HHS Public Access

Author manuscript

Eur J Surg Oncol. Author manuscript; available in PMC 2021 May 01.

Published in final edited form as:

Eur J Surg Oncol. 2020 May ; 46(5): 868–875. doi:10.1016/j.ejso.2019.11.520.

Survival outcome and perioperative complication related to neoadjuvant chemotherapy with carboplatin and paclitaxel for advanced ovarian cancer: A systematic review and meta-analysis

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Abstract

Objective—To compare the effectiveness and safety of neoadjuvant chemotherapy with carboplatin/ paclitaxel followed by interval debulking surgery (NACT-IDS) to primary debulking surgery plus postoperative chemotherapy (PDS) for advanced ovarian cancer.

Methods—A comprehensive systematic review and meta-analysis were conducted by an Expert Panel of the Japan Society of Gynecologic Oncology Ovarian Cancer Committee. Multiple public search engines including PubMed/MEDLINE and the Cochrane Database, were searched in March 2019 using the entry keywords “ovarian cancer [all fields]” AND “interval debulking surgery [all

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Author contributions

Conceptualization: M.M.; Data curation: H.T., H.M.; Formal analysis: H,T, H.M.; Funding acquisition: None; Investigation: all authors; Methodology: M.M.; Project administration: M.M.; Resources: H.T, H.M.; Software: H.T, H.M.; Supervision: M.M.; Validation: H.T, H.M.; Visualization: H.M.; Writing - original draft: H.M.; Writing - review & editing: all authors..

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Declaration of competing interest

Honorarium, Chugai, textbook editorial, Springer, and investigator meeting attendance expense, VBL therapeutics (K.M.); none for others.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.11.520.

fields]", AND "neoadjuvant chemotherapy [all fields]". Key inclusion criteria were prospective clinical trials examining platinum-based NACT for stage II-IV epithelial ovarian cancer. The primary outcome of interest was survival, and the secondary outcome was adverse events with each intervention.

Results—After screening 333 studies, four phase III randomized clinical trials were identified that met the inclusion criteria. These trials included 1692 women (847 receiving NACT-IDS and 845 receiving PDS). It was found that NACT-IDS and PDS had similar overall survival (hazard ratio [HR]: 0.97, 95% confidence interval [CI]: 0.87–1.07, $P = 0.53$) and progression-free survival (HR: 0.98, 95%CI: 0.90–1.08, $P = 0.74$). In contrast, NACT-IDS was associated with significantly lower rates of perioperative complications (odds ratio [OR] 0.27, 95%CI: 0.20–0.36, $P < 0.001$) and perioperative mortality (OR: 0.17, 95%CI: 0.06–0.50, $P < 0.001$) compared to PDS.

Conclusion—This systematic review and meta-analysis suggests that NACT-IDS with carboplatin and paclitaxel does not negatively impact the survival of women with advanced ovarian cancer compared to PDS, while perioperative complications and mortality are significantly reduced by 70–80%.

Keywords

Ovarian cancer; Neoadjuvant chemotherapy; Survival; Perioperative complication; Systematic review; Meta-analysis

Introduction

Worldwide, ovarian cancer is the 7th most common female malignancy, and more than half of the women with ovarian cancer have advanced disease at presentation [1]. The standard initial treatment for advanced ovarian cancer has been primary debulking surgery (PDS) followed by platinum-based chemotherapy [2]. The quality of surgery is an important prognostic factor for survival in women with advanced ovarian cancer, and performing maximal cytoreductive surgery to resect all macroscopic disease is the general principal for treating advanced ovarian cancer [3,4]. However, patients with advanced ovarian cancer frequently have unresectable disease or medical comorbidity that the primary surgery may not be feasible to conduct [5]. Complications after PDS may also delay the initiation of postoperative chemotherapy.

Previous randomized controlled trials (RCTs) have found no difference in the overall survival (OS) between women with advanced ovarian cancer who received neoadjuvant chemotherapy followed by interval debulking surgery (NACT-IDS) and those given only chemotherapy [6-8]. These trials did not compare NACT-IDS with PDS and did not assess carboplatin plus taxane chemotherapy that is currently considered the standard first-line therapy for ovarian cancer treatment [9,10].

Few comprehensive meta-analyses have investigated the survival, mortality, and morbidity in women with advanced ovarian cancer treated using these two different strategies. Therefore, we conducted a comprehensive meta-analysis to compare NACT-IDS with conventional PDS.

Materials and methods

A systematic review of literature and meta-analysis were performed by an Expert Panel of the Japan Society of Gynecologic Oncology Ovarian Cancer Committee. In March 2019, a literature search was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA). PubMed/ MEDLINE and the Cochrane Database were searched for relevant articles between January 2000 and December 2018 using the entry keywords “ovarian cancer [all fields],” “primary debulking surgery [all fields],” and “neoadjuvant chemotherapy [all fields]” (Supplemental Tables S1 and S2) 11]. This study period was chosen because taxane/carboplatin chemotherapy regimen was considered the standard therapy in the first-line treatment of women with advanced ovarian cancer for almost two decades.

Eligible studies compared PDS plus postoperative chemotherapy (PDS arm) with NACT followed by IDS (NACT-IDS arm) in women with stage II-IV ovarian cancer according to the International Federation of Gynecology and Obstetrics (FIGO) staging system [12]. All the histological studies of epithelial ovarian tumors, RCTs, meta-analyses, and case-control series reported in the English literature with adequate data on patient demographics, treatment, response, and follow-up were included.

The references of each selected article were reviewed, and any article that met the inclusion criteria was assessed. If multiple publications on the same clinical trial were available, the most recent publication or presentation was chosen for the analyses. Retrospective studies, systematic reviews, reports on nonepithelial histology (including borderline malignancy), and reports on chemotherapy except carboplatin plus paclitaxel were excluded.

Clinical information

The following variables were extracted from the selected studies: year of publication, age at diagnosis, performance status (PS), FIGO stage, histological subtypes, details of initial surgical treatment (operating time, estimated blood loss, performance of lymphadenectomy, and resection of other organs), details of chemotherapy (agents and number of administered cycles), perioperative and postoperative complications, residual disease after initial surgery (complete, optimal, and suboptimal surgery), and survival outcome (OS) and progression-free survival (PFS).

Surgical complications were defined as serious adverse events (SAEs) and were classified according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTC-AE) [13]. Complete surgery was defined as complete resection with no visible or palpable residual disease in the abdomen, and optimal surgery was defined as complete resection or residual disease <1 cm in diameter [14]. OS was defined as the time period between disease diagnosis and death from any cause. PFS was defined as the time period between initial treatment and tumor progression or death from any cause. Surgical mortality was defined as perioperative/postoperative death within 28 days of surgery.

Statistical analysis

The primary objective of this study was to examine whether NACT-IDS offers any advantages over conventional PDS for FIGO stage II-IV epithelial ovarian cancer. The secondary objective was to compare the mortality and complications between these two approaches.

Time-to-event data were calculated using the Parmer method [15], and the logarithm of the hazard ratio (HR) and its standard error were calculated. For dichotomous variables, the number of women in each treatment arm who experienced an event was compared to estimate the risk ratio (RR) [16]. For continuous variables, the final value and standard deviation were determined to find the difference in the mean values.

Data extraction and management

Data were entered into a reference database and extracted independently by three reviewers who were blinded for the review each other (H.M., H.T., and staff personnel from the Japan Medical Library Association). The quality of the studies was independently assessed by the reviewers (H.M. and H.T.); disagreements were resolved via discussion with a third reviewer from the Expert Panel of the Japan Society of Gynecologic Oncology Ovarian Cancer Committee.

If data were missing or methods were unclear, further information was obtained from other published literature on the same trials or by direct inquiry from the authors. For each study, we recorded the detailed methods, study population and sample size, inclusion and exclusion criteria, interventions and comparisons, perioperative complications, and survival outcome.

Assessment of the risk of bias

Using the Cochrane collaboration tool, the risk of bias was independently assessed by two authors for each study (H.M. and H.T.), including selection bias, detection bias, attrition bias, reporting bias, and other possible types of bias (Fig. 1) [17]. Because it was not possible to blind either participants or physicians to the assigned treatment, the blinding (performance bias and detection bias) was only assessed for outcomes. To investigate publication bias, we performed a funnel plot analysis [18].

Assessment of heterogeneity

Heterogeneity of each study was assessed by visual inspection of forest plots and by statistical evaluation using Cochran's Q test and the I^2 test [19]. Synthesis of data from the studies was performed to obtain overall estimates of treatment effects. Meta-analysis was done by using random effects models with inverse variance weighting [17]. Review manager software (version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was employed.

The level of confidence in summary data was examined by using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) for studies of interventions and diagnostic test accuracy [20]. All statistical analyses were two-tailed and P-value <0.05 was considered significant.

Results

The literature search identified 333 articles published during the target period (Fig. 2). Among them, 305 articles were excluded because of being reports on ongoing trials without survival outcomes, retrospective studies, reports on non-target diseases, or non-English articles. The remaining 28 articles met the criteria for further assessment, being reports of studies that compared PDS with carboplatin/taxane-based NACT followed by IDS for advanced epithelial ovarian cancer, and full content review of these articles was performed (Supplemental Table S3) [6-8,21-40].

Finally, four RCTs were identified (EORTC 55971, CHORUS, JGOG0602, and SCORPION), which enrolled patients with FIGO stage II-IV ovarian cancer and met the inclusion criteria for this review (Fig. 2) [39,41-43]. These 4 RCTs reported data on a total of 1692 women, including 845 women who received PDS and 847 women who received NACT-IDS.

The demographic profile of patients in the four RCTs is shown in Table 1. The PDS group and the NACT group had a similar median age at diagnosis (PDS *versus* NACT: 59.8 *versus* 59.2 years). The majority of women in the NACT group had a performance status of 0–1, stage III disease, serous histology, and received 6 cycles of carboplatin plus taxane chemotherapy. There were no significant differences of these factors between the NACT group and the PDS group (performance status 0–1: 85.3% *versus* 85.0%; stage III disease: 75.9% *versus* 75.0%; serous histology: 77.3% *versus* 72.3%; FIGO III stage: 75.9% *versus* 75.0%; carboplatin plus taxane chemotherapy: 77.8% *versus* 69.5%; all $P > 0.05$). Initial tumor size is strongly associated with the likelihood of complete primary debulking and survival [44,45], but it was not significant difference between the PDS group and NACT group in this study ($P < 0.79$).

Compared with the PDS group, the NACT group had a significantly shorter operating time (median 217 *versus* 400 min), a higher rate of pelvic and para-aortic lymphadenectomy (15.5% *versus* 10.0%), and a lower resection rate of other intra-abdominal organs (15.0% *versus* 27.0%) (all, $P < 0.05$).

The NACT-IDS and PDS groups showed a similar rate of discontinuing further treatment (NACT without IDS in 17.4% *versus* PDS without adjuvant chemotherapy in 17.3%, $P = 0.97$). In the NACT-IDS group, the main reason for not proceeding IDS was disease progression or death (38.0%), followed by complications of chemotherapy (16.2%). In the PDS group, the main reason for not receiving adjuvant chemotherapy was disease progression or death (50.0%), followed by postoperative complications (16.7%).

Meta-analysis of data from the four RCTs yielded the following results (Fig. 3). There was no significant difference of OS between the NACT-IDS group and the PDS group (HR: 0.97, 95% CI: 0.83 to 1.22, $P = 0.53$; Fig. 3A). There was also no significant difference of PFS between the two groups (HR: 0.98, 95% CI: 0.90 to 1.08, $P = 0.74$; Fig. 3B). When the extent of residual disease at the initial cytoreductive surgery was compared, complete resection was significantly more likely to be achieved in the NACT-IDS group compared with the PDS group (NACT-IDS *versus* PDS: 48.2% *versus* 23.2%, RR: 2.08, 95% CI: 1.80–

2.39, $P < 0.001$). Optimal surgery was also significantly more likely to be achieved in the NACT-IDS group than the PDS group (73.8% *versus* 49.7%, RR: 1.48, 95%CI: 1.37–1.61, $P < 0.001$).

SAEs and mortality related to surgery were also examined by meta-analysis of grade 3/4 SAEs reported during the perioperative period in the four RCTs. The frequency of SAEs was significantly lower in the NACT-IDS group compared to the PDS group (26.2% *versus* 8.6%, RR: 0.34, 95%CI: 0.26–0.44, $P < 0.001$; Fig. 3C).

When specific types of perioperative and postoperative SAEs were examined, grade 3/4 venous thromboembolism and grade 3/4 infection were significantly less frequent in the NACT-IDS group compared with the PDS group (venous thromboembolism: 0.6% versus 2.8%, RR: 0.26, 95%CI: 0.11–0.63, $P = 0.002$; and infection: 0.6% *versus* 2.8%, RR: 0.31, 95%CI: 0.18–0.56, $P < 0.001$). Surgical mortality was also significantly less frequent in the NACT-IDS group than in the PDS group (0.4% versus 3.3%, RR: 0.17, 95% CI: 0.06–0.50, $P = 0.001$; Fig. 3D).

Discussion

This investigation on women with advanced ovarian cancer revealed that survival after carboplatin plus taxane-based NACT-IDS was not inferior to survival after PDS. Moreover, perioperative morbidity and mortality were 70%–80% lower among women who underwent NACT-IDS than among those who underwent PDS, and complete resection was achieved more frequently with NACT-IDS.

These findings indicate that performing carboplatin plus taxane-based NACT followed by IDS does not negatively impact the survival in women with advanced-stage ovarian cancer; however, it significantly reduces perioperative complications and mortality. Our results may have particularly important implications for women with a poor performance status, significant comorbidities, or fragility, who are ineligible for conventional PDS and could be good candidates for the NACT-IDS.

Furthermore, perioperative complications, such as infection and venous thromboembolism, were significantly less frequent with NACT-IDS than with PDS. Perioperative and postoperative complications increase the health care costs and resource utilization [46]; thus, reduced treatment costs for patients with advanced ovarian cancer could be another advantage of NACT-IDS.

In patients with advanced ovarian cancer with unresectable tumor, NACT may be a reasonable strategy to achieve tumor shrinkage as well as obtain as much resection as possible at the subsequent IDS. In particular, this meta-analysis showed a lower resection rate of other intra-abdominal organs in the NACT group than in the PDS group. Surgery was less invasive in the NACT group, and the rates of complete resection were higher. These results suggest that adopting the NACT-IDS strategy may be beneficial for institutions with fewer resources, such as low-volume hospitals. Therefore, carboplatin plus taxane-based NACT followed by IDS may be more feasible and more effective than PDS in such settings.

However, there is a concern with respect to the use of the NACT-IDS strategy. In cases where the tumor is larger at the time of initial treatment, the risk of spontaneous mutation is higher, and this increases the likelihood of chemo-resistance [46,47]. The NACT-IDS strategy may led to the development of a progressive disease during NACT, called the platinum-refractory disease. Usually, women with platinum-refractory disease have poor prognosis [45]. Therefore, most of them may not be able to undergo IDS because of disease progression [45]. In fact, our study showed that approximately 7% of those in the NACT group did not undergo IDS because of disease progression. Therefore, we need to consider both the tumor burden and the risk of refractory/resistant disease before initiating NACT.

Another factor related to chemo-resistance is tumor histology. The histological subtype of ovarian cancer is an important prognostic factor, and the response to chemotherapy varies with tumor histology. High-grade serous carcinoma is reported to have a very high response rate of 73%–81% to platinum-based chemotherapy and a low incidence of progressive disease; however, clear cell carcinoma has a low response rate of 11%–45% and a high incidence of progressive disease [47,48]. Mucinous histology can be another factor; however, it has not been well investigated because of its rarity [49]. In the present meta-analysis, most patients had chemo-sensitive serous carcinoma. Therefore, further studies should be performed to explore whether NACT-IDS is also a suitable strategy for other histological types of ovarian cancer.

The main strength of this study was that we performed a systematic review and meta-analysis to collected information. Thus, the data we obtained were more reliable than those obtained from an individual investigation [50]. We assessed all the studies published during the previous 20 years, the period during which carboplatin plus taxane chemotherapy was considered the standard first-line treatment for ovarian cancer.

This study has certain limitations. We could not obtain information about cancer genetics, patient's comorbidities, type of surgeon (gynecological oncologist or general gynecologist), the quality of care, and the hospital type. These factors have been shown to influence the survival of patients with ovarian cancer [51,52]. The use of antiangiogenic agent (i.e., bevacizumab) following platinum-based chemotherapy has an impact on perioperative morbidity and more importantly on survival, especially in patients with residual disease [53]. Moreover, the likelihood of response to platinum-based chemotherapy in high-grade serous adenocarcinoma with advanced ovarian cancer could be influenced by BRCA mutation status [54].

Furthermore, the frequency of systematic lymphadenectomy and other surgical procedures varied widely among the studies we reviewed, and various procedures were employed for cytoreductive surgery even within each trial. Therefore, there might be substantial heterogeneity in the surgical methods among the four RCTs in this systematic review (Supplemental Fig. 3).

RCTs that are currently underway, such as the Study of Upfront Surgery Versus Neoadjuvant Chemotherapy in Patients with Advanced Ovarian Cancer (SUNNY trial) being performed in China, and the Trial on Radical Upfront Surgery in Advanced Ovarian Cancer (TRUST

trial) in Germany using antiangiogenic agent, may provide more detailed information about these factors [26,31].

Despite such limitations, the findings of this meta-analysis have important implications for women with advanced ovarian cancer, particularly those with unresectable disease, because NACT with carboplatin plus taxane followed by IDS appears an alternative strategy for their management. Our findings also suggest that patient selection for the NACT-IDS approach may be tailored based on tumor histology, with women who have high-grade serous tumors being candidates for the NACT-IDS strategy.

In conclusion, this meta-analysis demonstrated that women with advanced ovarian cancer had comparable survival after NACT-IDS and PDS; however, the perioperative mortality and morbidity were lower with NACT-IDS. Thus, appropriate patient selection for NACT-IDS would attribute to the improved survival in patients with advanced ovarian cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This project was assisted by an Expert Panel of the Japan Society of Gynecologic Oncology, via Medical Information Network Distribution Service which received financial support from the Ministry of Health, Labor and Welfare of Japan as a consignment project.

Funding support

None.

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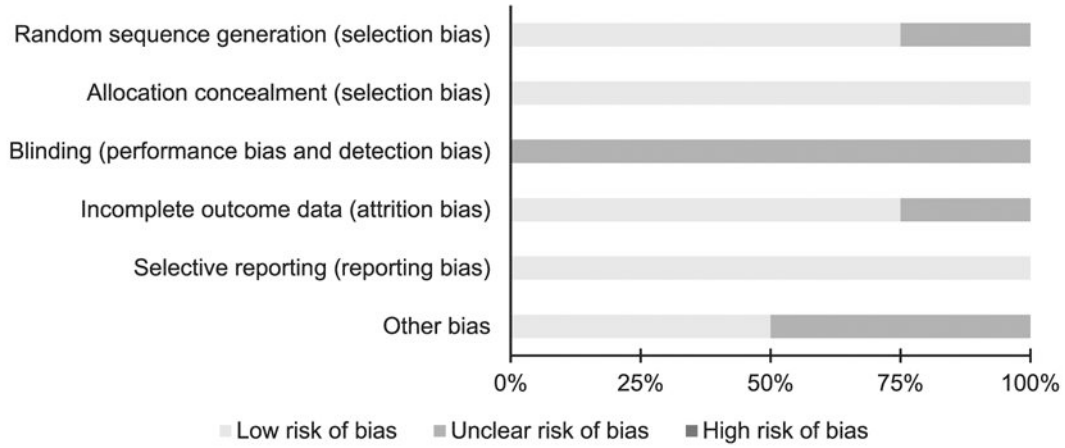
A. Judgments made by the authors each methodological quality item presented as percentages across all studies.



B. Summary of methodological quality

	EORTC55971	CHORUS	JCOG0602	SCORPION
Other bias	1	0	0	1
Selective reporting (reporting bias)	0	0	0	0
Incomplete outcome data (attrition bias)	0	0	0	0
Blinding (performance bias and detection bias)	1	1	1	1
Allocation concealment (selection bias)	0	0	0	0
Random sequence generation (selection bias)	1	0	0	0

Fig. 1.

Assessment of methodological quality. A. Judgments made by the authors each methodological quality item presented as percentages across all studies.B. Summary of methodological quality. Judgments made by the authors about each methodological quality item for each study are shown. Each item was scored as follows: high risk of bias = 2, intermediate or unclear risk of bias = 1, and low risk of bias = 0.

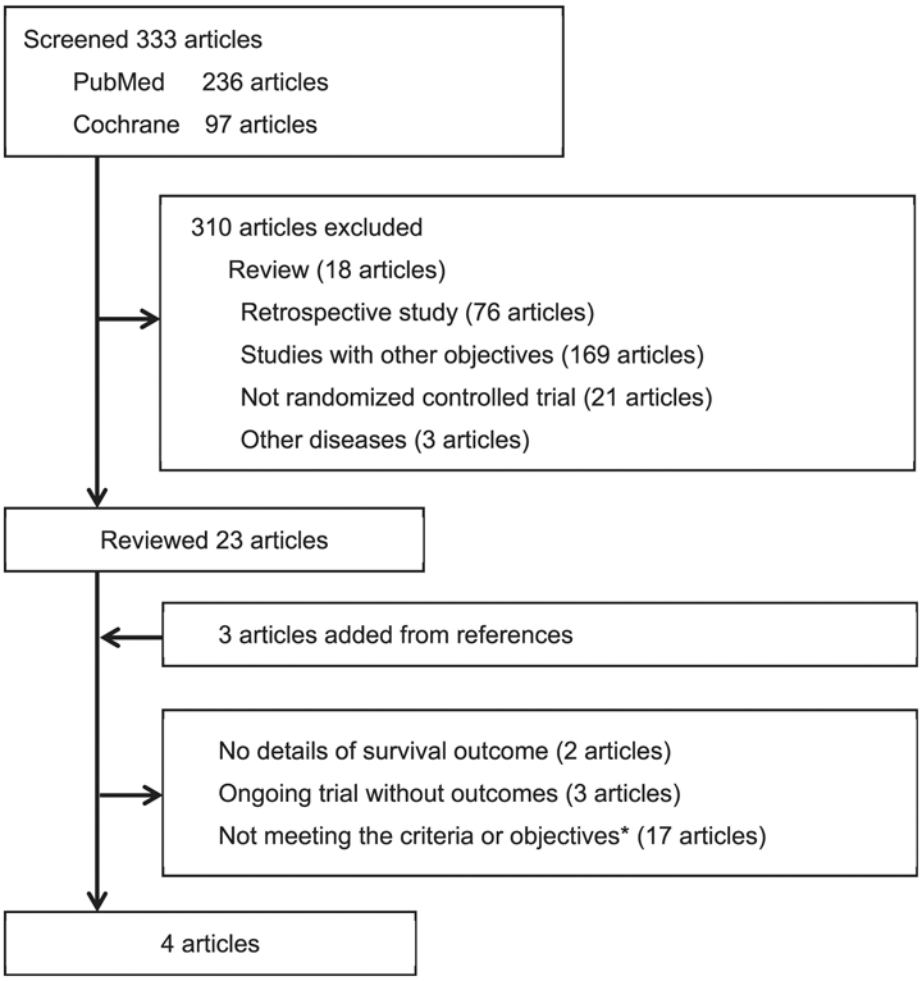
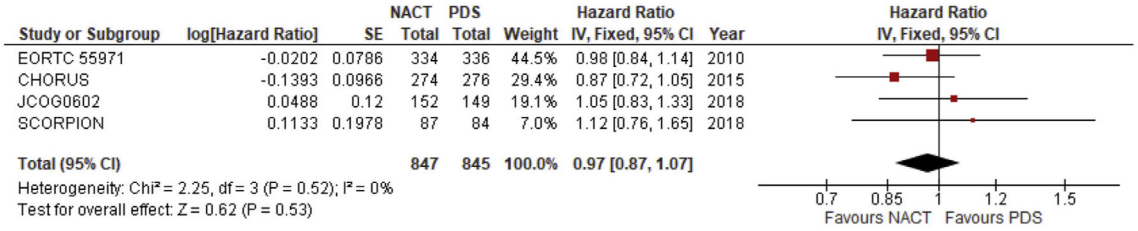


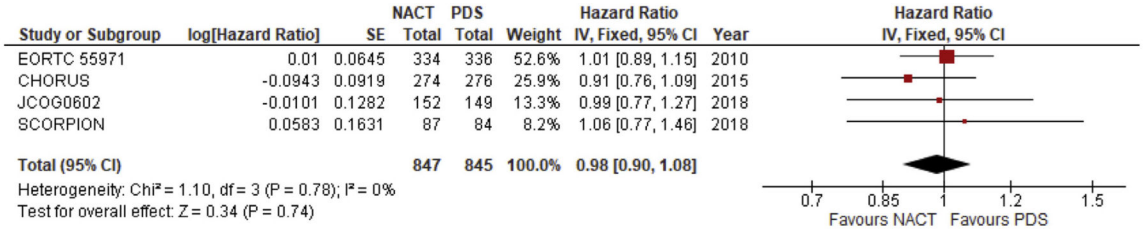
Fig. 2.

Flow diagram of study selection for systematic review.*Studies that did not compare PDS with NACT-IDS.

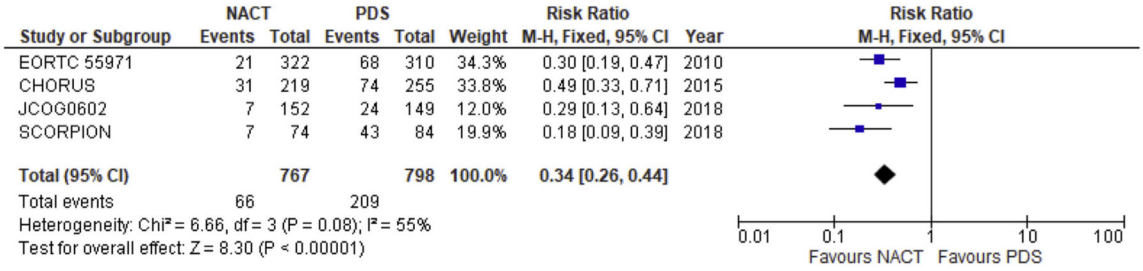
A. Overall survival



B. Progression-free survival



C. Grade 3/4 surgical-related sever adverse events



D. Death within 28 days after surgery

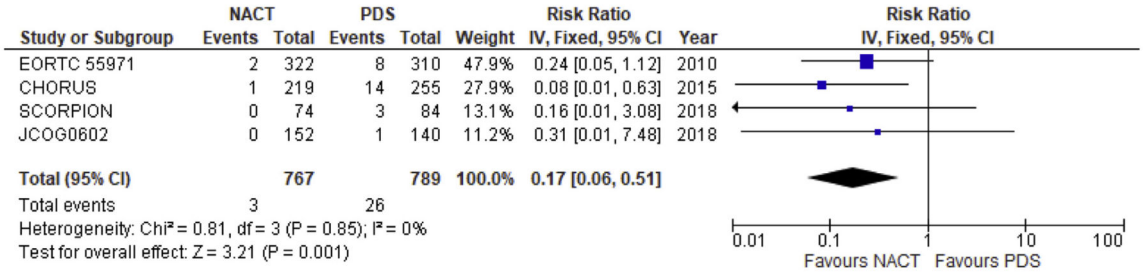


Fig. 3. Forest plots for comparison NACT-IDS *versus* PDS in advanced-stage ovarian cancer.
Weights were obtained from a fixed-effects model. Abbreviations: NACT, neoadjuvant chemotherapy; PDS, primary debulking surgery.

Table 1

Demographic profile of patients in the four studies of PDS *versus* NACT-IDS.

Study	**EORTC55971**	**CHORUS**	**JCOG0602**	**SCOPION**
Year of publication	2010	2015	2016[†]	2016[†]
Countries	Belgium, Canada, UK, Netherlands, Italy, Norway, and Spain	UK and New Zealand	Japan	Italy
No. of patients	336 vs 334	276 vs 274	*149 vs 152*	*84 vs 87*
Age (years)	62 vs 63	66 vs 65	59 vs 60.5	54.8 vs 56.2
PS				
0-1	294 (88) vs 290 (87)	221 (80) vs 221 (81)	130 (87) vs 131 (86)	51 (93) vs 50 (91)
2-3	40 (12) vs 44 (13)	54 (20) vs 53 (19)	19 (13) vs 21 (14)	4 (7) vs 5 (9)
Unknown	2 (0.6) vs 0	1 vs 0	0	0
CA125 (U/ml)	1130 vs 1180	Not specified	Not specified	2653 vs. 2100
Initial tumor size (cm)				
Up to 2 cm	4(1.2) vs 10(3)	13(5) vs 15(5)	32(22) vs 42(28)	Not specified
>2-5 cm	90(27) vs 85(25)	59(21) vs 60(22)	42(28) vs 51(34)	
>5-10 cm	90(27) vs88(26)	111(40) vs 110(40)	40(27) vs 35(23)	
>10cm	131(39) vs 137(41)	86(32) vs 86(32)	35(24) vs 24(16)	
Unknown	21(6.3) vs 14(4.2)	7(3) vs 5(2)	0 vs 0	
FIGO Stage				
II	0 vs. 0	12 (5) vs. 7 (3)	0 vs 0	0 vs 0
III	257 (77) vs. 253 (76)	190 (78) vs.165 (80)	100 (67) vs 105 (69)	71 (85) vs 79 (91)
IV	77 (23) vs. 81 (24)	41 (17) vs. 31 (15)	49 (33) vs 47 (31)	13 (16) vs 8 (9)
Others	2 (0.6) vs 0	12 vs 16	0	0
Histology			**	
Serous	220 (66) vs 194 (58)	219 (86) vs 185 (85)	116 (78) vs 110 (72)	82 (98) vs 87 (100)
Clear cell	6(2) vs 4 (1.2)	4 (2) vs 13 (6)	12(8) vs 4 (3)	1 (1.2) vs 0
Endometrioid	11 (3) vs 5 (1.5)	11 (4) vs 5 (2)	6 (4) vs 4 (3)	0 vs 0
Mucinous	8 (2) vs 11 (3)	2 (1) vs 4 (2)	2 (1.4) vs 2 (1.5)	0 vs 0
Others	91 (27) vs 120 (36)	19 (7) vs 12 (5)	12 (8) vs 18 (13)	1 (1.2) vs 0
Surgery				
Operating time (min)	165 vs 180	120 vs 120	341 vs 273	461 vs 253

Study	EORTC55971	CHORUS	JCOG0602	SCOPION
Blood loss (ml)	Not specified	Not specified	3447 vs 620	Not specified
Lymphadenectomy *	26(8) vs 49(15)	3(1) vs 1(0.5)	29(20) vs 64(49)	21(38) vs 7(14)
Abdominal organs resected	48(16) vs 28(9)	27(12) vs 18(8)	51(35) vs 33(25)	83(99) vs 33(38)
Complete surgery	61(19) vs 151(51)	39(17) vs 79(39)	45(31) vs 83(64)	40(48) vs 57(77)
Optimal surgery	131(42) vs 238(81)	96(41) vs147(73)	92(63) vs107(82)	78(93) vs 74(100)
Complications				
G3-4 postoperative AEs	68 (22) vs 21 (6.5)	74 (29) vs 31 (14)	24 (16) vs 7 (4.6)	39 (46) vs 7 (9.5)
G3-4 thromboembolism	8 (3) vs 0	5 (2) vs 0	7 (5) vs 5 (3)	Not specified
G3-4 infection	25 (8.1) vs 5(2)	16 (6) vs 8 (3)	1 (0.7) vs 1 (0.8)	Not specified
Postoperative death	8 (2.5) vs 2(0.7)	14 (6) vs1 (0.5)	1 (0.7) vs 0	3 (3.6) vs 0
Chemotherapy				
Carboplatin plus taxane	243 (78) vs 283 (88)	138 (61) vs 178 (70)	148 (100) vs150 (100)	50 (98) vs 52 (100)
Platinum only	25 (8) vs 20 (6)	89 (39) vs 75 (30)	0 vs 0	1(2) vs 0
Others	21 (7) vs 19 (6)	1(0.1) vs 1(0.1)	0 vs 0	0 vs 0
Cycles				Not specified
0	21 (7) vs 0	1 (1) vs 0	11 (7) vs 2 (1)	
1-3	25 (8) vs 39 (12)	24 (11) vs 36 (17)	6 (4) vs 17 (12)	
4-5	11 (4) vs 7 (2)	16 (5) vs 17 (7)	9 (6) vs 10 (7)	
>6	253 (82) vs 276 (86)	188 (82) vs 201 (79)	123 (83) vs 123 (81)	
PFS (months)	12 vs 12	11 vs 12	15.1 vs 16.4	Not specified
OS (months)	29 vs 30	23 vs 24	49 vs 44.3	Not specified

The number (%) or median is shown for PDS versus NACT-IDS.

* Lymphadenectomy includes the pelvic and paraaortic lymph nodes.

** For operated patients, histology was diagnosed from surgical specimens in the JCOG 0602 trial.

† Both study including latest data presented at ASCO 2018.

Abbreviations: PDS, primary debulking surgery; NACT-IDS, neoadjuvant chemotherapy followed by interval debulking surgery; No., number; AE, adverse event; PFS, progression-free survival; and OS, overall survival.