Systematic review of adjuvant care for women with stage I ovarian carcinoma

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CRD summary
This review aimed to determine the optimal strategy of adjuvant therapy in stage 1 ovarian cancer. There was some evidence that adjuvant chemotherapy improved 5-year overall and disease-free survival, but insufficient evidence to recommend radiotherapy. Surgical staging of suspected cases and further research is needed. The generalisability of the conclusions is uncertain given the insufficient reporting of review methods and study details.

Authors’ objectives
To assess the optimal strategy for adjuvant care for women with stage I ovarian cancer.

Searching
MEDLINE, Cancerlit, the Cochrane Library, PDQ, the Canadian Medical Association and the National Guideline Clearinghouse were searched for studies published between 1965 and April 2004; the search terms were reported. The authors searched proceedings of the meetings of the American Society of Clinical Oncology (1997 to 2003), as well as the reference lists of papers and review articles, for additional studies. Both abstracts and fully published papers were eligible for inclusion. Studies published in languages other than English were excluded.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
To be eligible for inclusion, studies had to compare two or more adjuvant treatments such as radiotherapy versus chemotherapy. However, some of the identified studies compared radiotherapy or chemotherapy versus no adjuvant treatment. Other treatment comparisons were: chemotherapy versus radiotherapy; chemotherapy versus intraperitoneal radioactive chromic phosphate; different types of chemotherapy. The chemotherapy agents assessed were platinum-based agents, melphalan, carboplatin (alone or with paclitaxel) and cisplatin (alone or with cyclophosphamide). Radiotherapy was either pelvic or whole-abdominal.

Participants included in the review
To be eligible for inclusion, studies had to report outcomes specifically for women with stage I ovarian cancer, or more than 60% of the participants had to have stage 1 disease.

Outcomes assessed in the review
Outcomes were not specified as part of the inclusion criteria. The outcomes assessed were overall survival at 5 years, disease recurrence at 5 years and adverse events. The median follow-up ranged from 19 to 120 months.

How were decisions on the relevance of primary studies made?
The authors did not state how they selected studies for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
The authors did not state how they extracted data for the review, or how many reviewers performed the data extraction. Overall and disease-free survival proportions were extracted together with hazard ratios (if reported). The numbers of
deaths and recurrences were used to calculate relative risks (RRs) with 95% confidence intervals (CIs). Adverse events for all women, not just those with stage I disease, were also extracted.

**Methods of synthesis**

How were the studies combined?
The studies were combined using a random-effects meta-analysis.

How were differences between studies investigated?
The adequacy of surgical staging was assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Guidelines and used to determine whether the studies should be combined. A narrative and tabular summary of differences between the studies was presented: this focused on surgical staging, treatment comparisons, age of the study, and stages of disease included in the studies. Statistical heterogeneity was assessed using a chi-squared test and the I-squared statistic.

**Results of the review**
The review included 13 RCTs (n approximately 2,902), eight of which reported findings solely for women with stage I ovarian cancer. The exact number of participants with stage I cancer was unclear as some trials included other cancer stages.

Adjuvant chemotherapy was associated with statistically significantly improved 5-year survival compared with no adjuvant treatment (RR 0.74, 95% CI: 0.58, 0.94, p=0.01) and reduced risk of recurrence (RR 0.70, 95% CI: 0.58, 0.86, p=0.0004). There was little heterogeneity (I-squared of 0% for each outcome). These findings were based on five RCTs where most of the participants did not undergo lymphadenectomy as part of surgical staging. When the four RCTs with optimal or modified surgery were pooled, there was no statistically significant difference in 5-year survival (RR 0.81, 95% CI: 0.58, 1.21) or disease recurrence (RR 0.73, 95% CI: 0.52, 1.02).

Two RCTs compared adjuvant radiotherapy versus no adjuvant radiotherapy, but both had methodological limitations such as small sample sizes and one had excluded over 50% of the patients from the analysis. Conclusions could not be drawn.

Three RCTs compared chemotherapy versus radiotherapy, but the findings were not pooled as two studies were more than 20 years old and used outdated treatment regimens. None of the studies reported statistically significant differences in survival between groups, although one did report a statistically significant difference in disease recurrence (6% for chemotherapy versus 30% for radiotherapy, p<0.05).

Four RCTs compared adjuvant chemotherapy with radioactive chromic phosphate. None of the studies reported statistically significant differences in survival between groups and the trials were not pooled.

Two RCTs compared two different forms of chemotherapy, but both were reported as abstracts so only limited information was available. Neither reported statistically significant differences in survival or recurrence.

The authors provided a narrative summary of the toxicity associated with each regimen, but noted that the measurement scales used varied between studies and were not reported.

**Authors’ conclusions**

There is evidence that adjuvant chemotherapy improves survival and decreases disease recurrence in women with stage I ovarian cancer. There is a need to define which population of stage I patients would benefit most from adjuvant treatment, the optimal chemotherapy regimen, and the dose and duration of treatment. There was insufficient evidence to make any recommendations about pelvic or whole-abdominal radiotherapy, or chromic phosphate.

**CRD commentary**

This review searched a wide range of sources and had defined inclusion and exclusion criteria, but the focus of the
review question could have been more clearly stated. The authors noted that studies were included if they compared 'two or more adjuvant treatments e.g. chemotherapy and radiotherapy', however, a large part of the analysis focused on comparing adjuvant chemotherapy versus no adjuvant therapy. Not all studies were of stage I cancer only, some studies included other stages and did not report the results for stage I women separately. Some of the trials in the pooled analysis included other stages, so it was unclear if the observed survival benefits related to stage I disease only. Studies in abstract form were included but non-English papers were excluded, therefore some studies might have been missed.

The authors did not describe the methods used to select the studies, assess validity or extract the data. Relevance for pooling was assessed in relation to the surgical staging of disease but not the methodological quality of the studies. A formal quality assessment did not appear to have been performed, although the authors did highlight some methodological problems in their discussion. Only limited details of the participants and treatments were reported.

The authors justified their decisions about whether or not to pool different sets of studies. The method of analysis used appeared appropriate given the data available. However, as these are survival data, it might have been appropriate to pool hazard ratios if this information was available in all of the studies.

Owing to a lack of comparative data and methodological limitations in studies of other therapies, the authors' conclusions focused on whether or not adjuvant chemotherapy should be used rather than the most appropriate form of adjuvant therapy. The conclusions from the pooled analysis may be optimistic as they did not apply solely to stage I patients and not all women had optimal surgical staging. The limited reporting of the review methods and study details made it difficult to assess the generalisability of the review findings.

**Implications of the review for practice and research**

**Practice:** The authors stated that women with suspected ovarian cancer should undergo optimal surgical staging (as outlined by the EORTC guidelines). Women with stage I cancer who have not had optimal surgical staging should be offered platinum-based chemotherapy as they may have higher stage disease.

**Research:** The authors stated that further research is needed to assess the role of adjuvant chemotherapy in optimally staged stage I ovarian cancer. Research into the optimal chemotherapy regimen, including dose and duration, is also needed. As the completeness of surgical staging is a prognostic factor for survival, future studies should compare similar patient populations.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.