

Original Article



Efficacy and safety of neoadjuvant chemotherapy versus primary debulking surgery in patients with ovarian cancer: a meta-analysis

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Trial Registration

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ABSTRACT

Objective: Neoadjuvant chemotherapy (NACT) for the treatment of epithelial ovarian cancer (EOC) has remained controversial. This meta-analysis was performed to systematically assess the efficacy and safety of NACT versus primary debulking surgery (PDS) in patients with EOC.

Methods: PubMed, Embase, ClinicalTrials.gov, and Cochrane Library were queried to assess the therapeutic value of NACT versus PDS in EOC. Electronic databases were queried by using the keywords “ovarian cancer/neoplasms”, “primary debulking surgery”, and “neoadjuvant chemotherapy”.

Results: The available trials were pooled, and hazard ratios (HRs), relative risk ratios (RRs) and associated 95% confidence intervals (95% CIs) were determined. Sixteen trials involving 57,450 participants with EOC (NACT, 9,475; PDS, 47,975) were evaluated. We found that NACT resulted in markedly decreased overall survival than PDS in patients with EOC (HR=1.30; 95% CI=1.13–1.49; heterogeneity: $p < 0.001$, $I^2=82.7\%$). Furthermore, our results demonstrated that the NACT group displayed increased completeness of debulking removal (RR=1.69, 95% CI=1.32–2.17; heterogeneity: $p < 0.001$, $I^2=81.9\%$), and reduced risk of postsurgical death (RR=0.18, 95% CI=0.06–0.51; heterogeneity: $p=0.698$, $I^2=0\%$) and major infection (RR=0.29, 95% CI=0.17–0.51; heterogeneity: $p=0.777$, $I^2=0\%$) compared with patients administered PDS.

Conclusions: This meta-analysis indicated that NACT results in increased completeness of debulking removal, and reduced risk of postsurgical death and major infection compared with PDS, while PDS is associated with improved survival in comparison with NACT in EOC patients.

Trial Registration: PROSPERO Identifier: [CRD42019120625](https://doi.org/10.1111/1751-2220.120625)

Keywords: Neoadjuvant Therapy; Debulking Surgical Procedure; Epithelial Ovarian Cancer; Meta-Analysis

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Author Contributions

Conceptualization: C.S.; Investigation: L.X., Z.X., R.C.; Methodology: L.X., Z.X., R.C.; Writing - original draft: L.X.; Writing - review & editing: C.S.

INTRODUCTION

Epithelial ovarian cancer (EOC) represents the 5th deadliest malignancy in female. It constitutes the first reason for death from gynecological malignancies and ranks number 2 among gynecologic malignancies worldwide [1]. In 2012, there are over 238,700 newly diagnosed cases and 151,900 EOC caused deaths worldwide [2]. In the past 10 years, EOC incidence in China has increased by 30% while the mortality rate has increased by 18% [3]. Due to this disease originating from the fallopian tube, as well as lacking adequate screening methods and early manifestations, most EOC cases are detected at International Federation of Gynecology and Obstetrics (FIGO) stage IIIc or IV. Most patients relapse within the first 5 years of the initial treatment, and only 20%–25% patients are effectively cured [4]. Primary debulking surgery (PDS) represent a key therapy in EOC, and PDS combined with chemotherapy destroys any gross or microscopic residual tumor cells [5]. The goal of PDS is to eliminate as many bulky tumors as possible, with effective surgery yielding tumor residues with maximal diameters below 1 cm, resulting in improved survival compared with ideal tumor cell elimination [6].

Neoadjuvant chemotherapy (NACT) is treatment with platinum-containing chemotherapeutics followed by interval debulking surgery (IDS) to decrease tumor size, and represents a viable substitute of PDS in advanced EOC cases [7,8]. EOC is a chemosensitive tumor with response rates between 70% and 80% [9]. According to a previous report, cases unable to undergo PDS could be treated with 3 cycles of platinum-based regimens before IDS, prolonging progression-free survival (PFS) as well as overall survival (OS) [10]. Since then, NACT is mainly employed to decrease disease burden in cases showing bulky tumors, increasing the likelihood of effective debulking. Previously, 2 randomized controlled trials (RCTs) [7,8] aimed to determine whether platinum-based primary chemotherapy followed by surgery was superior to other treatment combinations. The results from these two studies proved no inferior outcome for EOC patients receiving NACT and surgery, compared to surgery first. Two previous meta-analytical studies [11,12] addressed the question of whether patients who achieve microscopic residual disease with NACT have an equally good prognosis and survival as do patients who undergo PDS. However, the role of NACT and PDS is still under controversy. To provide a comprehensive assessment of efficacy and safety of NACT compared with PDS for ovarian cancer, we performed a meta-analysis of published studies.

MATERIALS AND METHODS

1. Sources

The present meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [13]. Electronic databases, such as PubMed, Embase, ClinicalTrials.gov, and Cochrane Library, were queried by using the keywords “ovarian cancer/neoplasms”, “primary debulking surgery”, and “neoadjuvant chemotherapy”. The last search was updated on March 15, 2018 with publication years ranging from 2005 to 2018.

2. Study selection

Studies were included if meeting the following criteria: 1) patients with EOC; 2) comparison of NACT with PDS; 3) reporting OS, PFS, completeness of debulking removal, residual disease of ≤ 1 cm and/or complications as primary outcome measures; and 4) studies reported in the English language.

Data extraction was performed by 2 investigators in an independent manner, with disagreements settled by a third contributor. The retrieved data comprised first author's name, year of publication, country, mean age, intervention, follow-up time, and outcome assessment. We evaluate the quality of RCTs with the Cochrane Collaboration's tool for assessing risk of bias [14]. The Cochrane Collaboration's tool has 7 domains of bias: a) random sequence generation (selection bias), b) allocation concealment (selection bias), c) blinding of participants and caregivers (performance bias), d) blinding of outcome assessment (detection bias), e) incomplete outcome data (attrition bias), f) selective outcome reporting (reporting bias), and g) other bias. For each domain, reviewers judged whether the risk of bias in a given study was "low," "high," or "unclear." The nine-star system by Newcastle-Ottawa Scale was employed to assess cohort studies for quality, and a high-quality study was defined as one with ≥ 7 stars [15].

Indirect techniques were utilized to extract log hazard ratio (HR) and variance, because of the scarcity of prognostic studies directly reporting such values [16], which were determined from HRs and 95% confidence intervals (95% CIs) if applicable, log rank p values, or Kaplan-Meier survival curves. The pooled risk ratios (RRs) with corresponding 95% CIs were estimated. Heterogeneity was evaluated by the Q-test. At $I^2 < 50\%$, pooled HRs or RRs of various studies were obtained by the fixed-effects model; otherwise, the random-effects model was employed. In sensitivity analysis, relative influences of various studies on pooled results were estimated by omission of one trial at a time. Publication bias evaluation was performed by assessing Begg's funnel plots and using the Egger's test [17] ($p < 0.05$ was considered statistically significant). Statistical analysis was performed using STATA 12.0 (StataCorp, College Station, TX, USA).

RESULTS

A total of 283 articles were obtained. Of these, 234 were excluded upon reviewing the titles. Then, the abstracts were evaluated, and 33 full-text reports were thoroughly evaluated for inclusion. Initially, 16 publications [7,8,18-31], including 57,450 patients were eligible for inclusion (**Table 1** for detailed characteristics). **Fig. 1** depicts the selection procedure as well as the reasons for exclusion. Average patient ages were between 50.7 and 76.5 years. A summary of selection, detection, performance, reporting, attrition, and other biases in various individual RCTs are shown in **Supplementary Fig. 1**. Two studies had one domain (performance bias) judged as high risk of bias and other domains judged as low risk. The methodological qualities of included observational trials are displayed in **Table 2**. The observational trials generally showed high quality, with 10 and 4 studies having 8 and 7 stars, respectively.

The efficacy and safety of NACT versus PDS in 16 studies including 57,450 EOC patients were evaluated.

OS: A total of 16 trials assessed OS, and all compared NACT and PDS. Significant heterogeneity ($p < 0.001$, $I^2 = 82.7\%$) was found, and the random-effects model was employed for assessment. Pooled data indicated that NACT resulted in significantly reduced OS compared with PDS in patients with OC (HR=1.30, 95% CI=1.13-1.49; heterogeneity: $p < 0.001$, $I^2 = 82.7\%$) (**Fig. 2A**).

Table 1. Characteristics of the studies included in this meta-analysis

First authors/ year of publication	Country	Mean age (yr)	Study design	No. of patients in intervention		Stage	Period of study (yr)	Outcomes assessed
				NACT	PDS			
Loizzi/2005 [18]	Italy	NACT: 64±11.35 PDS: 58±10.57	A case-control study	30	30	IIIC, IV	1994–2003	OS, PFS, and residual disease ≤1 cm
Vergote/2010 [7]	Belgium	NACT: 63±12 PDS: 62±15.25	RCT	334	336	IIIC, IV	1998–2006	OS, PFS, completeness of debulking removal, residual disease ≤1 cm, postsurgical death, and major infection
Milam/2011 [19]	USA	NACT: 61±13.5 PDS: 57±17	Cohort study	46	217	IIIC, IV	1993–2005	OS, PFS
Glasgow/2012 [20]	USA	NACT: 76.9±4.75 PDS: 75.9±4.75	Cohort study	42	62	IIIC, IV	1996–2009	OS, PFS, completeness of debulking removal, residual disease ≤1 cm, postsurgical death, major infection, and wound complication
Zheng/2012 [21]	China	NACT: 55.8 PDS: 54.5	Cohort study	30	37	IIIC, IV	2006–2009	OS, PFS
Taskin/2013 [31]	Turkey	NACT: 60.5±11.3 PDS: 56.4±12.6	Cohort study	74	23	IIIC, IV	2001–2010	OS
Worley/2013 [22]	USA	NACT: 74±3.5 PDS: 75±6.25	Cohort study	40	125	IIIC, IV	2000–2010	OS, PFS, postsurgical death, major infection, and wound complication
Colombo/2014 [23]	France	NA	Cohort study	147	220	IIIC, IV	1995–2010	OS
Fagö-Olsen/2014 [24]	Denmark	NACT: 66±3.25 PDS: 65±4.25	Cohort study	515	990	IIIC, IV	2005–2011	OS, completeness of debulking removal, and residual disease ≤1 cm
Kehoe/2015 [8]	UK	NACT: 65±13.5 PDS: 66±15.25	RCT	274	276	III, IV	2004–2010	OS, PFS, completeness of debulking removal, residual disease ≤1 cm, postsurgical death, and major infection
Bian/2016 [25]	China	NACT: 53±10.25 PDS: 50.7±15.75	Cohort study	114	225	IIIC, IV	2005–2010	OS, PFS, completeness of debulking removal, and residual disease ≤1 cm
Kessous/2016 [26]	Canada	NACT: 64.8±12.5 PDS: 58±11.5	Cohort study	127	136	IIIC	2003–2015	OS, PFS
Lim/2017 [27]	Korea	NACT: 57 PDS: 53	Cohort study	136	143	III, IV	2000–2009	OS, PFS
May/2017 [28]	USA	NACT: 62.2±12.25 PDS: 59.3±11	Cohort study	161	142	IIIC, IV	2004–2011	OS, completeness of debulking removal, and residual disease ≤1 cm
Seagle/2017 [29]	USA	NACT: 65±4 PDS: 61±4.5	Cohort study	7,348	44,970	III, IV	1998–2011	OS
Siesto/2018 [30]	Italy	NACT: 63.2±10.1 PDS: 60.8±10.7	Cohort study	50	50	IIIC, IV	2009–	OS, PFS, completeness of debulking removal, residual disease ≤1 cm, major infection, and wound complication

NACT, neoadjuvant chemotherapy; OS, overall survival; PDS, primary debulking surgery; PFS, progression-free survival; RCT, randomized controlled trial.

PFS: This was reported in eleven trials, and all compared NACT and PDS. Heterogeneity showed a statistical significance ($p=0.042$, $I^2=47.1\%$), and the random-effects model was employed for assessment. Pooled data showed no statistical significance in PFS between the NACT and PDS groups ($HR=0.98$, $95\% CI=0.87-1.10$; heterogeneity: $p=0.042$, $I^2=47.1\%$) (**Fig. 2B**).

Completeness of debulking removal: This was assessed by seven studies, which all compared NACT with PDS. Heterogeneity was statistically significant ($p<0.001$, $I^2=81.9\%$), and the random-effects model was used. Pooled data showed the NACT group achieved increased completeness of debulking removal in comparison with women who underwent PDS ($RR=1.69$, $95\% CI=1.32-2.17$; heterogeneity: $p<0.001$, $I^2=81.9\%$) (**Fig. 2C**).

Residual disease ≤1 cm: This was assessed by 8 studies, which all compared NACT with PDS. Heterogeneity showed no statistical significance ($p=0.061$, $I^2=48\%$), and the fixed-effects model was used. Pooled data revealed similar values for residual disease ≤1 cm between the NACT and PDS groups ($RR=1.01$, $95\% CI=0.90-1.13$; heterogeneity: $p=0.061$, $I^2=48\%$) (**Fig. 2D**).

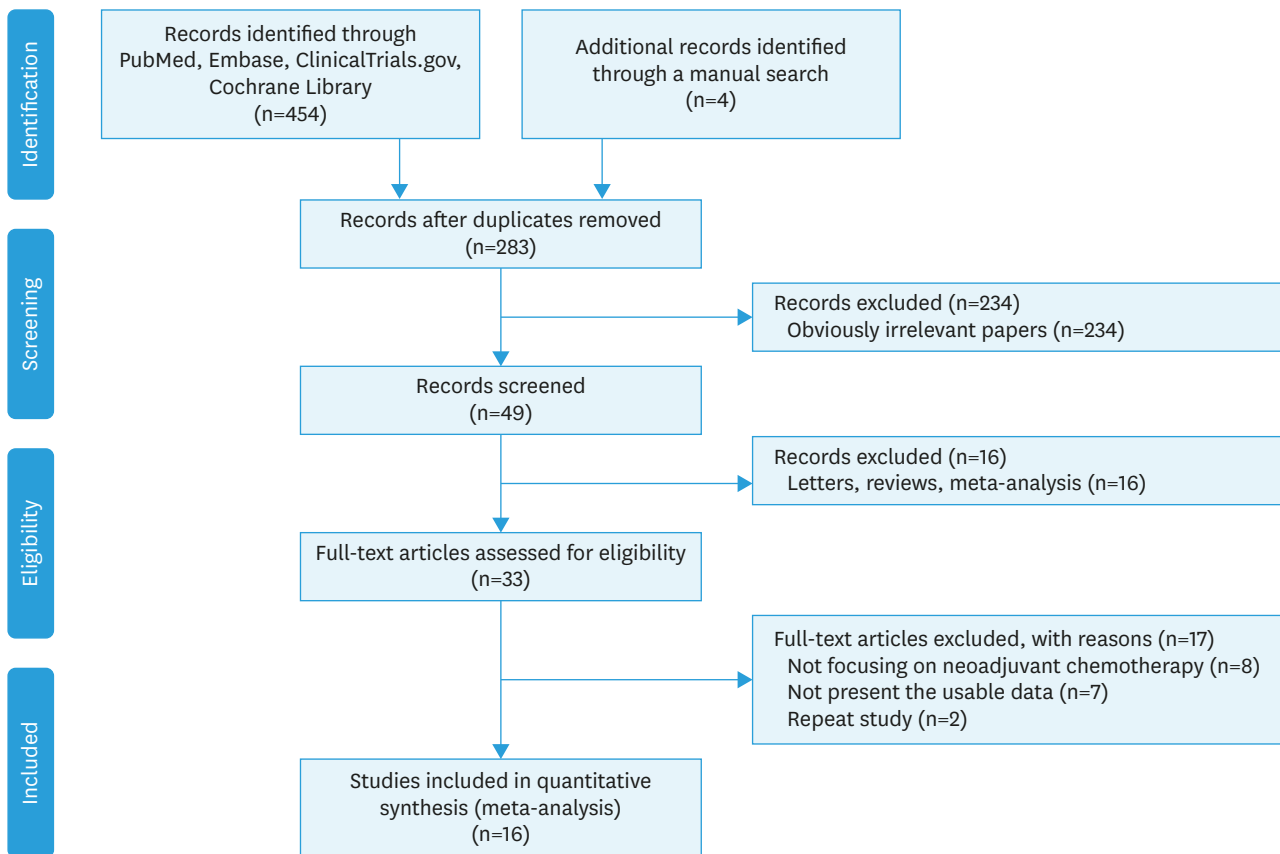


Fig. 1. Flow diagram of study inclusion.

Postsurgical death: This was assessed by 4 studies, which all compared NACT with PDS. No heterogeneity was found ($p=0.698$, $I^2=0\%$), and the fixed-effects model was employed. Pooled data demonstrated NACT markedly decreased the risk of postsurgical death in comparison with PDS (RR=0.18, 95% CI= 0.06–0.51; heterogeneity: $p=0.698$, $I^2=0\%$) (**Fig. 3A**).

Table 2. Methodological quality of observational studies included in the meta-analysis*

First author/ year of publication	Representativeness of the exposed cohort	Selection of the unexposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study	Control for important factor or additional factor	Outcome assessment	Follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Total quality scores
Loizzi/2005 [18]	☆	☆	☆	☆	☆	☆	☆	☆	8
Milam/2011 [19]	☆	☆	☆	-	☆	☆	☆	☆	7
Glasgow/2012 [20]	☆	☆	☆	☆	☆	☆	☆	☆	8
Zheng/2012 [21]	☆	☆	☆	☆	☆	☆	-	☆	7
Taskin/2013 [31]	☆	☆	☆	☆	☆	☆	☆	☆	8
Worley/2013 [22]	☆	☆	☆	☆	☆	☆	☆	☆	8
Fagö-Olsen/2014 [24]	☆	☆	☆	☆	☆	☆	☆	☆	8
Colombo/2014 [23]	☆	☆	☆	☆	☆	☆	-	☆	7
Bian/2016 [25]	☆	☆	☆	☆	☆	☆	☆	☆	8
Kessous/2016 [26]	☆	☆	☆	☆	☆	☆	☆	☆	8
May/2017 [28]	☆	☆	☆	☆	☆	☆	☆	☆	8
Lim/2017 [27]	☆	☆	☆	☆	☆	☆	☆	☆	8
Seagle/2017 [29]	☆	☆	☆	☆	☆	☆	☆	☆	8
Siesto/2018 [30]	☆	☆	☆	☆	☆	☆	-	☆	7

*A study could be awarded a maximum of one star for each item except for the item control for important factor or additional factor.

NACT vs PDS in ovarian cancer

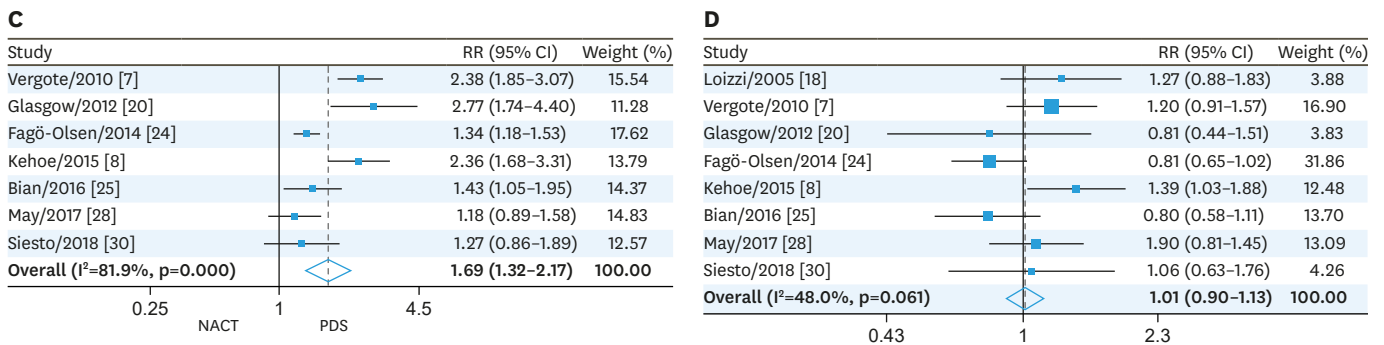
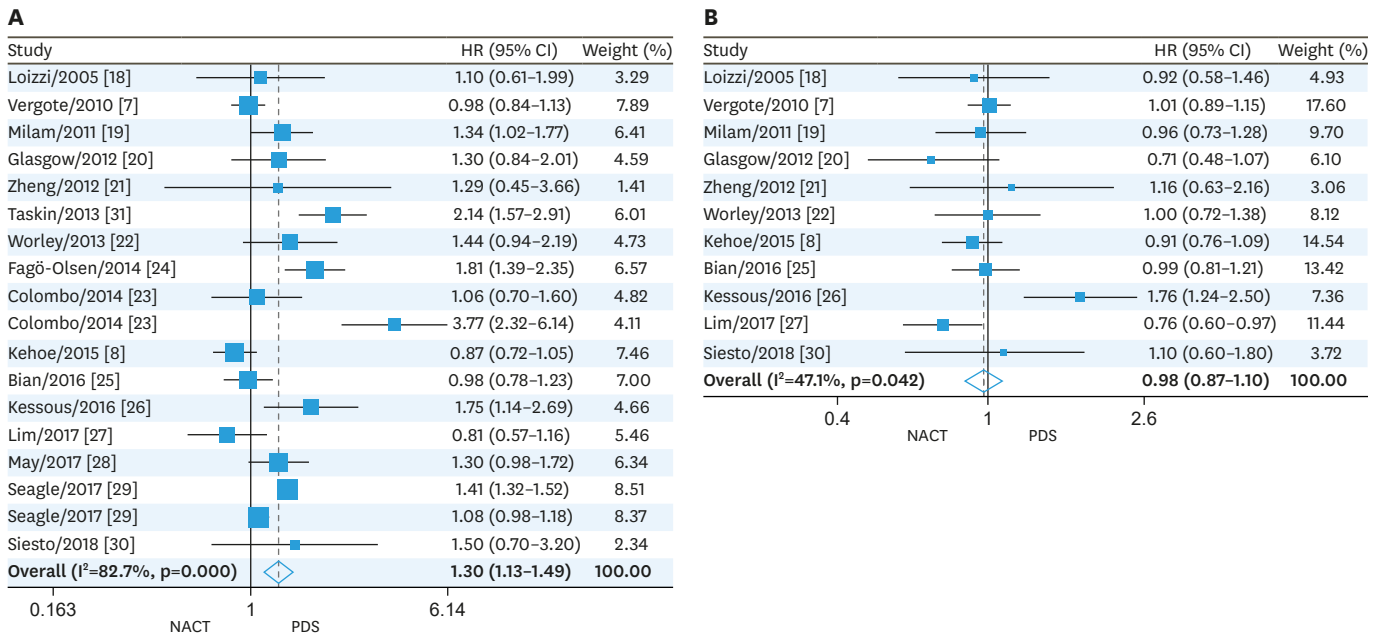


Fig. 2. Forest plots for survival and extent of surgical debulking. (A) OS, (B) PFS, (C) Completeness of debulking removal, and (D) Residual disease ≤ 1 cm. CI, confidence interval; HR, hazard ratio; NACT, neoadjuvant chemotherapy; PDS, primary debulking surgery; RR, risk ratio.

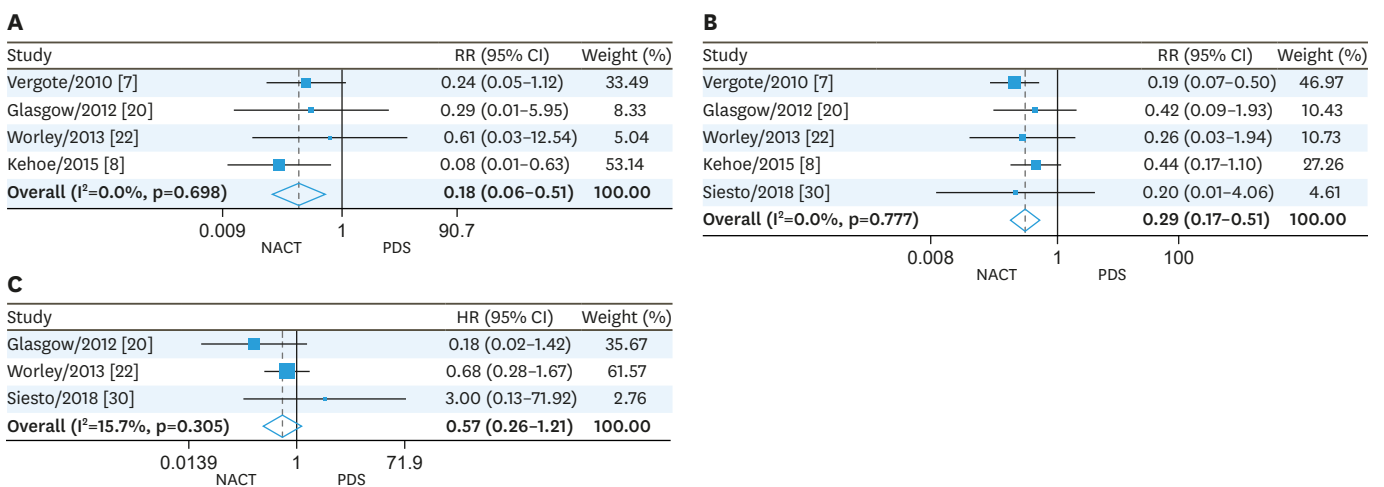


Fig. 3. Post-operative complications and mortality. (A) Postsurgical death, (B) Major infections, and (C) Wound complications. CI, confidence interval; NACT, neoadjuvant chemotherapy; PDS, primary debulking surgery; RR, risk ratio.

Major infection: This was assessed by 5 studies, which all compared NACT with PDS. No heterogeneity was found among trials ($p=0.777$, $I^2=0\%$), and the fixed-effects model was employed. Pooled data demonstrated NACT starkly decreased the risk of major infection in comparison with PDS (RR=0.29, 95% CI=0.17–0.51; heterogeneity: $p=0.777$, $I^2=0\%$) (**Fig. 3B**).

Wound complications: This was assessed by 3 studies that compared NACT with PDS. No heterogeneity was detected ($p=0.305$, $I^2=15.7\%$), and the fixed-effects model was employed. Pooled results showed similar incidence rates of wound complications between the NACT and PDS groups (RR=0.57, 95% CI=0.26–1.21; heterogeneity: $p=0.305$, $I^2=15.7\%$) (**Fig. 3C**).

As depicted in **Supplementary Fig. 2**, Sensitivity analyses were performed to assess the influence of individual dataset on the overall results by sequentially removing each eligible study. Any single study was omitted, while the overall statistical significance does not change, indicating the stability of the pooled results.

Finally, the Begg's and Egger's regression tests revealed no publication bias, with symmetrical funnel plots for OS ($p=0.363$ and $p=0.676$, respectively), PFS ($p=0.640$ and $p=0.769$, respectively) and completeness of debulking removal ($p=0.548$ and $p=0.270$, respectively) (**Supplementary Fig. 3**).

DISCUSSION

This work aimed to compare NACT and PDS for therapeutic value in EOC. This was the largest study so far analyzing data from 16 trials with 57,450 participants (NACT, 9,475; PDS, 47,975) and comparatively evaluating the therapeutic values of NACT and PDS in EOC cases. Our results showed that NACT achieved more completeness of debulking removal, reduced the risk of postsurgical death and major infections in comparison with PDS. Moreover, PDS was associated with improved survival in comparison with NACT in EOC patients.

The therapeutic values of NACT and PDS in EOC have been assessed in multiple meta-analyses [11,12]. Yang and collaborators [11] carried out a comprehensive meta-analysis assessing NACT and PDS in advanced epithelial OC, and the results showed that NACT had superior optimal cytoreduction, reduced perioperative morbidity and postoperative mortality. Compared to the study by Yang et al. [11], we extracted HRs and 95% CIs from survival curves and found that PDS was associated with improved survival in comparison with NACT in EOC patients. Another meta-analysis reported by Zeng et al. [12] assessed NACT in patients with advanced epithelial OC; compared to the study by Zeng et al. [12] which analyzed only four studies with 1,922 participants, we identified more eligible studies. Recently, Qin et al. [32] conducted a meta-analysis of NACT followed by IDS for advanced EOC patients and indicated that treatment with NACT-IDS improves perioperative outcomes and optimal cytoreduction rates. Here, we found that NACT results in increased completeness of debulking removal, reduced risk of postsurgical death and major infection, and starkly reduced OS in comparison with PDS in EOC patients.

Optimal debulking, whether performed before or after chemotherapy, represents the main prognostic factor that prolongs the survival time [7,33]. Mounting evidence indicates that NACT improves the performance status of advanced EOC cases, reduces the incidence and degree of surgical complications, and increases the chance of optimal cytoreductive surgery

[7,10]. Therefore, it is natural to consider NACT followed by IDS as a valid substitute to routine PDS for advanced EOC, and assume that patients undergoing NACT would have better survival in comparison with the PDS group. Intriguingly, the increase in optimal tumor cell ablation in the NACT group caused no improvement of survival outcomes. The majority of trials had comparable OS rates for the NACT and PDS groups. This work demonstrated that PDS was associated with improved survival in comparison with NACT in EOC patients. To some extent, this finding was not in accordance with the results of the two RCTs. In their studies, similar outcomes with regards to OS and progression free survival were observed in EOC patients receiving primary chemotherapy versus primary surgery. Patients who receive NACT are likely to have worse functional status, more aggressive tumor biology and higher disease burden which could not be adjusted for the observational study design. This may explain some of the improved survival seen in the PDS group. There may be high risk of selection, and selective reporting bias from the cohort studies, though some of them reported plenty of cases. Surgery performed by gynecologic oncologists is associated with better staging, optimal cell loss, lower morbidity, and better survival. Both mass hospitals and sub-specialization were independent predictors of survival [34,35]. These may also explain why these patients had better cytoreduction, less infection, and less perioperative death but still experienced poor outcomes. In addition, less studies were included in these comparisons could also influence these outcomes.

Given the recent data on the molecular origin of EOC, the heterogeneity of clinical behavior associated with histological subtypes becomes easier to understand [36,37]. According to these data, EOC can be divided into two types, which develop independently along different molecular pathways and have significant differences in biological behavior and prognosis. Both types develop outside the ovary and involve it secondarily [36]. Type 1 EOC (non-hazardous or low-grade serous tumors) is usually indolent and appears in the first stage, developed by a mature precursor, known as a borderline ovarian tumor. Their genes are relatively stable. Type II EOC (high-grade serous) is composed of invasive tumors, advanced tumors, from the development of tubal epithelial carcinoma. Makar et al. [38] propose stratifying advanced ovarian cancer patients according to patterns of tumor spread. Individualized surgical procedures should consider clinical conditions, tumor biology, and chemosensitivity. Non-hazardous (type 1) tumors with good prognosis are less sensitive to chemotherapy, and ignoring optimal PDS will lead to poor prognosis. For patients with advanced serous ovarian cancer (type 2) with severe comorbidity or low functional status, NACT-IDS is the preferred option.

The limitations of the current meta-analysis should be mentioned. First, the included studies had significant heterogeneity, which might be due to the inclusion of different study designs, surgical techniques, chemotherapeutics regimens and surgical procedures. Secondly, although HRs and 95% CIs were obtained as previously proposed by Tierney et al. [39], Kaplan-Meier curve data might not have the same precision as those obtained directly from original articles. Thirdly, only English reports were included, which might introduce additional bias. Finally, definition of optimal debulking /optimal cytoreductive surgery that evolved with time from <2 cm to <1 cm to 0 cm. This has its impact while interpreting results of different trial.

In conclusion, this meta-analysis suggested that NACT achieves more completeness of debulking removal, and reduces the risk of postsurgical death and major infections, compared with PDS in EOC. Meanwhile, PDS was associated with improved survival in comparison with NACT in EOC patients. Moreover, these survival results are due to

retrospective studies with a lower level of evidence compared with RCTs which documented superimposable survival between the two strategies. These conclusions should be validated in large sample well-designed RCTs.

SUPPLEMENTARY MATERIALS

Supplementary Fig. 1

Risk of bias assessment for the randomized trials included in the current meta-analysis. (A) Risk of bias summary and (B) Risk of bias graph. Each symbols mean as follows: (+), low risk of bias; (?), unclear risk of bias; (-), high risk of bias.

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Supplementary Fig. 2

Sensitivity analysis examining the influence of individual studies on pooled results. (A) OS and (B) PFS.

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Supplementary Fig. 3

Funnel plots for publication bias assessment. Each point represents a separate study for the indicated association. (A) OS, (B) PFS, and (C) Completeness of debulking removal.

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