Secondary surgical cytoreduction for advanced epithelial ovarian cancer: patient selection and review of the literature

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Authors' objectives
To assess the risks and benefits of secondary surgical cytoreduction for advanced epithelial ovarian cancer.

Searching
MEDLINE was searched (search dates are unclear and search strategies are unspecified), and reference lists from original research and review articles were examined. The search appears to have been restricted to English language literature.

Study selection
Study designs of evaluations included in the review
The inclusion criteria relating to study design were not clearly specified. Among the included studies were randomised and non-randomised controlled trials, retrospective comparative studies and case series.

Specific interventions included in the review
Surgical interventions to remove or debulk epithelial ovarian tumours.

Participants included in the review
Women with ovarian cancer who either: have a recurrence of the cancer after a clinical disease-free interval of over 6 months; are clinically and radiologically free of ovarian cancer after primary surgery and chemotherapy, but who are found to have macroscopic disease at second-look laparotomy; have a bulky, unresectable tumour discovered during initial surgery and undergo interval cytoreductive surgery after neoadjuvant chemotherapy; or have evidence of clinical disease progression while receiving first-line therapy.

Outcomes assessed in the review
The outcome was survival (either median survival in months, or percentage survival to up to 5 years). Morbidity associated with surgery was also recorded.

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

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

Data extraction
The authors do not state how the data were extracted for the review, or how many of the authors performed the data extraction. Tables provide brief details of study sizes, comparison groups and results in standardised forms.

Methods of synthesis
How were the studies combined?
The impact of secondary cytoreductive surgery on four types of patients (women with a recurrence of the cancer after a clinical disease-free interval of over 6 months; women clinically and radiologically free of ovarian cancer after primary surgery and chemotherapy, but who were found to have macroscopic disease at second-look laparotomy; women with a
bulky, unresectable tumour discovered during initial surgery and undergo interval cytoreductive surgery after neoadjuvant chemotherapy; or women with evidence of clinical disease progression while receiving first-line therapy) were considered separately. For each type of patient, a narrative summary of the available research was provided, and for the first three types, tables showing survival data were produced.

How were differences between studies investigated?
The authors do not state how differences between the studies were investigated.

**Results of the review**

Five studies (253 patients in total) reporting survival data after secondary cytoreductive surgery for recurrent ovarian cancer. None of these studies compared surgery with non-surgical interventions, although one study included 38 patients who all underwent laparotomy and then did or did not receive debulking surgery.

Eight studies (459 patients in total) reporting survival data after secondary cytoreduction at second-look laparotomy. None of these studies compared second-look laparotomy with no second-look laparotomy.

Five studies (524 patients in total), including 2 randomised controlled trials (RCTs) and 2 non-randomised controlled trials, comparing interval cytoreductive surgery with either no surgery or with optimal primary surgery.

Two case series (108 patients in total) reporting survival after secondary cytoreduction for progressive disease.

Survival after secondary cytoreductive surgery for recurrent ovarian cancer.

The median disease-free survival periods after surgery, reported from individual studies, ranged from 3 to 43 months. Longer median survival periods were reported among patients who had longer disease-free intervals before secondary surgery, and among those left with smaller amounts of residual disease after surgery. Of the patients included in the 5 case series studies, 35% experienced surgical morbidity including gastrointestinal complications (11%), pulmonary complications (6%) and death (1%).

Survival after secondary cytoreduction at second-look laparotomy.

The percentages of patients in comparison 'arms' of individual studies who survived for 4 or 5 years after secondary surgery ranged from 0 to 56%. In all of the included studies, higher proportions of patients with less residual disease survived for 4 or 5 years.

In a study excluded from the analysis of survival, 19% of 682 patients undergoing second-look laparotomy experienced surgical morbidity.

Survival after interval cytoreduction.

Two RCTs showed better survival rates among patients receiving interval surgery than among those not receiving it (56% compared with 46% of patients surviving to 2 years in the larger of the two trials, p=0.01). A retrospective study showed contradictory results (not statistically significant).

Among 232 patients involved in 4 studies of interval debulking, one of which was not included in the survival analysis, 26% were reported to have suffered surgical morbidity.

Survival after secondary cytoreduction for progressive disease.

Two studies followed-up patients with progressive disease who received cytoreductive surgery. In one, slightly longer median survival time (12 months compared with 7.8 months) was seen among patients left with less than 1cm of residual disease after surgery, but in the other, no difference was seen. Operative morbidity was recorded in 24% of patients in the former study.
Authors' conclusions
Heterogeneous patient populations and a variety of study protocols complicate analysis of the published data on secondary cytoreductive surgery. Nevertheless, several conclusions can be drawn from the available data. Many patients with persistent ovarian cancer after primary therapy are able to undergo optimal tumour resection. The morbidity associated with these procedures reflects the surgical radicality that is often required. In as much as survival benefits are generally limited to those patients reduced to minimal residual disease, aggressive efforts at secondary resection should be confined to those patients in whom optimal cytoreduction appears feasible and beneficial. There is compelling evidence that patients with recurrent ovarian cancer, particularly after a prolonged clinical remission, can derive a significant survival benefit from optimal secondary debulking.

Patients in complete clinical remission with macroscopic disease detected at the time of second-look laparotomy benefit from secondary debulking surgery, but the most significant survival impact is observed in those patients who are cytoreduced to microscopic residual tumour.

Secondary cytoreduction should be avoided in patients with disease progression during primary chemotherapy, or with recurrence shortly after completing primary therapy.

This therapeutic intervention requires additional evaluation, preferably in the form of prospective randomised protocols, before it can be considered as the standard of care.

CRD commentary
The results of studies included in the tables, which report survival after secondary cytoreductive surgery in specific groups of patients, are clearly presented.

Only limited details are provided of the methods used to undertake this review. The search strategy appears to have been somewhat limited, and it is possible that additional evidence might be available from studies published in languages other than English. The inclusion criteria are not stated clearly. Several studies are mentioned in the text but not included in the tables, and the reasons for their exclusion are not always explicit.

It is important to remember that, with the exception of three studies of interval surgery, the surgical interventions were not compared with no surgery: most of the comparisons presented are between people left with little or more residual disease tissue after secondary surgery.

Implications of the review for practice and research
Research is needed to compare the survival of women undergoing secondary cytoreductive surgery for advanced epithelial ovarian cancer with similar women not undergoing such surgery; the authors note that one such trial is underway.

Certain subgroups of women with advanced epithelial ovarian cancer are more likely to benefit from secondary cytoreductive surgery than others. There are trade-offs to be made between likely survival advantages and surgery-associated morbidity.

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Record Status
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.