann 1986

Kaesemann H, Caffier H, Hoffmann FJ, Crombach G, Würz H, Kreienberg R, et al. Monoclonal antibodies in the diagnosis and follow-up of ovarian cancer CA 125 as a tumor marker A cooperative study of the Gynecologic Tumor Marker Group GTMG. *Klinische Wochenschrift* 1986;**64**(17):781-5.

Kerr-Wilson 1995

Kerr-Wilson RH, McCrum A. Follow-up of patients with gynaecological cancer. *Australian and New Zealand Journal of Obstetrics and Gynaecology* 1995;**35**(3):298-9.

Kew 2005

Kew FM, Roberts AP, Cruickshank DJ. The role of routine follow-up after gynecological malignancy. *International Journal of Gynecological Cancer* 2005;**15**(3):413-9.

Kew 2006

Kew FM, Cruickshank DJ. Routine follow up after treatment for a gynaecological cancer: a survey of practice. International Journal of Gynecological Cancer 2006; Vol. 16:380-4.

Khan 1986

Khan O, Cosgrove DO, Fried AM, Savage PE. Ovarian carcinoma follow-up: US versus laparotomy. *Radiology* 1986;**159**(1):111-3.

Khoo 1974

Khoo SK, Mackay EV. Carcinoembryonic antigen by radioimmunoassay in the detection of recurrence during long-term followup of female genital cancer. *Cancer* 1974;**34**(3):542-8.

Khoo 1979

Khoo SK, Whitaker S, Jones I, Mackay E. Predictive value of serial carcinoembryonic antigen levels in long-term follow-up of ovarian cancer. *Cancer* 1979;**43**(6):2471-8.

Kim 2007

Kim CK, Park BK, Choi JY, Kim B-G, Han H. Detection of recurrent ovarian cancer at MRI: comparison with integrated PET/CT. *Journal of Computer Assisted Tomography* 2007;**31**(6):868-75.

Kitajima 2008

Kitajima K, Murakami K, Yamasaki E, Domeki Y, Kaji Y, Fukasawa I, et al. Performance of integrated FDG-PET/contrast-enhanced CT in the diagnosis of recurrent ovarian cancer: comparison with integrated FDG-PET/non-contrast-enhanced CT and enhanced CT. *European Journal of Nuclear Medicine & Molecular Imaging* 2008;**35**(8):1439-48.

Kobayashi 1989

Kobayashi H. Clinical usefulness of serum sialyl Lex-i measurement in patients with ovarian cancer. *Nippon Sanka Fujinka Gakkai Zasshi* 1989;**41**(1):15-9.

Kubik 2000

Kubik HRA, Dörffler W, von SGK, Marincek B, Köchli OR, Seifert B, et al. Value of 18F-FDG positron emission tomography, computed tomography, and magnetic resonance imaging in diagnosing primary and recurrent ovarian carcinoma. *European Radiology* 2000;**10**(5):761-7.

Kunkler 1991

Kunkler IH, Kerr GR, Ludgate SM. The value of follow-up in stage II carcinoma of the cervix. *Clinical Oncology* 1991;**3**(1):28-31.

Lahousen 1987

Lahousen M, Stettner H, Pickel H, Urdl W, Pürstner P. The predictive value of a combination of tumor markers in monitoring patients with ovarian cancer. *Cancer* 1987;**60**(9):2228-32.

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

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

13

Lenehan 1986

Lenehan PM, Dembo AJ, Miceli PN, Malkin DG, Malkin A. Clinical correlations of carcinoembryonic antigen in post-operative patients with epithelial ovarian cancer. *Tumour Biology : the journal of the International Society for Oncodevelopmental Biology and Medicine* 1986;**7**(5-6):389-405.

Lenhard 2008

Lenhard MS, Burges A, Johnson TR, Stieber P, Kumper C, Ditsch N, et al. PET-CT in recurrent ovarian cancer: impact on treatment planning. *Anticancer Research* 2008;**28**(4C):2303-8. [PUBMED: 18751410]

Low 1999

Low RN, Saleh F, Song SY, Shiftan TA, Barone RM, Lacey CG, et al. Treated ovarian cancer: comparison of MR imaging with serum CA-125 level and physical examination--a longitudinal study. *Radiology* 1999;**211**(2):519-28.

Mangili 2007

Mangili G, Picchio M, Sironi S, Vigano R, Rabaiotti E, Bornaghi D, et al. Integrated PET/CT as a first-line re-staging modality in patients with suspected recurrence of ovarian cancer. *European Journal of Nuclear Medicine & Molecular Imaging* 2007;**34**(5):658-66.

Menczer 2006

Menczer J, Chetrit A, Sadetzki S, Golan A, Levy T. Follow-up of ovarian and primary peritoneal carcinoma: the value of physical examination in patients with pretreatment elevated CA125 levels. *Gynecologic Oncology* 2006;**103**(1):137-40.

Moore 2002

Moore S, Corner J, Haviland J, Wells M, Salmon E, Normand C, et al. Nurse led follow up and conventional medical follow up in management of patients with lung cancer: randomised trial. *BMJ* 2002;**325**:1145.

Nakamoto 2001

Nakamoto Y, Saga T, Ishimori T, Mamede M, Togashi K, Higuchi T, et al. Clinical value of positron emission tomography with FDG for recurrent ovarian cancer. *American Journal of Roentgenology* 2001;**176**(6):1449-54.

Oehler 1999

Oehler MK, Sütterlin M, Caffier H. CASA and Ca 125 in diagnosis and follow-up of advanced ovarian cancer. *Anticancer Research* 1999;**19**(4A):2513-8.

Okai 1992

Okai T, Kagawa H, Masuda H, Kozuma S, Mizuno M. Assessment of ovarian tumors by transvaginal scanning and clinical significance of ultrasonic examination in postoperative follow up. *Rinsho Byori. The Japanese Journal of Clinical Pathology* 1992;**40**(4):363-8.

Olaitan 2001

Olaitan A, Murdoch J, Anderson R, James J, Graham J, Barley V. A critical evaluation of current protocols for the follow-up of women treated for gynecological malignancies: a pilot study. *International Journal of Gynecologic Cancer* 2001;**11**(5):349-53.

Palmer 2006

Palmer C, Pratt J, Basu B, Earl H. A study to evaluate the use of CA125 in ovarian cancer follow-up: a change in practice led by patient preference. *Gynecologic Oncology* 2006;**101**(1):4-11.

Parker 2006

Parker PA, Kudelka A, Basen-Engquist K, Kavanagh J, de Moor J, Cohen L. The associations between knowledge, CA125 preoccupation, and distress in women with epithelial ovarian cancer. *Gynecologic Oncology* 2006;**100**(3):495-500. [PUBMED: 16242759]

Parmar 1998

Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Erratum in Statistics in Medicine 2004 Jun 15;23(11):1817. *Statistics in Medicine* 1998 Dec 30;**17**(24):2815-34.

Prayer 1993

Prayer L, Kainz C, Kramer J, Stiglbauer R, Schurawitzki H, Baldt M, et al. CT and MR accuracy in the detection of tumor recurrence in patients treated for ovarian cancer. *Journal of Computer Assisted Tomography* 1993;**17**(4):626-32.

Renehan 2002

Renehan AG, Egger M, Saunders MP, O'Dwyer ST. Impact on survival of intensive follow up after curative resection for colorectal cancer: systematic review and meta-analysis of randomised trials. *BMJ* 2002;**324**:813.

Renehan 2005

Renehan AG, Egger M, Saunders MP, O'Dwyer ST. Mechanisms of improved survival from intensive follow up in colorectal cancer: a hypothesis. *British Journal of Cancer* 2005;**92**(3):430-3.

Roberts 2009

Roberts K, Clarke C. Future disorientation following gynaecological cancer: Women's conceptualisation of risk after a life threatening illness. *Health, Risk & Society* 2009;**11**(4):353–366.

Rustin 1996a

Rustin G, Tuxen M. Use of CA 125 in follow-up of ovarian cancer. *Lancet* 1996;**348**(9021):191-2.

Schorge 2004

Schorge JO, Drake RD, Lee H, Skates SJ, Rajanbabu R, Miller DS, et al. Osteopontin as an adjunct to CA125 in detecting recurrent ovarian cancer. *Clinical Cancer Research: an official journal of the American Association for Cancer Research* 2004;**10**(10):3474-8.

Sella 2001

Sella T, Rosenbaum E, Edelmann DZ, Agid R, Bloom AI, Libson E. Value of chest CT scans in routine ovarian carcinoma follow-up. *American Journal of Roentgenology* 2001;**177**(4):857-9.

Shimizu 1986

Shimizu Y, Akagaki E, Hirota K, Kono M, Miura S, Okudaira Y, et al. Significance of immunosuppressive acidic protein in the diagnosis and follow-up of patients with ovarian cancer, in

particular as a marker for chemotherapeutic effects. *Nippon Sanka Fujinka Gakkai Zasshi* 1986;**38**(4):554-60.

Shinozuka 1994

Shinozuka T, Miyamoto T, Hirazono K, Ebisawa K, Murakami M, Kuroshima Y, et al. Follow-up laparoscopy in patients with ovarian cancer. *The Tokai Journal of Experimental and Clinical Medicine* 1994;**19**(1-2):53-9.

Sliutz 1995

Sliutz G, Tempfer C, Kainz C, Mustafa G, Gitsch G, Koelbl H, et al. Tissue polypeptide specific antigen and cancer associated serum antigen in the follow-up of ovarian cancer. *Anticancer Research* 1995;**15**(3):1127-9.

Stewart 2001

Stewart DE, Duff S, Wong F, Melancon C, Cheung AM. The views of ovarian cancer survivors on its cause, prevention, and recurrence. *Medscape Women's Health* 2001;**6**(5):5.

Sugiyama 1996

Sugiyama Y, Shimizu Y, Umezawa S, Yamauchi K, Hasumi K. Feasibility of peritoneal washing cytology through the totally implanted reservoir for early detection of peritoneal recurrence of ovarian cancer. *Nippon Sanka Fujinka Gakkai Zasshi* 1996;**48**(3):213-9.

Tempfer 1998

Tempfer C, Hefler L, Haeusler G, Reinthaller A, Koelbl H, Zeisler H, et al. Tissue polypeptide specific antigen in the follow-up of ovarian and cervical cancer patients. *International Journal of Cancer. Journal International du Cancer* 1998;**79**(3):241-4.

Testa 2002

Testa AC, Ciampelli M, Mastromarino C, Lopez R, Zannoni GF, Mancuso S, et al. Detection of central pelvic recurrent disease with transvaginal color Doppler ultrasound in women treated for gynecological malignancy. *Ultrasound in Obstetrics & Gynecology* 2002;**19**(5):490-5.

Testa 2005

Testa AC, Fruscella E, Ludovisi M, De V Rosa, Malaggese M, Corrado G, et al. The role of sonographic examination in the follow-up of gynecological neoplasms. *Gynecologic Oncology* 2005;**99**(3):696-703.

Thrall 2007

Thrall MM, DeLoia JA, Gallion H, Avril N. Clinical use of combined positron emission tomography and computed tomography FDG-PET/CT in recurrent ovarian cancer. *Gynecologic Oncology* 2007;**105**(1):17-22.

Torizuka 2002

Torizuka T, Nobezawa S, Kanno T, Futatsubashi M, Yoshikawa E, Okada H, et al. Ovarian cancer recurrence: role of whole-body positron emission tomography using 2-fluorine-18-fluoro-2-deoxy- D-glucose. *European Journal of Nuclear Medicine and Molecular Imaging* 2002;**29**(6):797-803.

Tuxen 2002

Tuxen MK, Sölétormos G, Dombernowsky P. Serum tumor marker CA 125 for monitoring ovarian cancer during follow-up. *Scandinavian Journal of Clinical and Laboratory Investigation* 2002;**62**(3):177-88.

Vaidya 2003

Vaidya AP, Curtin JP. The follow-up of ovarian cancer. *Seminars in Oncology* 2003;**30**(3):401-12.

VillaSanta 1980

VillaSanta U, Jovanovski D. Follow-up study of ovarian carcinoma by cytology of cul-de-sac aspirates. *Gynecologic Oncology* 1980;**10**(1):58-62.

Vinokurov 1992

Vinokurov VL, Dudarev AL, Jurkova LE, Lapchenkov VI, Barbanel EJ. Tumor marker CA 125 in diagnosis, monitoring management and follow-up of patients with ovarian tumors. *European Journal of Gynaecological Oncology* 1992;**13**(2):205-8.

Vuento 2007

Vuento M, Salmi T, Klemi P, Grénman S. Ultrasonographic-guided pervaginal cul-de-sac cytology in the follow-up of ovarian carcinoma. *Anticancer Research* 2007;**27**(2):1015-8.

Zhu 2002

Zhu X, Shen K, Lang J, Wu M, Huang H, Pan L. Role of positron emission tomography in detecting recurrent epithelial ovarian carcinoma. *Zhonghua Fu Chan Ke za Zhi* 2002;**37**(6):356-8.

Zimny 2001

Zimny M, Siggelkow W, Schröder W, Nowak B, Biemann S, Rath W, et al. 2-Fluorine-18-fluoro-2-deoxy-d-glucose positron emission tomography in the diagnosis of recurrent ovarian cancer. *Gynecologic Oncology* 2001;**83**(2):310-5.

CHARACTERISTICS OF STUDIES

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

Rustin 2010

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)

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

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

15

Rustin 2010 *(Continued)*

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 1996-2005, 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: 53-68); 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)
	• 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)
Notes	Intention-to-treat analysis
	Median follow-up from randomisation was 56.9 (IQR 37.4 to 81.8) months

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

16

Rustin 2010 *(Continued)*

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 to 10.5) 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 patients 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 patients and investigators were blinded to the results, which were only available to the trials units".
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
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 sub-scales of EORTC QLQ-C30 questionnaire (Table 4 in trial report). For example, for the emotional sub-scale in the functional QoL category the upper 95% CI was 1.02 and the P value was 0.02. Similarly, significant sub-scale 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

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

17

IQR = interquartile range
QoL = quality of life

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

Study	Reason for exclusion
Alexandre 2012	Primary or secondary outcomes not assessed
Bapsy 2012	Not a randomised control trial
Buys 2012	Incorrect participants. Not a randomised control trial
Fuso 2011	Not a randomised control trial. A retrospective study
Geurts 2011	Not a randomised control trial
Hall 2011	Not a randomised control trial
Kitajima 2012	Not a randomised control trial
Lajtman 2011	Not a randomised control trial
Madry 2011	Not a randomised control trial
Pastalozzi 2011	Not a randomised control trial
Pignata 2011	Not a randomised control trial
Rustin 2011	Not a randomised control trial
van de Poll-Franse 2011	Primary outcome not assessed

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

Lanceley

Trial name or title	Randomised study comparing satisfaction with follow-up led by a trained cancer nurse versus conventional medical follow-up after primary treatment for ovarian cancer
Methods	Prospective RCT
Participants	Women undergoing treatment for ovarian cancer
	The trial recruited 113 women, and closed to recruitment on 31 December 2008. The study completed in December 2010 and is yet to be reported
Interventions	Conventional medical follow-up
	Follow-up care led by a trained cancer nurse
Outcomes	Primary outcome measures are patient satisfaction and QoL
Starting date	1 November 2005
Contact information	Ms A Lanceley Gynaecological Oncology

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

18

Lanceley *(Continued)*

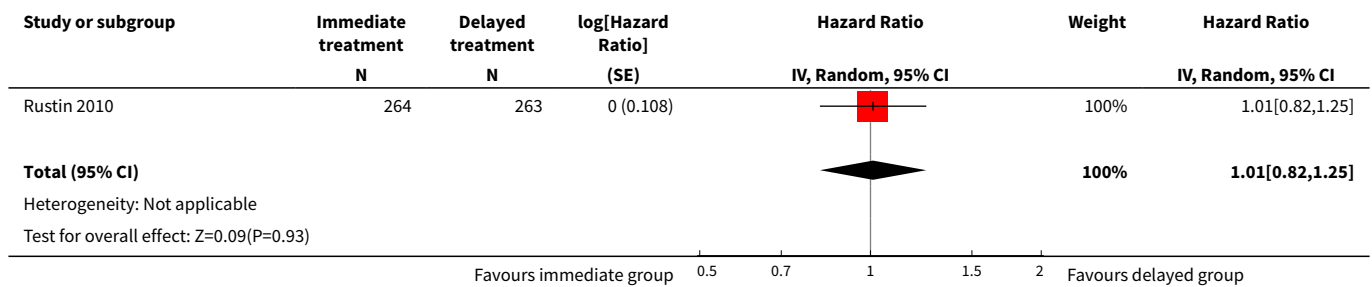|	Gynaecological Cancer Research Centre Institute for Women's Health University College London, Maple House, 149 Tottenham Court Road London
Notes	

DATA AND ANALYSES

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

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	1	527	Hazard Ratio (Random, 95% CI)	1.01 [0.82, 1.25]

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

Study or subgroup	Immediate treatment	Delayed treatment	log[Hazard Ratio]	Hazard Ratio	Weight	Hazard Ratio
	N	N	(SE)	IV, Random, 95% CI		IV, Random, 95% CI
Rustin 2010	264	263	0 (0.108)		100%	1.01[0.82,1.25]
Total (95% CI)					**100%**	**1.01[0.82,1.25]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.09(P=0.93)						

Favours immediate group 0.5 0.7 1 1.5 2 Favours delayed group

APPENDICES

Appendix 1. 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.

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

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

19

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 2. 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 3. 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 4. Tumour markers

Tumour marker	Paper	Summary

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

20

(Continued)

IGF-1	Bese **Add paper**	No correlation with disease
CA125 + b2m	Hernádi 1992	b2m has low specificity for detection of ovarian cancer. CA125 performs better
CA72.4	Fayed 1998	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	Serial samples were useful in predicting relapse in a small number of women; clinical role is limited to a small subset of patients
	Lenehan 1986	
CA72.4, CA19.9	Fioretti 1992	Useful for detecting recurrence in patients with normal CA125 at diagnosis
PLAP-A, PLAP-C	Fisken 1989	No correlation with disease
Anti-p53	Gadducci 1995	Not clinically useful
CYFRA 21-1	Gadducci 1998	
D-dimer	Gadducci 2001	
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	Upto 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

Evaluation of follow-up strategies for patients with epithelial ovarian cancer following completion of primary treatment (Review) **21**

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Date	Event	Description
12 September 2018	Amended	Eleven references added to 'Classification pending' after a horizon scanning literature search in August 2018.

HISTORY

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

Date	Event	Description
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

Fiona Kew was the lead author of the original review published in 2011. Tilean Clarke updated the content for this update (2014). Raj Naik developed the original title, protocol and search strategy. He performed the original search and reviewed the papers and assisted in writing the review. Khadra Galaal reviewed the data and assisted in writing the original review and update. Andy Bryant provided statisical and methodological expertise.

DECLARATIONS OF INTEREST

Tilean Clarke: none known
Raj Naik: none known
Khadra Galaal: none known
Andrew Bryant: none known

SOURCES OF SUPPORT

Internal sources

- R&D Department, Queen Elizabeth Hospital, Gateshead, UK.

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 dialog datastar. 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. Disease free survival has been removed as an outcome. This is because time to detection of recurrence is not an adequate surrogate marker for overall survival. 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.

INDEX TERMS

Medical Subject Headings (MeSH)

CA-125 Antigen [blood]; Carcinoma, Ovarian Epithelial; Follow-Up Studies; Neoplasms, Glandular and Epithelial [blood] [*mortality] [*therapy]; Ovarian Neoplasms [blood] [*mortality] [*therapy]; Randomized Controlled Trials as Topic

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

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

22

MeSH check words

Female; Humans

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

23