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

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Abstract

Background—Ovarian cancer is the sixth most common cancer and seventh cause of cancer death in women worldwide. Traditionally, many patients who have been treated for cancer undergo long-term follow up in secondary care. Recently however it has been suggested that the use of routine review may not be effective in improving survival, quality of life (QoL), and relieving anxiety. In addition, it may not be cost effective.

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

Search methods—We searched the Cochrane Gynaecological Cancer Group Trials Register, Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, 2010, Issue 4), MEDLINE and EMBASE (to November 2010). We also searched CINAHL, PsycLIT, registers of clinical trials, abstracts of scientific meetings, 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 patients 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—We found only one RCT (Rustin 2010) that met our inclusion criteria. This trial included 529 women and reported data on immediate treatment versus delayed treatment in

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CONTRIBUTIONS OF AUTHORS

Fiona Kew is the main author. She developed the protocol and search strategy, performed the search, reviewed the papers and wrote the review. Raj Naik developed the title, protocol and search strategy. He performed the search and reviewed the papers and assisted in writing the review. Khadra Galaal performed the search strategy, reviewed the papers, assisted in writing the review and edited the final version. Andrew Bryant assisted with the search strategy, performed data extraction and reviewed the evidence.

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DECLARATIONS OF INTEREST

None known

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women with confirmation of remission and with normal CA125 concentration and no radiological evidence of disease after surgery and first-line chemotherapy.

Overall survival showed no significant difference between the immediate and delayed arms 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 = 0·85). Time from randomisation to first deterioration in global health score or death was significantly shorter in the early group compared with the delayed group (HR 0·71, 95% CI 0·58 to 0·88; P < 0·01). The trial was at low risk of bias.

Authors' conclusions—There is a lack of randomised studies on most aspects of follow-up care after treatment for epithelial ovarian cancers. Limited evidence from a single trial suggests that routine surveillance with CA125 in asymptomatic patients, with treatment at CA125 relapse, does not seem to offer survival advantage when compared to treatment at symptomatic relapse. Randomised controlled trials are needed to compare different types of follow up on the outcomes of survival, quality of Life, cost and psychological effects.

Medical Subject Headings (MeSH)

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

MeSH check words

Female; Humans

BACKGROUND

Description of the condition

Ovarian cancer is the sixth most common cancer among women (GLOBOCAN 2002). 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 age 75 years varies between countries, ranging from 0.5% to 1.6% (IARC 2002). This corresponds to an age-standardised rate of ovarian cancer varying between countries from 5 to 14 cases per year in 100,000 women under 75 years. 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 already at an advanced stage (Jemal 2008).

Traditionally, many patients who have completed primary treatment for cancer undergo long-term, even life-long follow up in specialist care (Barnhill 1992; Kerr-Wilson 1995; Kew 2006). The primary rationale is that if a recurrence of cancer is picked up early, that is before the onset of symptoms, it is more likely to be amenable to treatment and therefore survival will be improved (Kunkler 1991). Furthermore, it is proposed that routine review provides other opportunities including management of symptoms, either from the disease itself or from treatment side effects, and access to supportive and palliative care. Patients may also be provided with reassurance that the cancer has not returned, which could

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maintain psychological well-being, allow the collection of outcome data, and provide positive feedback for the clinicians involved in a patient's care (Kerr-Wilson 1995).

Description of the intervention

Recently it has been suggested that the use of routine review may not be effective in achieving these aims. Detection of recurrence may be delayed because some women do not present with symptoms until their next routine appointment (Olaitan 2001). Evidence in endometrial, cervix and vulval cancers has called in to question the benefit of detecting recurrence at an asymptomatic stage (Kew 2005). In most cases detection of recurrent disease at an asymptomatic stage does not appear to confer any survival benefit. However, it would appear that studies in gynaecological cancers are hampered by being retrospective and of poor methodological quality (Kew 2005). A recent meta-analysis of randomised controlled trials of follow up after bowel cancer has suggested a benefit from intensive follow up compared to little or no follow up. The effect was most pronounced in the trials that used computed tomography 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 may be attributable to other factors. These factors included increased psychological well-being, altered lifestyle, improved treatment of coincidental disease through regular medical contact, any of which may contribute to the remaining lives saved (Renehan 2005).

How the intervention might work

Qualitative work in gynaecological cancer on patients who have been treated for early stage disease, including those who have been treated for ovarian cancer, has shown that the overriding reason that women want continued follow up is fear of recurrence. In one survey (Stewart 2001) 82% of women attributed their lack of cancer recurrence to close medical follow up. 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 the women from attending (Bradley 2000). A recent 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 equally effective as the traditional secondary care model albeit in more common cancer types. However, their impact on quality of life has not been assessed.

Why it is important to do this review

The objectives of follow up include psychological support and audit, as well as treatment of recurrent epithelial ovarian cancer. The treatment of recurrent ovarian cancer represents a challenge with options invariably including chemotherapy, which has poor long-term prognosis (Gadducci 2007). Whilst there is no curative salvage treatment for recurrent

ovarian disease in those previously responding to platinum-based chemotherapy, surgery with or without chemotherapy offers an opportunity to produce significant periods of disease remission after the recurrence (Bristow 2009). The follow up of asymptomatic patients generally includes complete clinical history, serum cancer antigen (CA)125 assay, physical examination and often ultrasound examination, whereas additional radiologic imaging techniques are usually performed when symptoms or signs appear (Gadducci 2007).

It is difficult to extrapolate results in 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 review set out to systematically evaluate the available evidence 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)

Types of participants

- Patients of any age diagnosed with primary ovarian cancer of epithelial histological subtype following completion of 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 (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

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

Electronic searches—See: Cochrane Gynaecological Cancer Group methods used in reviews.

The following electronic databases were searched:

- The Cochrane Gynaecological Cancer Review Group Trial Register;
- Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2010, Issue 4);
- MEDLINE (to November 2010);
- EMBASE (to November 2010);
- CINAHL (to November 2010);
- PsycLIT (to November 2010).

The MEDLINE, EMBASE and CENTRAL search strategies aimed to identify RCTs comparing follow-up strategies in patients with epithelial ovarian cancer are presented in Appendix 1,Appendix 2 and Appendix 3 respectively.

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

Searching other resources

Unpublished and grey literature: Metaregister, Physicians Data Query, www.controlled-trials.com/rct, www.clinicaltrials.gov, www.cancer.gov/clinicaltrials, NHMRC Clinical Trials Register, UKCCCR Register of Cancer Trials and Gynaecologic Oncologists of Canada (http://www.g-o-c.org) were searched for ongoing trials.

Handsearching: Reports of conferences were handsearched in the following sources:

- Gynecologic Oncology (Annual Meeting of the American Society of Gynecologic Oncologists);
- International Journal of Gynecological Cancer (Annual Meeting of the International Gynecologic Cancer Society);
- British Journal of Cancer;

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- British Cancer Research Meeting;
- Annual Meeting of European Society of Medical Oncology (ESMO);
- Annual Meeting of the American Society of Clinical Oncology (ASCO);
- BioMed (open text publisher);
- American Association for Cancer Research (AACR) conferences;
- European Society of Gynecological Oncology (ESGO) conference.

We additionally searched the Journal of Ovarian Research: http://www.ovarianresearch.com/home/.

Reference lists of articles and other reviews on the subject were also checked for the purpose of retrieving further information, either published or unpublished; researchers involved in this area were contacted.

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 the review authors (KG, RN, FK) independently. Those studies which clearly did not meet the inclusion criteria were excluded. The full texts for potentially relevant studies were obtained for independent assessment of eligibility by the three review authors.

Data extraction and management—Data extraction was performed on the only suitable trial identified. Data extraction on to pre-designed forms was conducted by two independent review authors (AB, KG). Data extracted included the following.

- 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 of 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.

Data on outcomes were extracted as below.

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

Both unadjusted and adjusted statistics were extracted, where reported.

Where possible, all data extracted were those relevant to an intention-to-treat analysis, in which participants were analysed in the groups to which they were assigned.

The time points at which outcomes were collected and reported were noted.

Assessment of risk of bias in included studies—The risk of bias in the included RCT was assessed using the Cochrane Collaboration's tool and criteria specified in Chapter 8 of the Cochrane Handbook 2008. This included assessment of:

- sequence generation;
- allocation concealment;
- blinding (of participants, healthcare providers and outcome assessors);
- incomplete outcome data, where 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 the satisfactory level of loss to follow-up for each outcome as:
- ◇ Yes, if fewer than 20% of patients were lost to follow up and reasons for loss to follow up were similar in both treatment arms,
- ◇ No, if more than 20% of patients were lost to follow up or reasons for loss to follow up differed between treatment arms,
- ◇ Unclear if loss to follow up was not reported;
- selective reporting of outcomes;
- other possible sources of bias.

The risk of bias tool was applied independently by two review authors (AB, KG). Differences were resolved by discussion between the two authors. Results are presented in a risk of bias graph.

Measures of treatment effect—We used the following measure of the effect of treatment:

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

Dealing with missing data—We did not impute missing outcome data.

Data synthesis—We only identified one included trial so it was not possible to perform meta-analysis. Therefore it was not relevant to assess heterogeneity between results of trials and we were unable to assess reporting biases using funnel plots or conduct any subgroup or sensitivity analyses.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Results of the search—The search strategy identified 1107 unique references. The titles and abstracts of these were read independently by three review authors and articles which obviously did not meet the inclusion criteria were excluded at this stage. Seven articles were retrieved in full and translated into English where appropriate; up-dated versions of relevant studies were identified. The full-text screening of these seven references excluded six of them for the reasons described in the table Characteristics of excluded studies. However, one completed RCT was identified that met our inclusion criteria and is described in the table Characteristics of included studies. Searches of the grey literature did not identify any additional trials.

Included studies—One prospective study was identified (Rustin 2010). This is a randomised controlled, multi-centre trial in ovarian cancer (OC) looking at early 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 patients of whom 529 were randomly assigned to treatment groups and were included in the analysis. All 529 were assessed at the end of the trial (265 early, 264 delayed). All 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 last follow up or death from any cause.

Women assigned to early treatment started chemotherapy 4·8 months (95% CI 3·6 to 5·3 months) earlier 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 (186 early, 184 delayed) in the trial. Median age at registration was 61 years (range 53 to 68 years); 81% were FIGO stage III/IV. Second-line chemotherapy started a median of five months earlier in the immediate arm and the chemotherapy treatment was given according to local institutional protocols. Predominant histologies were serous and endometrioid, involving 53% and 17% of participants respectively. Median follow up from randomisation was 49 months.

Median survival from randomisation was 25·7 months (95% CI 23·0 to 27·9) for patients on early 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 early, 184 delayed).

Median time spent with a good global health score was 7·2 months (95% CI 5·3 to 9·3) for women assigned to early and 9·2 months (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 following stratification factors were used 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, WHO performance status, and time from doubling of CA125 concentration to randomisation. The trialists also reported a HR adjusting 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 at three years for EORTC 55955 was also performed for overall survival.

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) and time to third-line treatment or death were also reported in the trial, 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 European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire.

Subgroup analyses of individual components of the QLQ-C30 subscales were also carried out. The following functional QoL components were reported: physical, role, emotional, cognitive and social. Some of these were then subdivided into symptom QoL components. The HRs and their 95% CIs, for most components in Table 4, were not consistent with the reported significance probabilities and it was unclear as to what adjustment had been made on the estimates.

Toxic outcomes were not included as a secondary outcome measure.

Excluded studies—Six references were excluded after obtaining the full text, for the following reasons.

- Chan 2008

This is a retrospective study on the role of regular eaxmination during follow up, not a randomised trial.

- Gadducci 2007

This is a literature review on surveillance procedures for patients treated for epithelial ovarian cancer, not a randomised trial.

- Goonewardene 2007

A review of the literature, not a randomised trial.

- Maggino 1983

Not a randomised trial.

- Olaitan 2001

A retrospective review of routine follow-up modalities in the detection and management of recurrent gynaecological cancer. Not a randomised trial.

- Rustin 1996

Not a randomised trial.

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

Risk of bias in included studies

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

The trial reported the method of generation of the sequence of random numbers used to allocate women to treatment arms and made an effort to conceal this allocation sequence from the patients and healthcare professionals involved in the trial. It also reported that the patients, healthcare professionals and outcome assessors were blinded. All women who were randomised were analysed but it was unclear whether outcomes had been selectively reported. 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 the EORTC QLQ-C30 questionnaire (Table 4), so we scored the ‘free of other bias’ item as being at high risk of bias.

Effects of interventions

Immediate versus delayed treatment in patients with increased CA125 levels

—We found only one trial (Rustin 2010) that met our inclusion criteria. The trial which included 529 women reported data on immediate versus delayed treatment in women who had had confirmation of remission with 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 = 0·85). The unadjusted estimate was robust to estimates that were adjusted for the stratification factors of 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 of 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 (median 3·2 months, 95% CI 2·4 to 4·3) in the early group compared with the delayed group (5·8 months, 95% CI 4·4 to 8·5; HR 0·71, 95% CI 0·58 to 0·88; P = 0·002). The trial authors claimed that subgroup analyses of individual components of the QLQ-C30 subscales showed deterioration in score sooner in the early 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 early treatment. However this is not consistent with the 95% CIs in Table 4 and it was unclear as to what adjustment had been made on the estimates. It was also mentioned that since the QLQ-C30 questionnaire asks about symptoms only 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

We found one RCT (Rustin 2010), which included 529 women, that met our inclusion criteria. This trial reported data on immediate treatment versus delayed treatment in women with confirmation of remission when they had had 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 early treatment based on a raised serum marker level alone. There were a total of 370 deaths in the trial and there was no evidence of a difference in overall survival between the immediate and delayed treatment arms. Therefore, there may be no value in the routine quarterly measurement of CA125 in the follow up of ovarian cancer patients after complete clinical remission following primary surgery and first-line platinum-based chemotherapy (Analysis 1.1).

Women treated in the immediate treatment arm received on average 12 more total cycles of chemotherapy (30 versus 18 months in the immediate versus delayed treatment arms, respectively). Early treatment appeared to negatively impact on QoL. The observed decrease in QoL in the trial may have been attributable to additional cycles of chemotherapy that resulted in additional toxicity (for example neuropathy or hospital admissions secondary to neutropenias) and more time spent in physicians' offices, and which may have resulted in an

hastened demise due to the toxicities. 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 various retrospective case series are of inadequate quality and in many instances do not allow for comparison. The main limitation of this review is the fact that conclusions are based on single trial analysis.

Overall completeness and applicability of evidence

To date, one RCT has compared early 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) as the review comprised evidence from only one included trial, although the trial was of 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 (Rustin 2010) was adjudged to have been at low risk of bias, the fact that there were no accompanying trials to support the evidence resulted in a downgrade of evidence to reflect the uncertainty in the single trial analysis.

Quality of the evidence

The one trial included a reasonably large number of women (n = 529) and was at low risk of bias, largely because it was a well conducted and reported trial. Outcomes were analysed using the appropriate statistical techniques and a hazard ratio was used for time-to-event data. This is the best statistic to summarise the difference in risk in two treatment groups over the duration of a trial when there is ‘censoring’, that is the time to death is unknown for some women as they are still alive at the end of the trial. The trialists also performed sensitivity analyses to test the robustness of unadjusted estimates by adjusting for important stratification and prognostic factors. However, the confidence intervals and significance probabilities in subgroup analyses of individual components of the QLQ-C30 subscales 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 too much since the quality of the trial appears to be reasonably good, but the amount of available evidence does not allow robust conclusions for the comparison of different follow-up strategies.

Potential biases in the review process

A comprehensive search was performed, including a thorough search of the grey literature. All studies were sifted and data extracted independently by at least two review authors. The review was restricted to RCTs, which 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 treatment to have been effective may not have been published. We were unable to assess this possibility since we found only one included trial.

Agreements and disagreements with other studies or reviews

A recent review (Gadducci 2007) suggested that it is uncertain whether the early detection of recurrence is beneficial in terms of survival as the clinical advantage of an intensive follow up program has not yet been demonstrated. Therefore, the definition of specific guidelines for the surveillance of patients with this malignancy is still controversial. Moreover, retrospective analyses assessing the value of postoperative surveillance programs have some potential bias (lead time, length time biases).

Apart from OVO5 (Rustin 2010), all other studies on follow-up strategies use the detection of recurrence as the primary endpoint. This is problematic as 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 on 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 tumours have a longer pre-clinical course and are therefore more likely to be detected by periodic tests. In turn, the 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. However, it does permit consideration of strategies for future studies.

Authoritative guidelines—Three sets of national or international guidelines were identified.

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 they recommended three or four monthly follow up for the first two years after completion of primary therapy, with frequency reducing after this time. At each visit they recommended complete history, physical examination including rectal and vaginal examination and CA125. They recommended that radiological investigations should be individualised.

European Society of Medical Oncology (European, 2008 Annals of Oncology) —(Aebi 2008)

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. Each visit should include history and physical examination including pelvic

examination. They recommend that CA125 should be performed at each follow-up visit. Computerised tomography (CT) scan should be performed if there is clinical or CA1215 evidence for progressive disease.

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

ACR Appropriateness Criteria 2007—(Javitt 2007)

No recommendations were given for follow up.

Early detection of recurrence—See table in Appendix 4.

Physical examination—Physical examination alone is a poor tool for detecting recurrence, with sensitivity of only 39.4% (Menczer 2006). Chan found that 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 precedes clinical and radiological relapse by between one and nine months (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 (Rustin 2010) has shown no survival advantage from early treatment at the time of CA125 relapse, when compared with treatment at symptomatic relapse. Second-line chemotherapy was given on average five months earlier in the early treatment arm. Furthermore, knowledge of the CA125 result has been shown to have an association with depression and anxiety (Parker 2006). Some anxiety can be reduced by having the CA125 result available at the clinic visit rather than waiting for the clinic to take the blood and then receiving the result at a later stage (Palmer 2006).

Other tumour markers—Multiple other tumour markers have been investigated, either alone or in combination with CA125, in order to improve detection of recurrence. None provide evidence of benefit in terms of survival if recurrence is detected earlier.

Carcinogenic embryonic antigen (CEA) has been investigated in several papers. It is raised in 65% if women with ovarian cancer (Khoo 1979) and is more likely to be raised in mucinous tumours. It may be of use in such tumours when the CA125 is normal at diagnosis (Lenehan 1986).

Imaging—Multiple papers have looked at different imaging modalities to try to detect recurrence.

Ultrasound (USS) has been shown to be more sensitive than clinical examination alone in detecting recurrence (Khan 1986) and has an overall accuracy of 98% when compared to findings at laparotomy. In women with no clinical or biochemical signs of relapse, USS has

been shown to have a positive predictive value of 100% with only one false negative out of 275 cases (Testa 2005). However, CA125 and clinical examination in combination discover 98% of recurrences (Fehm 2005). CT, or where inconclusive magnetic resonance imaging (MRI), are more useful than USS for proving macroscopic disease recurrence (Prayer 1993; Testa 2005). USS may have a role in the detection of extraperitoneal lesions (Okai 1992).

Women in whom recurrence is suspected on the basis of CA125 and clinical review require imaging to plan treatment (Fehm 2005). CT or MRI remain the imaging modes 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 radiology and imaging specialists positron emission tomography (RIS/PET) and PET CT has yet to be fully established. In one paper PET seemed to have no benefit when compared to MRI or CT (Kubik 2000). However initial data in small series (Barzen 1990; García 2003; Grabiec 2006; Hauth 2005; Kim 2007; Mangili 2007; Nakamoto 2001; Thrall 2007;Torizuka 2002; Zhu 2002; Zimny 2001) would seem to suggest that its role is likely to be in the diagnosis of recurrence where initial CT or MRI has been inconclusive. There may also be an additional role in determining the mode of treatment of recurrence, in particular the place of surgery and prediction of resectability (Kitajima 2008; Lenhard 2008). However, it is probably inferior to CA125 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 (Engblom 1995) of 577 aspirations of the Pouch of Douglas in 110 women being followed up after ovarian cancer showed a sensitivity of 60%. 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 the Gynaegnost test (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 reduced the false negative rate in comparison to CA125 (Shinozuka 1994) but required an invasive procedure without evidence of additional benefit.

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AUTHORS' CONCLUSIONS

Implications for practice

There is no evidence in this review of one large trial that routine surveillance with CA125 in asymptomatic patients and treatment at CA125 relapse offers any survival advantage when compared to treatment at symptomatic relapse.

In the absence of symptoms and with a normal CA125 result, clinical examination is not mandatory.

The addition of other tumour markers does not offer significant advantage in terms of detecting recurrence when compared with CA125 alone. Routine radiological examination has not been shown to be of benefit in asymptomatic women.

Early treatment with chemotherapy appeared to negatively impact on QoL; this may be attributable to additional cycles of chemo-therapy resulting in additional toxicity.

Implications for research

More effective salvage treatments are required for relapsed ovarian cancer and further research into follow up is needed, directed towards QoL issues and psychological impact in addition to survival outcomes and cost effectiveness. Development of novel treatments may required re-evaluation of early detection and treatment of recurrence.

Prospective trials are needed to evaluate hospital-based follow up versus other follow-up strategies including nurse led, patient initiated, telephone or by a general practitioner.

Cancer services within primary care must develop skilled professionals and educational interventions to provide appropriate and timely support for women following cancer treatment, so that they are able to manage the uncertain future that comes with a diagnosis of ovarian cancer.

Since ovarian cancer is a disease with many relapses and since there is no value in early detection with currently available treatments, further prospective studies should consider QoL, costs and survivorship.

Prospective trials on follow-up methods need to be evaluated in women treated with surgery for recurrent ovarian cancer to determine the effect of timing of surgical treatment on survival and QoL issues.

Prospective trials are needed to evaluate interventions during follow up that may help 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 follow up, telephone follow up and patient initiated follow up. Individual patient needs and patient choice also require further investigation as part of a long-term survivorship assessment. However, such alterations in practice would need prospective evaluation.

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Internal sources

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

External sources

- Department of Health, UK.

NHS Cochrane Collaboration Programme. Grant Scheme CPG-506

Appendix 1. MEDLINE search strategy

Medline 1950 to Nov Week 3 2010

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 2. Embase search strategy

Embase 1980 to 2010 Week 49

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

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Appendix 3. Central search strategy

CENTRAL Issue 4, 2010

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
IGF-1		No correlation with disease
CA 125 + b2m	Hernádi 1992	b2m has low specificity for detection of ovarian cancer. CA 125 performs better
CA72.4	Fayed 1998	Added to CA 125 it improves sensitivity and specificity for detecting recurrence, especially in mucinous tumours
CEA	Khoo 1974 Khoo 1979 Lenehan 1986	Persistently low levels are consistent with a good prognosis serial samples were useful in predicting relapse in a small number of women; clinical role is limited to a small subset of patients
CA72.4, CA19.9	Fioretti 1992	Useful for detecting recurrence in patients with normal CA 125 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	Lack tumour specificity
SLX	Iwanari 1989	May be of benefit in combination with CA 125
CA 125 + CA15.3 + CA72.4 + SCC + 90K	Garzetti 1991	Includes all gynaecological malignancies. CA 125 plus 90K identified 86% of recurrences
CA 125 + CEA + ferritin + TPA	Lahousen 1987	If normal can avoid second look laparotomy
CA 125 + CASA	Oehler 1999	CASA less sensitive than CA 125, CASA may be useful when CA 125 inconclusive
Sialyl Le(x)-i	Kobayashi 1989	Upto 96% showed rise in levels with tumour progression

Tumour marker	Paper	Summary
OPN	Schorge 2004	inferior to CA 125 in determining response to treatment, but showed an earlier rise in recurrent disease
CA 125 + TPS	Sliutz 1995	improved detection of recurrence when compared to CA 125 alone
IAP	Shimizu 1986	May have a role in early detection of recurrence
TPS	Tempfer 1998 Zakrzewska 2000	TPS is useful, but cannot replace CA 125 TPS may rise before CA 125 rises in women with recurrence

CHARACTERISTICS OF STUDIES

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

Rustin 2010

Methods	A randomised controlled, multi-centre trial in ovarian cancer (OC) of early treatment of relapse based on CA 125 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 early treatment based on a confirmed elevation of CA 125 levels versus delaying treatment until clinically indicated Patients whose CA 125 levels rise to more than two times the upper limit of normal are randomised to one of two treatment arms Randomisation to early or delayed treatment groups (1:1 ratio) was done independently by each coordinating centre 1442 patients were registered from 59 sites in 10 countries (centres across the UK, Spain, Norway, the Netherlands, France, Russia, Belgium, Ireland, Austria, and South Africa) between 1996 and 2005. Randomisation closed on March 31, 2008 with 529 patients (265 immediate and 264 delayed) randomised and when the targeted number of events (deaths) were reached
Participants	Eligible patients included women with ovarian cancer in clinical complete remission following first-line platinum-based chemotherapy and a normal CA 125 The following histologies were included: epithelial ovarian cancers, fallopian tube cancers or primary serous peritoneal carcinoma For randomised patients 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 patients
Interventions	**Interventions** Patients whose serum CA-125 levels exceeded twice the upper limit of normal were randomised to receive either: • ***Arm I:*** the clinician was informed of the initial rise in CA 125 level. A confirmatory test was performed immediately. Within 4 weeks of the initial CA 125 elevation, patients with a second confirmed elevation received treatment for recurrent disease according to standard local practice. Patients with a normal CA 125 on the confirmatory test received no treatment until clinically indicated. • ***Arm II:*** the clinician was blinded to the CA 125 results. Patients underwent normal monitoring. When clinically indicated, patients 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** The primary outcome measure was 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);
- Quality of life with duration of good quality of life 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	Analysis was by intention to treat. 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 patients on early 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 early, 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 early and 9·2 months (95% CI 6·4 to 10·5) for those assigned to delayed treatment Quality of life was assessed at baseline, at each follow-up visit, and, if treatment was instituted, before each chemotherapy course Patients were followed every three 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 CA 125 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	"CA 125 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	% analysed: 529/529 (100%) for primary outcome and overall survival was analysed using appropriate statistical techniques which accounted for censoring 21 (4%) women were lost to follow up.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement.
Other bias	High risk	Point estimates and 95% confidence intervals 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). 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 sub-scale factors appeared to have a vastly decreased P value from what you might expect given the point and CI estimates It was also unclear what the HRs in Table 4 were adjusted for

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

Study	Reason for exclusion
Chan 2008	Not a randomised trial A retrospective study on the role of regular examination during follow up
Gadducci 2007	A review of the literature, not a randomised trial
Goonewardene 2007	A review of the literature, not a randomised trial
Maggino 1983	Not a ranodomised trial
Olaitan 2001	Not a randomised trial A retrospective review of routine follow up modalitiesin the detection and management of recurrent gynaecological cancer
Rustin 1996	Not a randomised trial

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	This is a prospective RCT
Participants	Women undergoing treatment for ovarian cancer The trial recruited 113 women, and closed to recruitment on 31st December 2008. The study completes in December 2010 and will report in Spring 2011
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	01/11/2005
Contact information	Ms A Lanceley Gynaecological Oncology 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

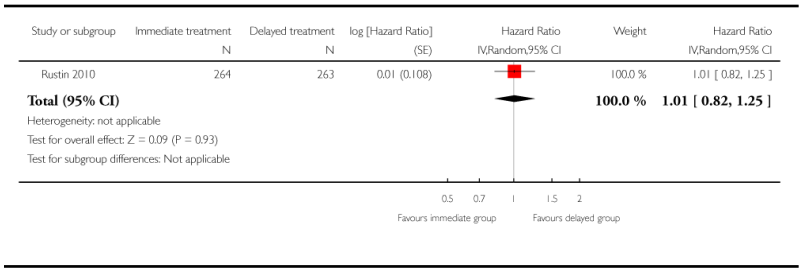
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	1	527	Hazard Ratio (Random, 95% CI)	1.01 [0.82, 1.25]

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

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

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

Outcome: 1 Overall survival



HISTORY

Protocol first published: Issue 3, 2006

Review first published: Issue 6, 2011

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 on 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.

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* *Indicates the major publication for the study*

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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 patients who have been treated for cancer undergo long-term follow up in hospitals. Whilst there may be other benefits from follow up, it has been suggested that the use of routine review may not result in women with this disease living longer given that recurrent ovarian cancer is incurable. We set out to review the evidence for different types of follow up of women who have completed treatment for the commonest type (epithelial, that is coming from the surface of the ovary) of ovarian cancer. Only one good quality randomised (toss of a coin to choose which group) trial was found which could give any evidence on what to do. This trial suggested no increase in length of life from early treatment with chemotherapy for women with recurrence that was identified by a tumour marker (CA125) blood test compared to waiting to give treatment when women developed symptoms from their cancer. We conclude that the very limited evidence suggests that there may be no benefit from early detection by the blood test and subsequent early chemotherapy for recurrent ovarian cancer. Also, the women having early chemotherapy treatment of their relapsed cancer may have led to a decreased quality of life for these women compared to the group who were treated when they noticed symptoms.

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

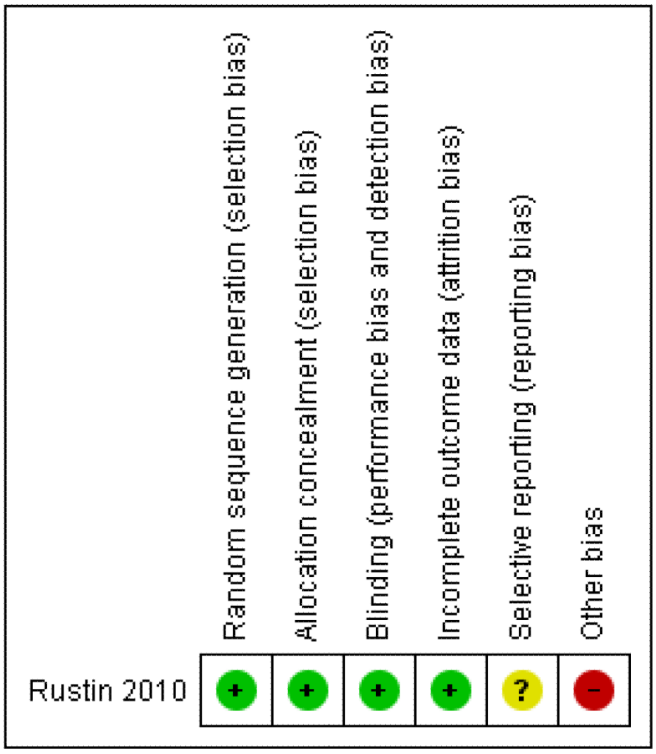

Figure 1.
Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

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