Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis

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Authors' objectives
To evaluate the relative effect of percentage maximal cytoreduction surgery and other prognostic variables on survival among cohorts of patients with advanced-stage ovarian carcinoma, who were being treated with platinum-based chemotherapy.

Searching
MEDLINE was searched for articles published in English between 1 January 1989 and 31 December 1998. The headings and keywords were 'ovarian neoplasms', 'ovarian carcinoma', 'ovarian cancer' and 'surgery'. The bibliographies of the selected articles were reviewed for potentially relevant studies.

Study selection
Study designs of evaluations included in the review
Randomised prospective studies, non-randomised prospective studies and retrospective cohort studies were eligible for inclusion in the review.

Specific interventions included in the review
Studies that assessed patients undergoing initial cytoreductive surgery followed by chemotherapy, which involved either cisplatin or carboplatin, were eligible for inclusion in the review. The actual chemotherapy agents in the included studies were carboplatin and cisplatin, used either alone or in combination with chloramycin, cyclophosphamide, doxorubicin, epirubicin, etoposide, hexamethylmelamine, ifosfamide, melphelan, mitoxantone or paclitaxel. The weighted, mean platinum dose-intensity was 0.98 (range: 0.57 to 3.71).

Participants included in the review
Studies in which the participants were predominantly (greater than 90%) patients with stage III or IV epithelial ovarian cancer were eligible for inclusion. The mean percentage of patients with stage IV cancer was 21.56%. Maximal cytoreductive surgery was defined according to the largest diameter of residual disease, with the following distribution: less than 2 cm in 40.7% of the patients, less than or equal to 2 cm in 38.2%, less than or equal to 1 cm in 12.3%, less than 1 cm in 3.7%, less than 3 cm in 2.5%, less than or equal to 1.5 cm in 1.2%, and less than 0.5 cm in 1.2%. The median age was not reported for 8 patient cohorts; for the remaining 73 cohorts, the mean weighted median age was 57 years (range: 47 to 72).

Outcomes assessed in the review
The outcome of interest was the median survival time.

How were decisions on the relevance of primary studies made?
Two reviewers assessed the studies for selection. The authors did not state whether this was undertaken independently, or how any disagreements were resolved.

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

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.
The following data were extracted and tabulated: study design; year the study was published; the number of patients; median patient age; the percentage of patients with stage IV disease; specified definition of maximal cytoreductive surgery and the percentage of patients achieving it; chemotherapy agents administered; dosage and prescribed administration schedule of the platinum compound used; and reported median survival time.

Methods of synthesis
How were the studies combined?
Simple linear regression models were generated to examine the effect of median age of the study cohort, publication year, percentage of patients with stage IV disease, percentage of patients undergoing maximal cytoreductive surgery, platinum dose-intensity and cumulative platinum dose on median survival time. The regressions were weighted by the number of patients in each cohort. Multiple linear regression analysis was then used to derive the independent effects of the variables on log survival time, simultaneously controlling for other measured variables that could potentially affect survival. All of the results were quoted as two-sided P-values and 95% confidence intervals; a P-value of less than 0.05 was considered statistically significant.

How were differences between studies investigated?
Differences between the studies were not formally investigated.

Results of the review
Fifty-three studies including 81 patient cohorts (n=6,885) were included in the review. Fifty-five cohorts (n=5,442) came from randomised prospective trials, 24 (n=1,333) from non-randomised prospective trials, and 2 (n=110) from retrospective reviews.

There was a statistically significant positive correlation between percentage maximal cytoreduction and log median survival time; this correlation remained significant after controlling for all other variables (P<0.001). Each 10% increase in maximal cytoreduction was associated with a 5.5% increase in median survival time. When actuarial survival was estimated, cohorts with less than or equal to 25% maximal cytoreduction had a mean weighted median survival time of 22.7 months, whereas cohorts with more than 75% maximal cytoreduction had a mean weighted median survival time of 33.9 months an increase of 50%. The relationship between platinum dose-intensity and log median survival time was not statistically significant.

Authors’ conclusions
During the platinum era, maximal cytoreduction was often the most powerful determinant of cohort survival among patients with stage III or IV ovarian carcinoma. Consistent referral of patients with apparent advanced ovarian cancer to expert centres for primary surgery may be the best means currently available for improving overall survival.

CRD commentary
The authors addressed a clear review question in terms of the interventions, participants, study designs and outcome measures that were to be included and assessed in the review. However, the literature search was poor with only MEDLINE being searched for studies published in the English language. It is therefore possible that both publication and language bias were introduced into the review process, and other relevant studies were missed. Two reviewers assessed the relevance of the primary studies for inclusion in the review, but the authors did not provide any details of whether the validity of the included studies was assessed. This makes it very difficult for the reader to assess the quality of the studies included in the review. The authors provided adequate details of the primary study characteristics for the reader to assess whether the authors’ results and conclusions were consistent with the evidence base reviewed. The statistical analysis was appropriate, but the effect of study design on the results was not explored.

Overall, a number of biases could have been introduced into the review process, particularly in the literature search. The authors’ results and conclusions were consistent with the evidence base reviewed, but should be treated with caution as other relevant studies may have been missed.
Implications of the review for practice and research
Practice: The authors stated that consistent referral of patients with advanced ovarian carcinoma to expert centres for initial surgery may be the best means currently available for improving the overall survival rate.

Research: The authors did not state any implications for further research.

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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.