original reports

# Secondary Cytoreductive Surgery in Platinum-Sensitive Recurrent Ovarian Cancer: A Meta-Analysis

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abstract

**PURPOSE** The survival impact of secondary cytoreductive surgery in patients with platinum-sensitive recurrent ovarian cancer was studied.

**METHODS** We identified published studies from 1983 to 2021 following our inclusion criteria from MEDLINE, EMBASE, and Cochrane library. To integrate the effect size of single-arm studies, meta-analysis was performed using death rate as a primary outcome. The effect of complete cytoreduction and optimal cytoreduction on survival was evaluated using meta-regression. The pooled death rate was presented with a 95% CI. The publication bias was evaluated with the funnel plot and Egger's test, and sensitivity analysis was performed. To overcome missing death rates, the linear regression model was performed on log-transformed median overall survival (OS) time using study size as a weight.

**RESULTS** Thirty-six studies with 2,805 patients reporting death rates were used for this meta-analysis of the 80 eligible studies. There was strong heterogeneity, with the $P$ value of the Cochrane Q test of $< 0.0001$ and Higgins's $I^2$ statistics of 86%; thus, we considered a random effect model. The pooled death rate was 44.2% (95% CI, 39.0 to 49.5), and both the complete and optimal cytoreductions were associated with better survival outcomes as significant moderators in the meta-regression model ($P < .001$ and $P = .005$, respectively). Although 14 studies were located outside the funnel plot, Egger's test indicated no publication bias ($P = .327$). A sensitivity analysis excluding 14 studies showed similar results. In the linear regression model on the basis of 57 studies, the median OS time increased by 8.97% and 7.04% when the complete and optimal cytoreduction proportion increased by 10%, respectively, after adjusting other variables.

**CONCLUSION** Secondary cytoreductive surgery, resulting in maximal tumor resection, significantly prolongs OS in platinum-sensitive recurrent ovarian cancer.

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## INTRODUCTION

Ovarian cancer remains one of the most deadly gynecologic malignancies with an estimated 21,750 new cases and 13,940 new deaths in 2020 in the United States[1] and 295,414 new cases and 184,799 deaths in 2018 worldwide.[2] The majority of ovarian cancer cases are diagnosed at an advanced stage, and > 80% of patients ultimately experience relapse and die from the resistant disease.[3] Primary cytoreductive surgery, consolidated by taxane and platinum adjuvant chemotherapy and targeted maintenance approaches, is the current standard first-line treatment of ovarian cancer.[4]

Earlier data have demonstrated that total macroscopic tumor clearance at secondary cytoreduction for platinum-sensitive ovarian cancer relapse improves overall survival (OS) and progression-free survival (PFS).[5,6] Optimal cytoreductive surgery, as defined in earlier studies to characterize a minimal residual disease, instead of complete clearance, has shown little association with improved OS in the recurrent setting.

A potential hypothesis could be that the residual disease drives an early development of drug resistance or that patients who cannot be debulked maximally even with expert teams have such an unfavorable profile that surgery cannot alter the outcome.

More recent prospective randomized data have shed additional light with more robust evidence on the true value of secondary cytoreductive surgery (SCS); however, the generated conflicting data have added to the controversy within the gynecologic oncology community.[7-9] The three prospective randomized studies that have reported and published mature data (GOG 213,[7] SOC-1,[8] and DESKTOP III[9]) have consistently demonstrated that patients who have undergone complete tumor resection at relapse have a significantly longer PFS than those treated with

ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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## CONTEXT

### Key Objective

Almost 80% of the patients with ovarian cancer have a relapse. The role of surgery in recurrent ovarian cancer has been controversial even with recent three randomized trials. This study is to evaluate the survival impact of secondary cytoreductive surgery in patients with platinum-sensitive recurrent ovarian cancer. It contains 36 studies for meta-analysis and 57 studies for linear-regression analysis and, to our knowledge, is the largest to date.

### Knowledge Generated

In the meta-regression model, both the complete and optimal cytoreductions were associated with better survival outcomes as significant moderators. In the linear regression model, the median overall survival time increased by 8.97% and 7.04% when the proportion of complete and optimal cytoreduction increased by 10%, respectively.

### Relevance

Secondary cytoreductive surgery with maximal tumor resection increased significantly overall survival in platinum-sensitive recurrent ovarian cancer.

chemotherapy alone. However, contradicting data were generated regarding the impact of secondary cytoreduction on OS. This variation of the results is possibly attributed to the lack of standardization and surgical quality assurance of the participating center selection, the diversity of the actual study design, and most importantly, the presence or absence of strict selection criteria for the identification of the ideal surgical candidates, resulting in a strongly heterogeneous patients' profile across the studies. This has resulted in a wide variation in the management of these patients between institutions worldwide, with a strong postcode lottery effect.[10]

Considering the tangible accumulation of knowledge about ovarian cancer and the vast advances in both the systemic and surgical treatment options since our last meta-analysis in 2013, a further updated meta-analysis on the clinical impact of SCS is warranted.[6,11]

## METHODS

### Search Strategy and Selection Criteria

The systematic review and meta-analysis were performed following the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[12,13]

All published articles in English from January 1983 to December 2021 were searched in MEDLINE, EMBASE, and Cochrane library databases. To find relevant articles, the combinations of search words used were recurrent ovarian cancer OR recurrent ovarian carcinoma AND secondary cytoreductive surgery OR secondary surgical cytoreduction.

Studies were searched and filtered according to the following inclusion criteria. The Patient, Intervention, Comparator, and Outcome study design was used to define the eligible studies.[13] The Patients had recurrent ovarian cancer. The Intervention was SCS. There was no Comparator in this study. The Outcome was the median OS time and proportion of death events. The exclusion criteria were duplicated studies, study results on platinum-resistant recurrent ovarian cancer, studies with irrelevant outcomes, and studies with no abstract or full text (Fig 1).

Complete cytoreduction was defined as no macroscopic residual disease, which was the main target in more recent studies; however, in earlier studies, patients were classified according to optimal residual disease, which was defined as $< 1$ cm or 0.5 cm or even 2-2.5 cm depending on the year of publication and country of origin.

Data extraction and quality assessment were performed. Two independent investigators (M.-H.B. and E.Y.P.) selected relevant articles and extracted data with quality assessment. Discrepancies were adjusted, and the consensus was reached through a discussion.

### Data Analysis

Since this meta-analysis was a single-arm–based study, death was defined as the ultimate aim. A linear regression model for log-transformed median OS along with meta-analysis was conducted to overcome missing death rates in the studies.

We performed a sensitivity analysis to resolve issues arising from the high heterogeneity of the included studies. After using four transformations (Freeman-Tukey double arcsine, arcsine, log, and logit), the pooled death rate was confirmed without large deviations. Arcsine transformation was ultimately selected, and forest plots and funnel plots according to the transformation are presented in the Data Supplement (online only). The number of missing studies was estimated using the trim and fill method, whereas the Egger's test was performed for publication bias. The same analysis was performed after excluding 14 studies outside the funnel plot.

Data on the author, year of publication, study design, median follow-up period, number of patients, age, morbidity, mortality, number of death events, median OS, median disease-free interval (DFI), the definition of

 

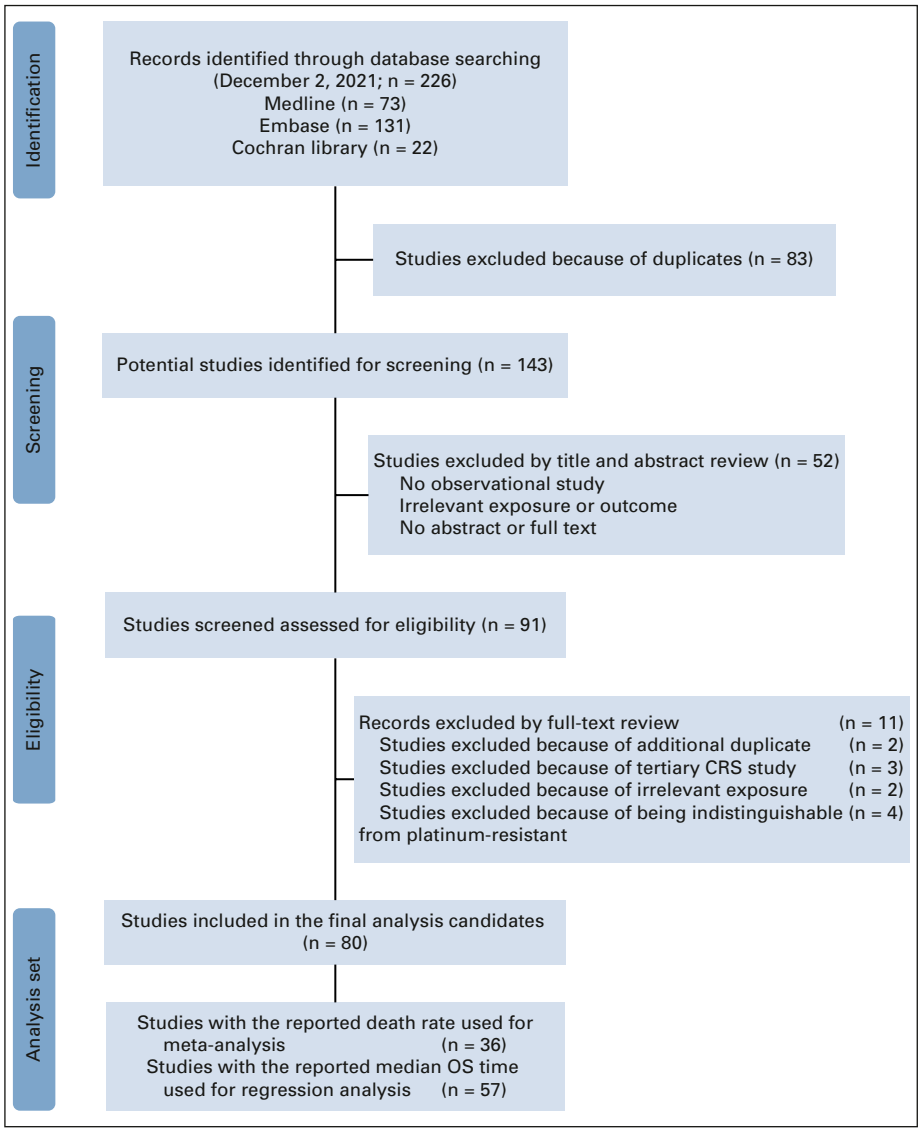


**FIG 1.** Flowchart of study selection for the analysis. CRS, cytoreductive surgery; OS, overall survival.

postoperative residual disease, and the proportion of patients with complete versus incomplete cytoreduction were extracted from each study (Data Supplement). In older studies where the term optimal cytoreduction was still used, defined as residual disease $< 0.5$ cm or 1 cm, the proportion of patients with optimal versus complete residual disease was calculated.

Median age and OS were calculated from the time of SCS or point of diagnosis of first relapse. The DFI was defined as the time after the primary treatment until recurrence. Major surgical morbidity and mortality were measured for the first 30 postoperative days.

As the first step, we performed a meta-analysis on the basis of the 36 studies with comprehensive reporting of the death events. The death rate was defined as the number of deaths divided by the total number of patients. The weights of individual studies were based on the inverse variance method; the pooled death rate was presented with a 95% CI. Cochran Q statistics and Higgins's $I^2$ statistics were used to evaluate the heterogeneity of death rates between studies, and the pooled death rate was reported on the basis of a random effect model. Meta-regression analysis was performed to investigate the role of complete cytoreduction or optimal cytoreduction as a moderator.

As a second step, a simple linear regression analysis was performed by treating each study as an independent observation. The association between the log-transformed median OS time and the proportion of complete cytoreduction, proportion of optimal cytoreduction, publication year, median age, type of study design, DFI, and the proportion of solitary recurrence were analyzed, assigning the size of each study as a weight. Multiple linear regression analyses were performed to evaluate the effect of complete

cytoreduction or optimal cytoreduction adjusting for other variables.

The two-sided *P* value of $< .05$ was considered statistically significant, and all statistical analyses were performed using R project software version 3.6.2.

## RESULT

A total of 226 studies conducted between 1983 and 2021 were initially identified, with 80 articles being in accordance with the above-described eligible criteria for full-text review. Thirty-six studies reporting death rates were used for the present meta-analysis, and 57 studies reporting both median OS time and study size were used for linear regression models, resulting in a final analysis of 64 studies (Fig 1).[7-9,14-26,27-43,44-60,61-74]

The 36 studies included in this meta-analysis were published between 1995 and 2021 and included 2,805 patients who underwent SCS. Study design was as follows: prospective randomized controlled study (n = 3), prospective nonrandomized studies (n = 7), and retrospective studies (n = 26). The median number of patients in each study was 39 (interquartile range [IQR]: 25.8-103.8), with a death rate of 43.1% (IQR: 32.6%-58.5%). The median patient's age across the studies was 56.5 years (range, 51-64 years), with a median follow-up time of 32.7 months (IQR: 26-40.6 months) in the 26 studies that reported it. The DFI ranged between 14 and 48.2 months in 28 studies, and the proportion of patients with solitary recurrence ranged from 13.3% to 73.3% in 19 studies. The median OS ranged from 21 to 82.2 months in 29 studies, whereas four studies did not reach the median survival time and three studies did not report (Data Supplement).

The definition of optimal secondary cytoreduction varied in each study. The SCS was deemed as optimal when the size of residual tumor (cm) was not grossly seen in seven studies, $< 0.25$ cm in three studies, $< 0.5$ cm in two studies, $\leq 0.5$ cm in five studies, $< 1.0$ cm in three studies, $\leq 1.0$ cm in 11 studies, $< 2$ cm in three studies, and $< 2.5$ cm in one study. The median rate of complete and optimal cytoreduction was 69.8% (range, 9.4%-100%) and 85.7% (range, 43.5%-100%), respectively. The median rate of major surgical morbidity and mean 30-day mortality reported in 29 studies were 16.4% (range, 0%-44%) and 0.74% (standard deviation 1.33), respectively (Data Supplement).

A strong heterogeneity was calculated between 36 studies that were included in the present meta-analysis. We considered a random effect model since the *P* value of the Cochran Q test was $< 0.0001$, and Higgins's $I^2$ statistics was 86% with a $tau^2$ value of 0.02 (0.01-0.05), indicating considerable heterogeneity. The Data Supplement shows the forest plot and funnel plot of death rate according to the four-transformation random effect model. Despite the heterogeneity, there was little change in the pooled death rate according to the transformation model. In particular, the log transformation was left-skewed, indicating that nine studies were estimated as missing according to the trim and fill method. The arcsine transformation was selected because of its random distribution, narrow CI, and easy back transformation.

The pooled death rate was 44.2% (95% CI, 39.0 to 49.5), with the death of nearly half of the patients within the study's follow-up period (Fig 2).

A meta-regression analysis between the proportion of complete versus optimal cytoreduction, publication year, median age, type of study design (retrospective *v* prospective), median DFI, and proportion of solitary to multifocal recurrence to determine the cause of heterogeneity demonstrated the proportion of complete and optimal cytoreduction to be statistically significant (Fig 3). In multivariable analysis, complete and optimal cytoreductions were significant moderators of survival, even after adjusting for other well-established prognostic factors such as age (Table 1). Although heterogeneity persisted, $I^2$ statistics decreased from 86% to 62.5%, resulting in a significant regression coefficient test, showing that the proportion of complete and optimal cytoreduction was an independent moderator. To measure the impact of cytoreductive effort on OS, we defined two cutoffs of the median proportion of patients who underwent complete or optimal cytoreduction, depending on what each study reported: 70% and 85%. The pooled death rate was 53.8% and 52.8% with the median proportion of complete or optimal cytoreduction at $\leq$ 70% and $\leq$ 85%, respectively. The effect of cytoreduction increased with higher cytoreductive effort, with the death rate decreasing to 34.6% and 36.5% at increasing complete and optimal resection rates of $>$ 70% and $>$ 85%, respectively (Data Supplement, Fig 1D). Although reported in only a few studies, when evaluating the role of SCS after separating the effects of chemotherapeutic agents by investigating the proportion of patients treated with platinum- and/or taxane-based chemotherapeutic agents, only cytoreduction was statistically significant after adjusting for the proportion of chemotherapeutic agents and median age.

Fourteen studies were located outside the funnel plot, but these were equally distributed on both sides of the plot (Data Supplement). When the present meta-analysis was repeated excluding these 14 studies, the pooled death rate was 44.4% (95% CI, 41.5 to 47.4), similar to the data derived when all the 36 studies were included (Data Supplement). Egger's test, a statistical test for publication bias, was not significant, so publication bias was not observed (*P* value = .095).

The results of the univariable linear regression model, with the study size as a weight, showed that higher proportion of complete or optimal cytoreduction, more recent publication year, and more advanced age were significantly associated with longer OS ($P < .001$ and $P = .001$, $P < .001$ and $P = .015$, respectively). The type of study design and patterns of relapse (ie, multifocal *v* solitary) did not significantly affect OS (Table 2).

 

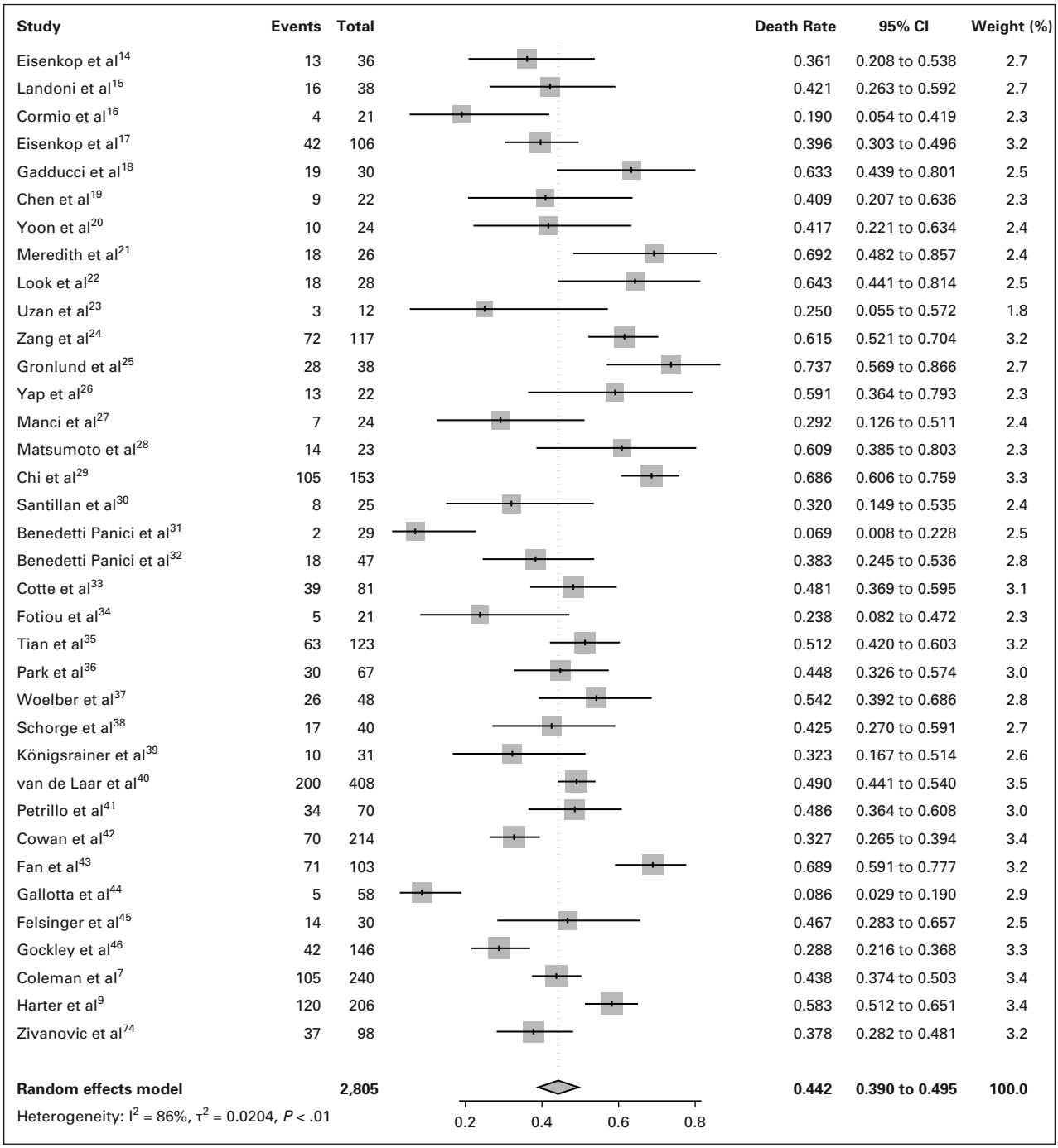


**FIG 2.** Forest plot summarizing the death rate for each study.

Figure 4 demonstrates the linear log relationship between median OS time and cytoreductive result, age, and publication year. The linear regression model is weighted by study sizes, with large studies being presented by larger circles.

The multivariable effect of the proportion of complete and optimal cytoreduction was also evaluated, adjusting the other variables. By the log-level model, the median OS time increases by 8.97% and 7.04% when the proportion of complete or optimal cytoreduction increases by 10% after adjusting for other variables. Similarly, when the publication year increased by 1-year with the other variables adjusted, the median OS time increased by 3.11% and 3.49% (Table 2).

## DISCUSSION

In this meta-analysis, we confirmed that maximal effort SCS resulted in a significant improvement of OS in patients in the platinum-sensitive relapse setting. Every 10% increase

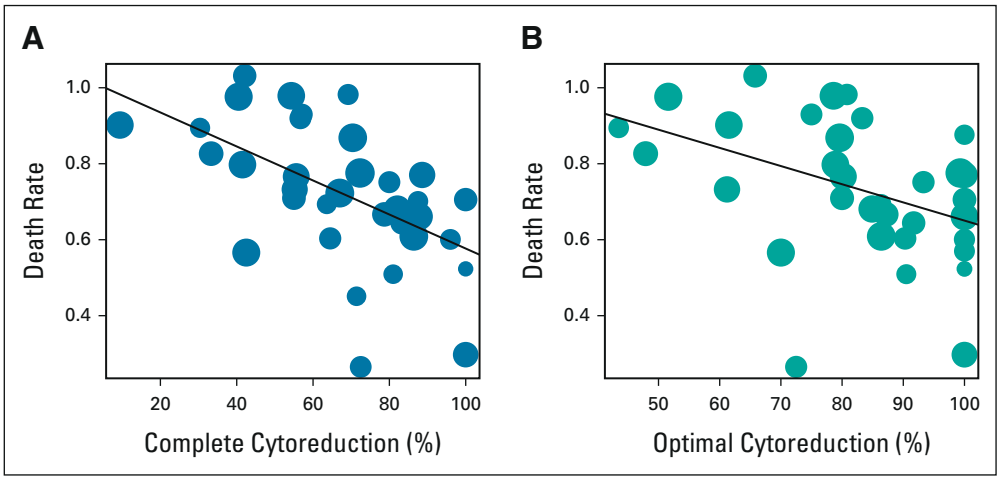


**FIG 3.** Bubble plot between the proportion of complete or optimal cytoreduction and the arcsine death rate.

of optimal/complete clearance rates led to an 8.97% and 7.04% increase in median OS of the affected patients' cohort across all types of study designs. The length of DFI and patterns of relapse (solitary *v* multifocal recurrence) failed to significantly affect OS.

Our findings reinforce the current trend of the gynecologic oncology community to apply maximal surgical effort even when relapse occurs, pairing the surgical advances with the rapidly developing systemic advances in epithelial ovarian cancer.

There are numerous hypotheses to explain why cytoreductive surgery appears to have such a consistently significant effect on the survival of patients with ovarian cancer. No or minimally visible residual tumor may enhance the effect of adjuvant cytotoxic agents on the tumor microenvironment, decreasing the risk of the early development of drug-resistant clones. Moreover, surgical clearance may positively modulate the inherited patient's immune response, and all these factors are reported to possibly delay the tumor regrowth time.[7] These mechanisms seem to apply in both the primary and recurrent

**TABLE 1.** Analysis of Moderators Using the Meta-Regression Model

| Variable | Estimate | SE | 95% CI | *z* | *P* | No. of Studies | $I^2$ (%) | $R^2$ (%) |
|---|---|---|---|---|---|---|---|---|
| Univariable analysis | | | | | | | | |
| Proportion of complete cytoreduction | | | | | | | | |
| Continuous | –0.005 | 0.001 | –0.007 to –0.002 | –4.010 | **< .0001** | 34 | 82.2 | 27.8 |
| Categorical (≤ 70% *v* > 70%) | –0.194 | 0.053 | –0.298 to –0.090 | –3.648 | **< .0001** | 34 | 84.9 | 10.0 |
| Proportion of optimal cytoreduction | | | | | | | | |
| Continuous | –0.005 | 0.002 | –0.008 to –0.001 | –2.805 | **.005** | 34 | 84.2 | 13.1 |
| Categorical (≤ 85% *v* > 85%) | –0.166 | 0.053 | –0.270 to –0.061 | –3.103 | **.002** | 34 | 83.7 | 16.2 |
| Publication year | –0.002 | 0.004 | –0.010 to 0.005 | –0.609 | .543 | 36 | 86.2 | 0.0 |
| Median age | 0.015 | 0.009 | –0.002 to 0.031 | 1.708 | .088 | 30 | 85.4 | 0.0 |
| Type of study design | | | | | | | | |
| Prospective | –0.013 | 0.061 | –0.131 to 0.106 | –0.211 | .833 | 36 | 86.4 | 0.0 |
| DFI | 0.001 | 0.005 | –0.008 to 0.010 | 0.168 | .867 | 28 | 85.7 | 0.0 |
| Proportion of solitary meta | 0.000 | 0.002 | –0.004 to 0.004 | 0.134 | .893 | 19 | 84.6 | 0.0 |
| Multivariable analysis | | | | | | | | |
| Proportion of complete cytoreduction | –0.006 | 0.001 | –0.008 to –0.004 | –6.224 | **< .0001** | 28 | 62.5 | 71.2 |
| Median age | 0.020 | 0.006 | 0.009 to 0.031 | 3.537 | **< .0001** | | | |
| Proportion of optimal cytoreduction | –0.006 | 0.002 | –0.009 to –0.003 | –3.496 | **.001** | 29 | 77.6 | 35.2 |
| Median age | 0.018 | 0.007 | 0.004 to 0.031 | 2.475 | **.013** | | | |

NOTE. Bold values indicate statistical significance ($P < .05$).
Abbreviation: DFI, disease-free interval.

 

**TABLE 2.** Linear Regression Model Analysis for Median Overall Survival Time

| Variable | Beta | SE | *t*-value | *P* | Change in Median OS | |
|---|---|---|---|---|---|---|
| | | | | | Increase Unit | % |
| Univariable analysis | | | | | | |
| Proportion of complete cytoreduction | 0.011 | 0.002 | 4.509 | **< .001** | 10% | 11.57 |
| Proportion of optimal cytoreduction | 0.013 | 0.004 | 3.468 | **.001** | 10% | 14.05 |
| Publication year | 0.042 | 0.005 | 8.500 | **< .001** | 1 year | 4.30 |
| Median age | 0.040 | 0.016 | 2.538 | **.015** | 1 year | 4.12 |
| Type of study design: prospective | 0.095 | 0.125 | 0.755 | .454 | Prospective | 9.92 |
| DFI | 0.005 | 0.010 | 0.511 | .612 | 1 month | 0.49 |
| Proportion of solitary meta | 0.004 | 0.006 | 0.708 | .487 | 10% | 4.42 |
| Multivariable analysis | | | | | | |
| Proportion of complete cytoreduction | 0.009 | 0.002 | 3.991 | **< .001** | 10% | 8.97 |
| Publication year | 0.031 | 0.007 | 4.666 | **< .001** | 1 year | 3.11 |
| Median age | 0.003 | 0.012 | 0.272 | .787 | 1 year | 0.32 |
| Proportion of optimal cytoreduction | 0.007 | 0.003 | 2.107 | **.042** | 10% | 7.04 |
| Publication year | 0.034 | 0.007 | 4.597 | **< .001** | 1 year | 3.49 |
| Median age | 0.010 | 0.013 | 0.804 | .426 | 1 year | 1.05 |

NOTE. Bold values indicate statistical significance ($P < .05$).
Abbreviations: DFI, disease-free interval; OS, overall survival.

settings, justifying the continuous paradigm of the importance of residual tumor burden in those patients.

It is interesting to see the conflicting results of the recently reported prospective randomized phase III DESKTOP-III trial, which showed a contrast to the American counterpart study GOG 213 in demonstrating a significant prolongation of not only the PFS but also the OS.[7,9] The nonstandardized patient selection for surgery in the GOG 213, as opposed to the DESKTOP-III and SOC-1 study, is assumed to play a key role in the difference of outcomes.[7-9] Moreover, the different use of biologic agents and maintenance regimens across the three studies makes a direct comparison very challenging.[7-9,11] Another key difference is disease burden across the three studies. Although more than two third of the DESKTOP-III and SOC-1 populations presented with multifocal disease relapse, including peritoneal carcinosis, in the GOG213 study, women with peritoneal carcinosis made poor surgical candidates as the diffusion of the disease usually preclude complete cytoreduction as per the study protocol. This resulted in only 5% of the GOG213 patients having peritoneal carcinosis, a significantly lower number than the other two studies.[7] This crucial difference may indicate that maximal tumor debulking and reduction of tumor load appear to be especially important for high-burden patients in prolonging remission and shifting the time point in developing platinum resistance more toward the future. As opposed to that, in an asymptomatic patient with low volume, oligometastatic recurrence, and where the timing of initiation of treatment at relapse is not well defined, watch and wait strategies are also acceptable.[75] The principle of accurate identification of the adequate surgical candidates seems to be of crucial importance for surgical success at relapse, and robust algorithms need to be followed to achieve optimal stratification of the patients to the suitable treatment pathways.[7-9]

A closer look at the three studies sheds further light on the discrepancy of the GOG-213 compared with the other two studies. The 3-year OS in the tumor-free surgery arm of GOG-213 was 76%, the lowest among the three studies (84% in DESKTOP and 78% in SOC1), whereas the 3-year OS in the nonsurgery arm of GOG-213 was 75%, the highest (62% in DESKTOP and 66% in SOC1), making it clear that there are some fundamental differences in the basic patient and treatment profile across the three studies.[7-9]

Although the current practice clearly favors maximal surgical effort at relapse, the important impact of the evolving incorporation of new agents needs to be taken into account by the gynecologic oncology community.[76,77] Most studies that address the value of SCS have been conducted and completed in eras where the incorporation of novel targeted agents (such as antiangiogenic agents and poly [ADP-ribose] polymerase inhibitors) was not routinely implemented. Hence, a logical question arises whether the routine implementation of such agents would negate the value of surgical debulking or additionally potentiate it through a maximal effort approach across all therapeutic levels. This, we suspect, will remain an open question since it appears very challenging to conduct a confirmatory study with the routine implementation of PARPs and/or bevacizumab in the systemic treatment arm.

In the GOG213 study, the only trial of the three that had antiangiogenic therapy as standard treatment in one of the arms, all patients who received bevacizumab had similar

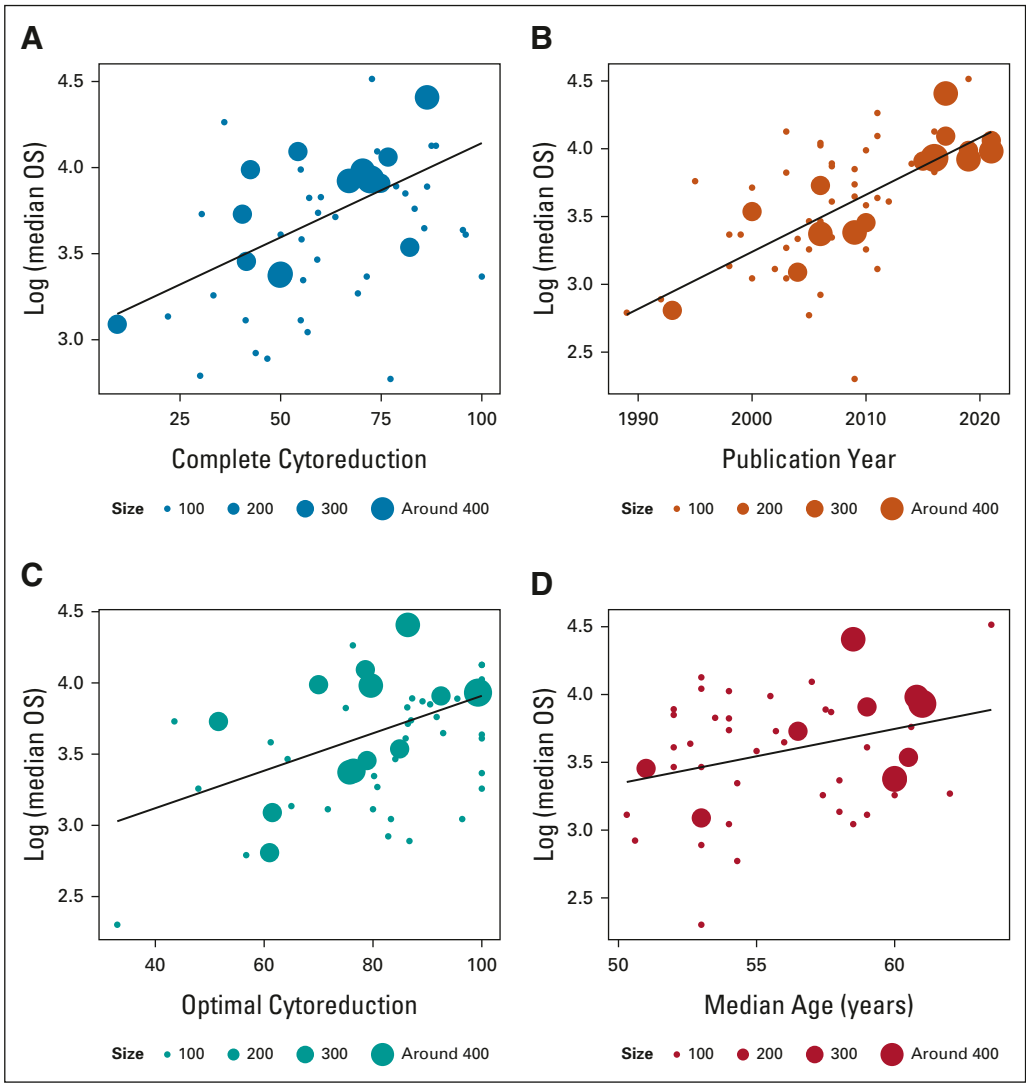


**FIG 4.** Linear relationship between the log median OS time and the proportion of complete and optimal cytoreduction, age, and publication year. OS, overall survival.

survival curves regardless of whether they were operated, whereas those patients who were operated and opted not to have bevacizumab had a detrimental OS as opposed to those receiving chemotherapy alone.[7] Although it is unknown if patients not receiving bevacizumab at the time of either random assignment were less likely to receive it in subsequent lines of therapy, such an imbalance could potentially affect long-term outcomes while giving a clear signal that the type of adjuvant treatment does indeed matter and influences surgical success.

A well-designed biomarker-driven phase III trial with prespecified subpopulation analysis appears perhaps rather ambitious but will surely elucidate further the true impact of SCS in the different ovarian cancer subpopulations. Also, the role of SCS has to be continuously reviewed considering the changing management of recurrent ovarian cancer over the period. Therefore, to separate the impact of those new therapies from the impact of secondary cytoreduction and to truly assess the surgical prognostic value, the regimen change of adjuvant salvage chemotherapy after secondary surgery was investigated. In our series, optimal and complete cytoreduction still remained an important favorable prognostic factor even when these evolutions and new paradigm shifts were considered.

More importantly, the overall treatment and the collective therapeutic effort rather than just consideration of one treatment over another is key. Patients, for example, with extensive but operable bowel disease at relapse, who normally, without surgery, could not receive bevacizumab or other targeted agents because of the high risk of perforation or obstruction, may become eligible for bevacizumab/targeted agents by having their bowel disease removed and their bowel anatomy and function restored before any systemic treatment. This illustrates that the maximal

 

therapeutic effort package across multiple levels that complement one another can collectively and significantly affect survival.

The impact of this collective effort is being indirectly reflected by the fact that more recently published series were associated with better survival outcomes than the older ones. This is a product of the vast improvement in disease management over the past 30 years, both surgically and systemically.

Doubtlessly, our meta-analysis harbors valid limitations. Despite our solid statistical efforts to homogenize the large heterogeneity between the studies, generalization to the entire patient population was challenging, while not all biases were overcome. Also, as we included earlier studies from four decades, there was broad variation in the definition of optimal residual disease with only the newer studies defining the optimal goal as no macroscopic residual disease. Since in these newer studies, patients with residual disease $< 1$ cm were clustered together with those who had a bulky residual disease, the value of a residual tumor diameter of $< 1$ cm might have been underestimated.

Considering the scarcity of clinical trials on this topic, and the role of human factors, since the completeness of cytoreduction largely depends on the ability, training, and affiliations of the surgeon, the study results have to be interpreted with caution.

In conclusion, our data confirm that maximal effort cytoreductive surgery resulting in maximal tumor debulking can significantly improve patients' survival at relapse and in combination with the vast systemic advances, surgery has contributed to the profound improvement of patients' outcomes over the decades.


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## DISCLAIMER

The funder of this trial had no role in study concept, study performance, including data collection and analysis, drafting, and finalization of the manuscript. The main authors had full access to all data in this trial and had final responsibility for the process of presentation and publication.

## EQUAL CONTRIBUTION

M.-H.B. and E.Y.P. have equally contributed to this work.
C.F. and R.E.B. have equally contributed to this study as cosenior authors.


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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.21.02085.

## DATA SHARING STATEMENT

External researchers can make written requests to the corresponding author (M.C.L.) for sharing of data before publication or presentation. Requests with submitting a brief analysis plan and synopsis will be assessed and approved on a case-by-case basis in the research team. The personal identification deleted data will be sent in password-protected files. All data sharing will abide by rules and policies defined by the sponsor; relevant institutional review boards; and local, state, and federal laws and regulations. Data sharing mechanisms will ensure that the rights and privacy of individuals participating in research will be guaranteed.

## AUTHOR CONTRIBUTIONS

**Conception and design:** Min-Hyun Baek, Myong Cheol Lim, Christina Fotopoulou, Robert E. Bristow
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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

**Secondary Cytoreductive Surgery in Platinum-Sensitive Recurrent Ovarian Cancer: A Meta-Analysis**

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