Impact of postoperative residual disease on survival in epithelial ovarian cancer with consideration of recent frontline treatment advances: A systematic review and meta-analysis

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HIGHLIGHTS

- Treatment strategies for primary EOC have evolved, but complete cytoreduction's value remains unassessed.
- 97 trials, 43,260 patients, studied residual disease impact on EOC survival after surgery in this meta-analysis.
- 10% rise in complete cytoreduction rate linked to a 12.97% increase in median log overall survival.

ARTICLE INFO

ABSTRACT

Background. Current treatment strategies for primary epithelial ovarian cancer (EOC) have significantly evolved, and the value of complete cytoreduction has not yet been reassessed. The study aimed to investigate the impact of residual disease after cytoreductive surgery for EOC on survival outcomes within the recent paradigm of frontline ovarian cancer treatment.

Methods. We searched relevant literature from the MEDLINE, Embase, and Cochrane Library databases to identify randomized controlled trials and prospective clinical trials of primary EOC published between 1 January 2000 and 22 September 2022. To evaluate the impact of postoperative residual tumors on progression-free survival (PFS) and OS, we constructed a linear regression model for log-transformed median PFS and OS. Patients who did or did not receive first-line maintenance therapy were examined.

Results. A total of 97 trials with 43,260 patients were included:2476 received poly(ADP-ribose) polymerase (PARP) inhibitors and 6587 received bevacizumab. Multivariable analysis of the linear regression model of all studies revealed that the median OS increased by 12.97% for every 10% increase in complete cytoreduction rates, independent of the use of systemic maintenance. In the subgroup analysis of patients receiving maintenance therapies, the effect of complete tumor clearance was potentiated, with a median OS increase of 19.13% for every 10% increase in complete cytoreduction rates.

Conclusion. Total macroscopic tumor clearance at the initial presentation of EOC significantly prolongs OS. Our results establish the importance of complete surgical cytoreduction, even after the introduction of recent advances in frontline treatment for EOC.

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1. Introduction

Ovarian cancer is a leading cause of death from gynecological malignancies, with an estimated 313,959 new cases and 207,252 deaths reported worldwide in 2020 [1]. Approximately 70% of patients with epithelial ovarian cancer (EOC) are diagnosed at an advanced stage, which is mainly attributed to the absence of early symptoms and effective screening tools and the pathogenetic origins of the disease [2]. Thus, EOC is associated with high disease recurrence and mortality rates [3]. The first-line treatment for EOC comprises cytoreductive surgery (CRS) with adjuvant platinum-based chemotherapy followed by targeted systemic maintenance therapies [2,4].

CRS aimed at total macroscopic tumor clearance is one of the strongest modifiable prognostic factors for the survival of patients with EOC [5–7]. Bristow et al. conducted a meta-analysis almost two decades ago and established an inextricable association between surgical outcome and survival, clearly demonstrating that each 10% increase in complete cytoreduction rates was associated with a 5.5% increase in the median overall survival (OS) of patients with advanced EOC who were treated with primary surgery followed by platinum-based chemotherapy [5]. However, therapeutic strategies for primary EOC have evolved significantly over the last two decades. The treatment landscape has been enriched by novel concepts such as maintenance, tumor biology, and genetically driven therapies. Neoadjuvant chemotherapy (NAC) is routinely introduced in patients who are not amenable to optimal debulking, especially in the presence of severe comorbidities. Landmark randomized controlled trials (RCTs), such as GOG-218 [8] and ICON7 [9], introduced the use of bevacizumab, a humanized antivascular endothelial growth factor monoclonal antibody, concurrent with first-line chemotherapy followed by maintenance therapy more than ten years ago. More recent RCTs, such as SOLO-1, [10] PRIMA, [11] VELIA, [12] and ATHENA-MONO, [13] have added to the maintenance use of poly (ADP-ribose) polymerase (PARP) inhibitors in EOC, bringing about a therapeutic breakthrough, especially for patients with *BRCA1/2* mutations or homologous recombination deficiency (HRD). Therefore, the standard of care for advanced EOC has revolutionized.

In view of these changes in the treatment landscape of this challenging disease, updating our knowledge base from that of the initial meta-analysis study of 2002 [5] is essential to reassess the value of postoperative residual disease on patient survival with respect to current systemic treatment strategies. Therefore, this meta-analysis aimed to investigate the impact of residual disease after CRS for EOC on survival outcomes within the current paradigm of frontline ovarian cancer treatment.

2. Methods

2.1. Search strategy and selection criteria

This study was registered in PROSPERO and conducted in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and AMSTAR (Assessing the Methodological Quality of Systematic Reviews) Guidelines (Supplementary Table 1) [14].

For this systematic review and meta-analysis, we searched relevant literature from the MEDLINE, Embase, and Cochrane Library databases, which were published between 1 January 2000 and 22 September 2022. Regarding the search strategy, the following terms were included: ovary ('ovarian' or 'ovary'), cancer ('cancer' or 'carcinoma' or 'neoplasm' or 'malignancy' or 'tumor'), survival outcomes ('survival' or 'prognosis' or 'outcome' or 'mortality' or 'recurrence'), and 'human.' The details of the search strategy are presented in Supplementary Table 2.

Based on the Patient, Intervention, Comparison, and Outcome approaches [15], we included RCTs or non-randomized prospective clinical trials that recruited patients with primary EOC and reported their outcomes (median survival time or hazard ratio [HR] of either progression-free survival [PFS] or overall survival [OS]) after CRS and a combination of cytotoxic chemotherapy and targeted agents. The timing of CRS was upfront or after NAC. We excluded non-original research articles, articles without full text, and non-English articles. We also excluded studies with irrelevant issues and those lacking specific data on residual diseases (Fig. 1). The status of residual disease was classified based on complete cytoreduction, which was defined as no macroscopic residual disease. However, we also extracted the status of optimal cytoreduction, which was operationally defined as residual disease ≤1 cm in diameter.

2.2. Data analysis

Two investigators (JHK and SIK) independently screened all retrieved studies identified by the search and selected the eligible trials. A third author (MCL) resolved any disagreements during the review process after discussion. Two investigators independently extracted the data using a standardized data collection form, and any discrepancies were addressed via joint revaluation with the third author. The following data were extracted from each study: names of authors, year of publication, type of study design, period of follow-up, allocated treatments or interventions in each study, median age of participants, stage according to the International Federation of Gynecology and Obstetrics (FIGO), histology, grade, timing of surgery, definition of residual disease, size of postoperative residual disease, postoperative adjuvant treatment including targeted agents, median PFS and OS, and HRs for PFS and OS with 95% confidence intervals (CIs).

The primary outcome was a linear regression analysis of the log-transformed median PFS and OS based on the findings of 97 studies. For studies that reported the respective median PFS and OS with two or more arms, each result was considered independently. The association between log-transformed median survival and the proportion of complete cytoreduction or optimal cytoreduction, publication year, median age, proportion of stage IV disease, proportion of HGSOC, use of maintenance targeted therapy, and proportion of patients who received NAC was analyzed, assigning the weight to the size of each study. Multivariable linear regression analyses were performed to evaluate the effect of residual disease after adjusting for other variables, including the use of targeted agents. Variables with P-value<0.2 were included in the multivariable model, and the final model was determined by applying the backward elimination method with an elimination criterion of P-value>0.05, except for the effect of residual disease, the variable of interest.

In addition, we performed an additional linear regression analysis of log-transformed median PFS and OS based on 15 studies in which enrolled patients received either bevacizumab or PARP inhibitors to identify the impact of residual disease in a particular subgroup of patients who received systemic maintenance therapy.

The secondary outcome was a meta-analysis of the HRs of PFS and OS for the association between survival outcomes and postoperative residual disease based on the extracted studies. We included studies in which the HR of PFS or OS, characterized by the proportion of residual disease, were reported. If patients treated in the experimental group comprised the reference group, the HRs were inverted, and 95% CIs were subsequently calculated. For studies in which the risk parameters were not presented numerically, we obtained the estimated risks with 95% CIs by analyzing the survival curves according to the statistical procedure described by Tierney et al. [16].

Cochran's Q statistics and Higgins' I^2 statistics were used to evaluate the heterogeneity of the pooled HR. When Higgins' I^2 values were > 50% [17], suggesting the presence of substantial heterogeneity, we used a random-effects model using the DerSimonian and Laird method [18]. To assess publication bias, we presented funnel plots with the effect size (HR for each study) on the x-axis and the standard error of the log HR on the y-axis and performed Egger's test. In the sensitivity analysis,
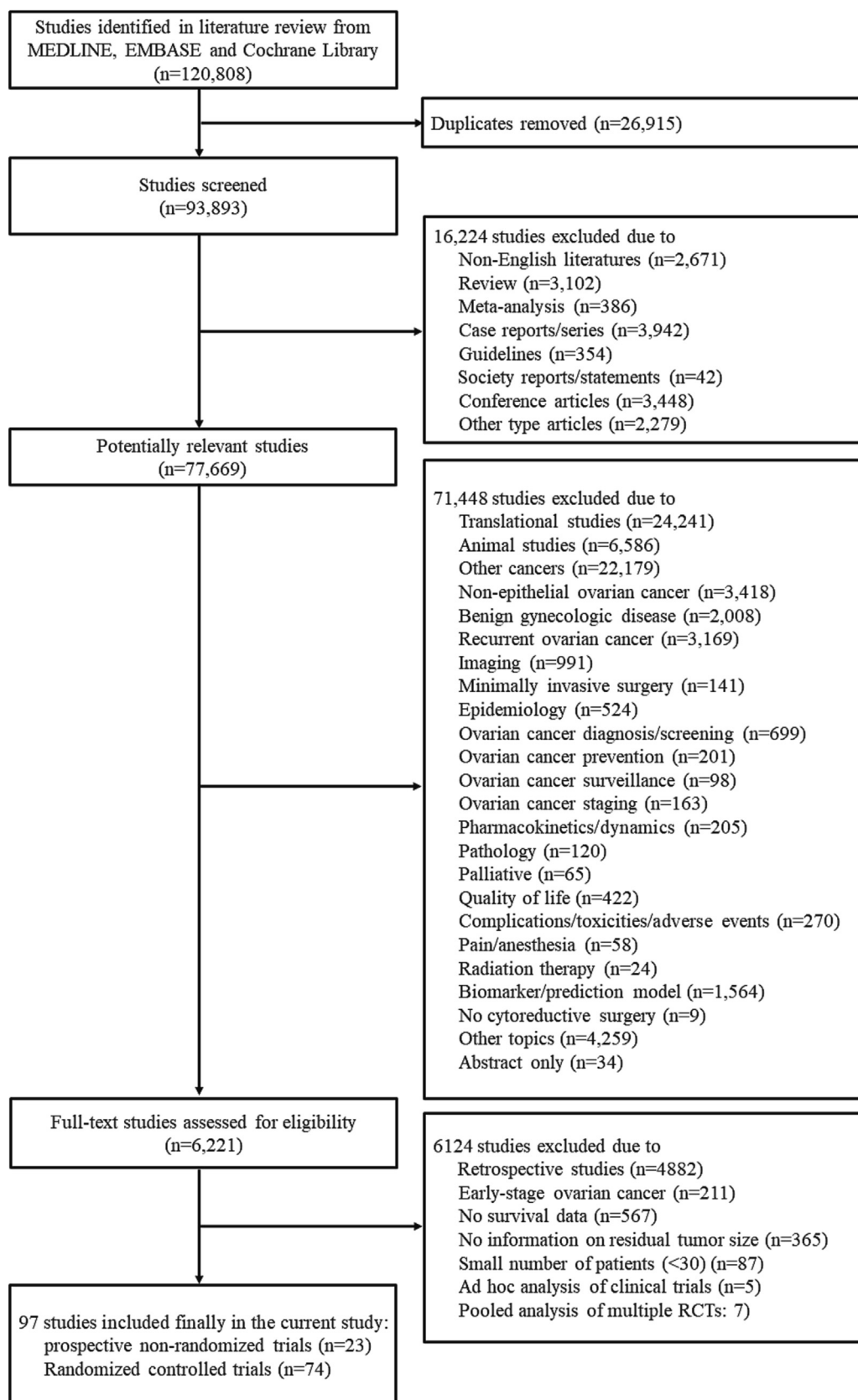
Studies identified in literature review from
MEDLINE, EMBASE and Cochrane Library
(n=120,808)

Duplicates removed (n=26,915)

Studies screened
(n=93,893)

16,224 studies excluded due to
    Non-English literatures (n=2,671)
    Review (n=3,102)
    Meta-analysis (n=386)
    Case reports/series (n=3,942)
    Guidelines (n=354)
    Society reports/statements (n=42)
    Conference articles (n=3,448)
    Other type articles (n=2,279)

Potentially relevant studies
(n=77,669)

71,448 studies excluded due to
    Translational studies (n=24,241)
    Animal studies (n=6,586)
    Other cancers (n=22,179)
    Non-epithelial ovarian cancer (n=3,418)
    Benign gynecologic disease (n=2,008)
    Recurrent ovarian cancer (n=3,169)
    Imaging (n=991)
    Minimally invasive surgery (n=141)
    Epidemiology (n=524)
    Ovarian cancer diagnosis/screening (n=699)
    Ovarian cancer prevention (n=201)
    Ovarian cancer surveillance (n=98)
    Ovarian cancer staging (n=163)
    Pharmacokinetics/dynamics (n=205)
    Pathology (n=120)
    Palliative (n=65)
    Quality of life (n=422)
    Complications/toxicities/adverse events (n=270)
    Pain/anesthesia (n=58)
    Radiation therapy (n=24)
    Biomarker/prediction model (n=1,564)
    No cytoreductive surgery (n=9)
    Other topics (n=4,259)
    Abstract only (n=34)

Full-text studies assessed for eligibility
(n=6,221)

6124 studies excluded due to
    Retrospective studies (n=4882)
    Early-stage ovarian cancer (n=211)
    No survival data (n=567)
    No information on residual tumor size (n=365)
    Small number of patients (<30) (n=87)
    Ad hoc analysis of clinical trials (n=5)
    Pooled analysis of multiple RCTs: 7)

97 studies included finally in the current study:
    prospective non-randomized trials (n=23)
    Randomized controlled trials (n=74)

Fig. 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow chart of inclusion and exclusion of studies.

We assessed the quality of the included studies using the Cochrane Risk of Bias 2 (ROB-2) tool for RCTs [19] and the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool for non-randomized prospective cohort studies [20]. The overall rating of each study is presented in Supplementary Table 3.

All statistical analyses were performed using R project software version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria), and a two-sided P-value of <0.05 was considered statistically significant.

3. Results

After our search, we retrieved 97 articles published between 1 January 2000 and 22 September 2022 and included them in the present analysis:74 RCTs and 23 prospective non-randomized trials with 43,260 patients. The search results and reasons for exclusion are detailed in Fig. 1.

The median age of the patients was 58.0 (range, 32.3–82.0) years, and the median observational period of the studies was 3.6 (range, 0.3–16.8) years. The median rate of high-grade serous histological subtype was 72.0% (range, 36.4–100%) and that of stage IV disease was 16.3% (range, 0–74%). The mean NAC rate was 19.5%, and the median rate of complete cytoreduction was 36.3% (range, 0–99.4%). A total of 35 trials included 14,332 patients who received neoadjuvant chemotherapy, 15 included 6587 patients who received bevacizumab, and five included 2476 patients who received PARP inhibitors. (Supplementary Table 4).

3.1. Linear regression analysis

In the linear regression analysis, we used 91 and 66 studies that reported median PFS and OS, respectively. In the univariable linear regression analysis with weights provided by each study size, changes in median PFS were significantly correlated with the rate of complete cytoreduction (2.79%/10%, $P = 0.049$), optimal cytoreduction to ≤1 cm (3.32%/10%, $P = 0.001$), advanced age as a continuous variable (−3.63%/year, $P < 0.001$), rate of stage IV disease (−7.83/10%, P = 0.001), and use of bevacizumab (17.26%, $P = 0.007$) and PARP inhibitors (30.18%, $P = 0.004$) (Table 1, Fig. 2).

Similarly, univariable analysis revealed that changes in median OS were significantly correlated with rate of complete (11.48%/10%, $P < 0.001$) and optimal (5.57%/10%, P < 0.001) cytoreduction, publication year (1.43%/year, P = 0.004), advanced age (−3.87%/year, P < 0.001), rate of stage IV disease (−9.96%/10%, P = 0.002), and use of bevacizumab (20.24%, P = 0.021) (Table 2, Fig. 2).

The linear log relationship for median PFS or OS after adjusting for multiple variables, including complete cytoreduction, age, and the use of targeted agents, is presented in Tables 1 and 2. Multivariable analyses demonstrated that a 10% increase in the complete cytoreduction rate was associated with a 12.97% increase in the median OS in the entire patient cohort. Advanced age (−2.06%/year, P = 0.007) and a 10% increase in the rate of NAC (−4.80%, P < 0.001) were associated with a decrease in OS. Equivalently, in multivariable analysis including the rate of optimal cytoreduction, each 10% increase in the rate of optimal cytoreduction (≤1 cm) was associated with a 5.05% increase in OS. Recent publication year was associated with a 2.27%/year increase in OS (P < 0.001), while advanced age (−3.51%/year, P < 0.001) and 10% increase rate of NAC (−3.60%, P = 0.001) were associated with a decrease in OS.

In the multivariable analysis, the correlation between PFS and post-operative residual disease was not evident ($P = 0.359$ for complete cytoreduction and $P = 0.069$ for residual disease ≤1 cm) (Table 1).

We conducted a subgroup analysis of studies published since 2010, based on the first publication of a clinical trial involving bevacizumab

Table 1
Linear regression modal analysis for median progression-free survival time.

Variables	Beta	S.E	t-value	P	No. of Studies	No. of Unique Studies*	Change in median PFS	
							increase unit	%
Univariable analysis								
Proportion of Complete cytoreduction	0.275	0.138	1.991	**0.049**	117	62	10%	2.79
Proportion of ≤1 cm	0.327	0.096	3.401	**0.001**	167	91	10%	3.32
Publication year	−0.001	0.004	−0.372	0.710	167	91	1 year	−0.10
Median age	−0.037	0.007	−5.177	**<0.001**	151	83	1 year	−3.63
Proportion of stage 4	−0.815	0.246	−3.305	**0.001**	159	87	10%	−7.83
Proportion of NAC	−0.161	0.105	−1.535	0.127	138	80	10%	−1.60
Proportion of HGSOC	−0.087	0.201	−0.431	0.667	143	78	10%	−0.87
Use of Bevacizumab								
No	1							
Yes	0.161	0.059	2.729	**0.007**	161	88	Yes	17.26
Use of PARP inhibitor								
No	1							
Yes	0.268	0.092	2.93	**0.004**	167	91	Yes	30.18
Multivariable analysis (Complete cytoreduction)								
Proportion of Complete cytoreduction	−0.134	0.145	−0.922	0.359	95	51	10%	−1.33
Median age	−0.038	0.007	−5.800	**<0.001**			1 year	−3.73
Proportion of stage 4	−0.615	0.293	−2.102	**0.038**			10%	−5.96
Use of Bevacizumab								
No	1							
Yes	0.297	0.058	5.092	**<0.001**			Yes	34.36
Use of PARP inhibitor								
No	1							
Yes	0.379	0.101	3.748	**<0.001**			Yes	45.34
Multivariable analysis (≤1 cm)								
Proportion of ≤1 cm	0.177	0.097	1.830	0.069	145	80	10%	1.79
Median age	−0.040	0.007	−5.849	**<0.001**			1 year	−3.92
Use of Bevacizumab								
No	1							
Yes	0.159	0.051	3.112	**0.002**			Yes	17.08
Use of PARP inhibitor								
No	1							
Yes	0.341	0.089	3.851	**<0.001**			Yes	40.08

* For studies that reported respective median PFS and OS with two or three arms, each result considered independently. Unique study refers to the original study which is considered entire arms as one study.
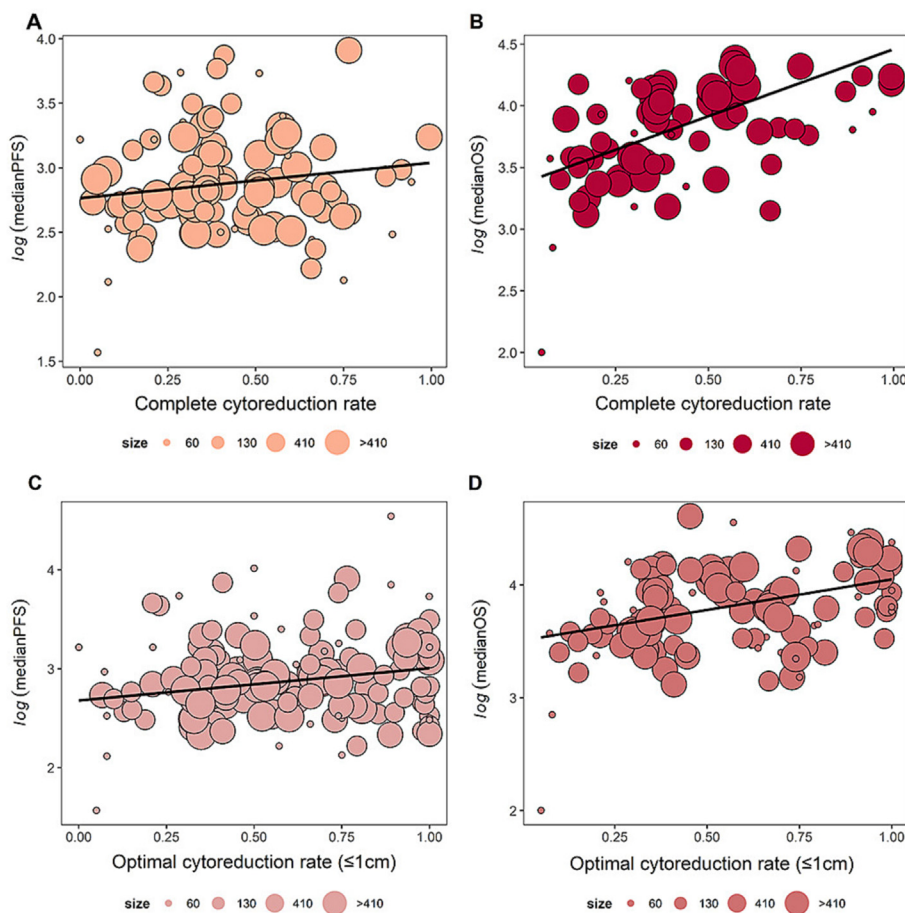
Fig. 2. Linear regression analysis between the proportion of complete or optimal cytoreduction and survival outcomes.

Table 2
Linear regression modal analysis for median overall survival time.

Variables	Beta	S.E	t-value	P	No. of Studies	No. of Unique Studies[*]	Change in median OS	
							increase unit	%
Univariable analysis								
Proportion of Complete cytoreduction	1.087	0.170	6.381	**<0.001**	78	43	10%	11.48
Proportion of ≤1 cm	0.542	0.124	4.387	**<0.001**	115	66	10%	5.57
Publication year	0.014	0.005	2.977	**0.004**	115	66	1 year	1.43
Median age	−0.039	0.008	−4.858	**<0.001**	105	61	1 year	−3.87
Proportion of stage 4	−1.049	0.337	−3.109	**0.002**	112	64	10%	−9.96
Proportion of NAC	−0.249	0.132	−1.883	0.063	99	58	10%	−2.46
Proportion of HGSOC	0.297	0.306	0.969	0.335	99	56	10%	3.01
Use of Bevacizumab								
No	1							
Yes	0.187	0.080	2.346	**0.021**	111	64	Yes	20.24
Use of PARP inhibitor								
No	1							
Yes	0.232	0.220	1.055	0.294	115	66	Yes	23.10
Multivariable analysis (Complete cytoreduction)								
Proportion of Complete cytoreduction	1.219	0.193	6.318	**<0.001**	57	33	10%	12.97
Median age	−0.021	0.007	−2.825	**0.007**			1 year	−2.06
Proportion of NAC	−0.492	0.113	−4.350	**<0.001**			10%	−4.80
Use of Bevacizumab								
No	1							
Yes	0.244	0.077	3.178	**0.003**			Yes	27.30
Multivariable analysis (≤1 cm)								
Proportion of ≤1 cm	0.493	0.119	4.127	**<0.001**	89	53	10%	5.05
Publication year	0.022	0.005	4.801	**<0.001**			1 year	2.27
Median age	−0.036	0.008	−4.605	**<0.001**			1 year	−3.51
Proportion of NAC	−0.366	0.110	−3.321	**0.001**			10%	−3.60

[*] For studies that reported respective median PFS and OS with two or three arms, each result considered independently. Unique study refers to the original study which is considered entire arms as one study.

in 2010. In the subgroup analysis of 55 studies published since 2010, univariable analysis confirmed a significant association between PFS, OS, and residual disease. Each 10% increase in complete cytoreduction rates and optimal cytoreduction (≤1 cm) rates led to a 3.68% (P = 0.023) and 5.08% (P < 0.001) increase in median PFS and a 13.19% (P < 0.001) and 7.29% (P < 0.001) increase in median OS, respectively (Fig. 3).

Furthermore, in the subgroup analysis of 15 studies that used systemic maintenance therapies, the univariable analysis confirmed the significant association of OS with postoperative residual disease. Each 10% increase in complete cytoreduction rates and optimal cytoreduction (≤1 cm) rates led to a 19.13% (P = 0.048) and 8.90% (P = 0.022) increase in the median OS, respectively (Supplementary Table 5). In addition, subgroup analysis of 11 studies that used bevacizumab revealed that the median PFS increased by 6.16% for every 10% increase in complete cytoreduction rates (P = 0.032) and by 8.24% for every 10% increase in optimal cytoreduction (≤1 cm) rates (P = 0.003) (Supplementary Table 6).

3.2. Meta-analysis

In the meta-analysis evaluating the association between patient survival and the size of postoperative residual disease, nine and 12 studies were included for PFS and OS, respectively. We used a random-effect model for the meta-analysis of both PFS and OS because the included studies showed strong heterogeneity with the Cochran Q test (P < 0.0001) and Higgins' I^2 statistics (77.9%, 85.6%), respectively. Although the number of studies was limited, we found that studies in the funnel plot were symmetrically distributed with respect to the pooled estimate. Moreover, Egger's test for publication bias indicated no statistical significance in either analysis (PFS, P = 0.691; OS, P = 0.736), suggesting no publication bias (Supplementary Fig. 1).

Compared with incomplete cytoreduction, complete CRS to no residual disease was associated with significantly higher PFS (HR, 0.53; 95% CI, 0.47–0.60) and OS (HR, 0.50; 95% CI, 0.42–0.59) in all studies (Supplementary Fig. 2). Our findings indicate a significant survival benefit in terms of both PFS (HR, 0.56; 95% CI, 0.37–0.84) and OS (HR, 0.53; 95% CI, 0.44–0.63) in the case of postoperative residual disease ≤1 cm.

4. Discussion

In this systematic review and meta-analysis involving 97 trials that enrolled 43,260 patients, we confirmed that maximal surgical effort to achieve complete cytoreduction was independently associated with increased OS, even after adjusting for the timing of surgery (primary CRS or interval CRS), advanced disease stage, and use of targeted agents, such as bevacizumab and PARP inhibitors. Across the evaluated studies, every 10% increase in complete cytoreduction led to a 12.97% increase in the median OS, and in the subgroup of maintenance therapies, this
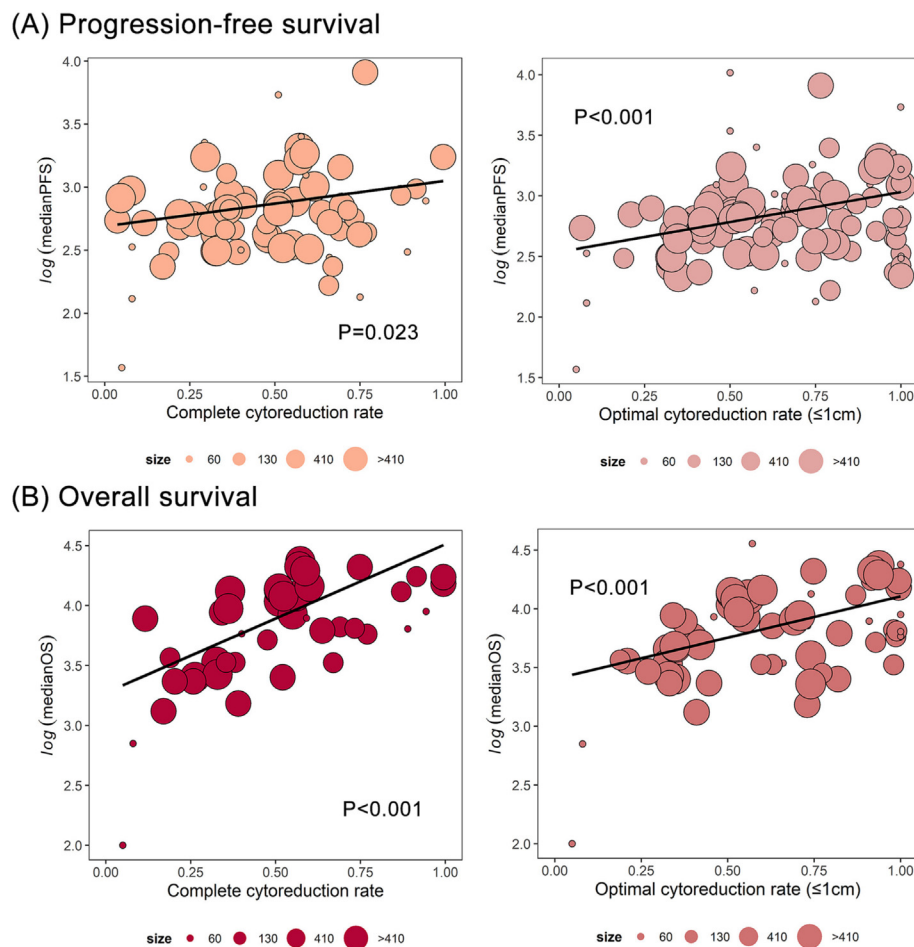
Fig. 3. Effect of residual tumor size on progression-free survival and overall survival for studies published since 2010, based on the first publication of a clinical trial involving bevacizumab in 2010.
A. Forest plot for progression-free survival in the included studies.
B. Forest plot for overall survival in the included studies.

effect was additionally potentiated with every 10% increase in complete cytoreduction, leading even to a 19.13% increase in the median OS.

Our study provides compelling evidence for the continued importance of maximal effort cytoreduction in the current treatment landscape of EOC. Our findings demonstrate that complete tumor clearance is a critical factor in optimizing patient outcomes and that this benefit is further amplified by pairing cytoreductive surgery with recent advances in frontline treatment strategies.

To the best of our knowledge, this study is the most up-to-date meta-analysis to evaluate the impact of postoperative residual disease on patient survival within the current paradigm of frontline treatment of EOC. Our findings reinforce the recommendation of current national and international guidelines [21,22] that place maximal effort in CRS at the center of all therapeutic algorithms for this challenging disease. The significance of our study is paramount considering that there are increasing views that targeted agents, such as bevacizumab and PARP inhibitors, are potent enough to negate the need for surgical cytoreduction.

Our study findings regarding the survival benefit of complete or optimal cytoreduction are consistent with those of a previous meta-analysis that demonstrated an increase in the median OS by 5.5%, with a remarkable 10% increase in maximal cytoreduction rates [5]. This archival meta-analysis evaluated the evidence generated between 1989 and 1998 using the definition of optimal residual disease with a postoperative tumor size of <2 cm. As per the standard of care, treatment with platinum-based chemotherapy is one of the main inclusion criteria. With time and the shift in definitions of postoperative residual disease, in the present meta-analysis, we separately evaluated the impact of complete versus near-complete cytoreduction (i.e. ≤1 cm), clearly showing that the maximal benefit is derived when complete tumor clearance is achieved. Our findings justify the current definition of 'optimal' cytoreduction as no visible residual disease [5,23,24].

When comparing the magnitude of survival improvement through complete versus near-complete cytoreduction, we identified a larger impact on OS through complete tumor resection versus leaving disease of ≤1 cm. This greater benefit in OS with complete cytoreduction has also been demonstrated in previous studies [25,26]. Residual disease of ≤1 cm seems to be associated with higher rates of platinum resistance development and lower response rates to first-line chemotherapy compared to complete cytoreduction [25,26]. Within expert teams, residual tumors, even if only low in volume, may be considered a surrogate marker of intrinsically more adverse tumor biology that in turn correlates with more severe tumor dissemination and progression [27]. Nonetheless, given the undeniable impact of tumor reduction to <1 cm in improving survival, it is imperative to pursue such maximal surgical efforts, even in patients with a high tumor burden. Recent data from real-world analyses using the entire ovarian cancer population of a country as a denominator [28] show that approximately 40% of all patients with EOC never undergo surgery at any stage of their disease, with all the detrimental impacts on survival that this entails. Comparative denominator studies have shown that the addition of surgery to the therapeutic algorithm for advanced EOC remains important even in patients with a high tumor burden [29].

4.1. Advancements in the treatment for EOC

Our study included articles published within the last 20 years, wherein frontline treatment has become highly individualized with the emergence of novel targeted agents, including PARP inhibitors and bevacizumab. The strength of our study is that we included studies related to NAC ($N = 80$) and targeted agents, including PARP inhibitors ($N = 5$) and bevacizumab ($N = 11$). Our finding that the magnitude of survival benefit derived from complete tumor clearance is potentiated when patients receive modern systemic maintenance strategies, which also correlates with the findings of lead RCTs that have established the use of PARP inhibitors and bevacizumab in EOC [30–33].

Subgroup or post-hoc analyses of PARP inhibitor studies [30,31] related to surgical outcomes have demonstrated a clear correlation between the magnitude of benefit derived from PARP-I and the size of postoperative residual disease. In the SOLO-1 trial, the most significant risk reduction in PFS was achieved in patients with no macroscopic residual disease (HR 0.33; 95% CI, 0.23–0.46) compared to patients with any visible residual disease (HR 0.44; 95% CI, 0.25–0.77) [30]. In the PRIMA trial, a greater risk reduction in PFS was not guaranteed in patients with no macroscopic residual disease (HR 0.70; 95% CI, 0.50–0.96) compared to patients with residual disease (HR 0.50; 95% CI, 0.38–0.67). However, the median PFS duration was the longest in patients with no residual disease (niraparib arm, 18.2; placebo arm; 11.0 months) [31].

Observations from the PAOLA-1 trial are also concurrent with these findings [32,33]. The most prominent PFS benefit was achieved in patients who had undergone complete CRS with no macroscopic residual disease (HR, 0.47; 95% CI, 0.29–0.75), particularly in the HRD subpopulation (HR, 0.15; 95% CI, 0.07–0.30). These data, in combination with our findings, demonstrate a clear synergistic effect between surgical effort and PAPR-I maintenance, with the magnitude of PARP-I-derived benefit being directly correlated with postoperative residual disease [30–32]. The message here is clear: advances in systemic treatment do not negate the need for surgical effort but on the contrary potentiate it, so that the entire treatment package of maximal effort approach across all levels results in the best possible oncologic outcome.

Despite its effect on OS, the lack of correlation between residual disease and PFS is unclear. Varying definitions of points of relapse between studies may have caused this discrepancy. PFS is the closest primary trial endpoint; however, relapse monitoring is not always standardized in real-world data [34,35]. Our findings may reflect that novel targeted therapy can overcome poor surgery in terms of remission; however, in none of the trials suboptimal resection and targeted therapy were compared to complete/optimal tumor resection without targeted therapy, so it would not be justified to make that claim. The significant effect on OS, in the absence of a significant PFS benefit, would potentially suggest an interaction between time of recurrence and opportunity for second and beyond lines of therapy, but again we have no solid basis to predict that. Evidence is still insufficient for the validity of PFS as a surrogate measure of OS, with previous meta-analyses showing a low correlation between PFS and OS at the first-line trial level, including maintenance treatment [35,36].

4.2. Limitations

The present study has certain limitations that need to be addressed. As we only assessed the studies without pooling the individual patient data, and as we included only studies that have reported survival by the size of residual disease, there will be selection bias that cannot be avoided. In addition, all evaluated studies enrolled only prognostically favorable patients who showed a clear response to 1st line platinum-based chemotherapy; otherwise, they would not be eligible for maintenance treatment, especially in the case of PARP inhibitors. This means that patients who progressed or relapsed early after 1st line treatment even despite optimal surgery were omitted from this study. With the rate of disease progression during chemotherapy ranging between 5 and 15%, the omission of prognostically poor patients would bias the results.

Furthermore, several studies had different time points for PFS and OS; thus, we operationally adjusted these to be defined at the same time point, which might have led to a lack of precision. Finally, we were able to include only a limited number of RCTs regarding targeted agents, and mature data on the impact of PARP inhibitors on OS are limited. Although the current study has strong statistical evidence, our results should be interpreted with a certain degree of caution, considering these limitations. Given the importance of targeted agents as a variable and their correlation with improved median overall

survival (OS) rates, it is imperative to conduct further investigations into the real-world outcomes and cost-effectiveness of targeted agents in combination with the impact of residual disease following cytoreductive surgery.

5. Conclusions

This study generated robust and clinically relevant insights into the importance of maximal surgical effort in primary EOC, even after the introduction of recent advances in frontline treatment. Complete CRS remains a key prognostic factor for the outcome of ovarian cancer. Pairing surgery with systemic advances appears to bring maximum benefit to patients.

Ethics committee approval

The study was approved by the Ethics Committee of the National Cancer Center, Korea.

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The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Data sharing statement

The datasets, statistical analysis plan, and scripts used in this study are available from the corresponding author upon request.

CRediT authorship contribution statement

MCL, CF had full access to all the data in the study and took responsibility for the integrity of the data and accuracy of the data analysis. JHK and SIK contributed equally to this study.

Conceptualization: JHK, SIK, MCL.
Investigation: JHK, SIK, HIH, JWK, RC, RB, SYP, CF, and MCL.
Formal analysis: JHK, SIK and EYP.
Validation: JHK, SIK, HIH and MCL.
Writing-original draft: JHK, SIK, CF and MCL.
Writing- review&editing: JWK, RC, RB, SYP, CF, and MCL.
Funding acquisition: MCL.
Supervision: JWK, RC, RB, SYP, CF, and MCL.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

MCL reported having a consulting or advisory role for AstraZeneca, Boryung, CKD Pharm, Genexine, Hospicare, GI Innovation, and Takeda and receiving research funding from AbbVie, Amgen, Astellas, AstraZeneca, BeiGene, Cellid, CKD Pharm, Clovis, Eisai, Genexine, GSK, Incyte, Merck, MSD, OncoQuest, Pfizer, and Roche outside the submitted work.

SYP reported having a consulting or advisory role for Boryung and Takeda and receiving research funding from AbbVie, Amgen, Astellas, AstraZeneca, BeiGene, Cellid, CKD Pharm, Clovis, Eisai, Genexine, GSK, Incyte, Merck, MSD, OncoQuest, Pfizer, and Roche outside the submitted work. No other disclosures have been reported.

CF reported a consulting or advisory role for GlaxoSmithKline, Roche/Genentech, Clovis Oncology, AstraZeneca, Global Oncology One, Aptitude Health, and Eisai and received research funding from the Myrovlytis Charity Trust.

The other authors declare that they have no conflicts of interest relevant to this article.

Appendix A. Supplementary data

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