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Original Article

Optimal number of neoadjuvant chemotherapy cycles prior to interval debulking surgery in advanced epithelial ovarian cancer: a systematic review and meta-analysis of progression-free survival and overall survival

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ABSTRACT

Objective: Neoadjuvant chemotherapy (NACT) represents a treatment option in patients with advanced epithelial ovarian cancer (AEOC) who are not good candidates for primary debulking surgery. Usually, 3 cycles of chemotherapy before surgery have been considered the best option for patient survival, although quite often some patients receive more than 3 cycles. The aim of this systematic review and meta-analysis was to identify the optimal number of NACT cycles reporting better survival in AEOC patients.
Methods: PubMed, Cochrane Library, and Scopus were searched for original articles that analyzed the relationship between the number of chemotherapy cycles and clinical outcomes in AEOC patients before interval debulking surgery (IDS). The main outcomes were progression-free survival (PFS) and overall survival (OS).
Results: A total of 22 studies comprising 7,005 patients diagnosed with AEOC were included in our analysis. In terms of survival, the reviewed studies dividing the patients in ≤3 NACT cycles vs. >3, showed a trend for a decrease in PFS and a significant reduction in OS with an increasing number of cycles, while a difference in both PFS and OS was revealed if early IDS included patients with 4 NACT cycles. These results should be interpreted with caution due to the complex characteristics of AEOC patients.
Conclusion: In conclusion, our review and meta-analysis revealed that there is not enough evidence to determine the optimal number of NACT treatments before surgery. Further research in the form of well-designed randomized controlled trials is necessary to address this issue.

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

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Keywords: Neoadjuvant Chemotherapy; Prognosis; Ovarian Cancer; Cytoreductive Surgery; Survival

INTRODUCTION

Epithelial ovarian cancer (EOC) is a rare but deadly disease [1]. Primary debulking surgery (PDS) associated to platinum-based chemotherapy represents the preferred therapy. Over the years, increased surgical aggressiveness led to improved survival, assuming that even the removal of extra-abdominal metastases could be performed with the aim of pursuing the absence of residual disease post-surgery [2,3]. However, in cases where PDS with optimal residual disease is not feasible, or in unfit patients, shrinkage of the disease through neoadjuvant chemotherapy (NACT) is attempted, followed by interval debulking surgery (IDS) [4]. The number of NACT cycles has been arbitrarily set at 3, due to the Chorus and EORTC 55971 trials that compared PDS and IDS performed after 3 NACT cycles [5,6]. The concept of performing surgery with the minimum number of cycles before IDS was also reaffirmed by a complex analysis by Bristow and Chi [7], who calculated a reduced survival of 4.1 months for each additional cycle of NACT. Currently, even though the optimal number of NACT cycles before IDS is not clearly defined, the international guidelines suggest 3–4 cycles, while in clinical practice the attitude seems to be 6 cycles prior IDS [8]. Generally, IDS is performed either early or delayed. Early IDS is conducted after 3 cycles in patients who are responding well to treatment or in high-volume medical centers. Delayed IDS, on the other hand, is performed after 5 or 6 cycles in slow-responding or unfit patients, or in low-volume medical centers.

The definition of the optimal number of cycles is extraordinarily complex, and around the world the treatment of ovarian cancer varies according to the availability of both medical expertise and economic resources linked to the patient's area of residence. Thus, the number of NACT cycles appears to be associated with both the disease response as well as with the availability of medical facilities and, therefore, a substantial proportion of women may not receive IDS. Reasons for not undergoing surgery may include poor response to NACT, death during treatment, coexisting medical conditions, frailty, and patient preference [9].

For the reasons listed above and given the multitude of studies in the literature on this topic, we attempted to group the results of studies that examined the relationship between prognosis and number of NACT cycles in patients undergoing IDS. Our study aims to provide clinicians with a clearer understanding of the optimal number of chemotherapy cycles in the management of ovarian cancer prior to IDS.

MATERIALS AND METHODS

1. Articles selection

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) principles [10] and aimed to answer the research question: "What is the optimal number of NACT cycles for the best survival outcomes in advanced epithelial ovarian cancer (AEOC) patients before IDS?" The study protocol was registered in the PROSPERO on June 4, 2022 (CRD42022334959).

The databases PubMed, Cochrane Library, and Scopus were searched for original articles that analyzed the relationship between the number of chemotherapy cycles and clinical outcomes in AEOC patients before IDS. The search was last updated on November 14, 2022. Relevant studies were selected using the Boolean combination of the following key terms: "neoadjuvant therapy" OR "neoadjuvant chemotherapy" OR "NACT" OR "NAC" and "treatment outcome" OR "treatment result" OR "treatment consequence" AND "ovarian cancer" OR "ovarian carcinoma" OR "ovarian neoplasm". A professional librarian conducted the construction of the search string, database queries, and results.

The population included AEOC patients treated with various numbers of NACT cycles before IDS. The main outcomes were progression-free survival (PFS) and overall survival (OS).

2. Inclusion criteria and study selection

Studies were included if they met the following criteria: 1) patients treated with standard NACT and IDS for AEOC; 2) AEOC stages International Federation of Gynecology and Obstetrics (FIGO) III–IV; 3) at least 2 years of survival and/or progression data; 4) comparison between number of NACT cycles and patients' outcomes (PFS, OS); 5) randomized controlled trials (RCTs), observational prospective and retrospective studies; 6) English language.

Exclusion criteria were: 1) studies conducted on other types of ovarian cancers (i.e., non-epithelial); 2) abstracts, editorials, letters, comments to editors, systematic and narrative reviews, meta-analyses without any new patient data, book chapters and case reports.

Three authors independently screened titles and abstracts of articles (G.D., G.R. and C.A.C.). Articles were loaded into the Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org) to eliminate duplicates and begin the reviewing process. Studies that failed to meet inclusion criteria were discarded. Full-text articles were independently assessed, and disputes were settled through consultation with a senior author (A.M.P.). The review results were discussed among all authors for interdisciplinary issues. Afterwards, data from each eligible study were extracted and tabulated. Quality assessment was performed using a National Institutes of Health developed Quality Assessment tool for Observational Cohort and Cross-Sectional Studies following their guidelines (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools). Quality Rating was done for each point using the following scale: good (11–14 out of 14 questions), fair (5–10 out of 14 questions), or poor (0–4 out of 14 questions), and reported in the quality assessment table.

3. Statistical analysis and meta-analysis

Descriptive statistics were presented as number and frequency for categorical variables while mean and standard deviation or median and range for continuous variables. Significance in the distribution of categorical variables was tested using the χ^2 test. Meta-analysis of PFS and OS data was done using the meta package in R (R Foundation for Statistical Computing, Vienna, Austria). When authors performed the hazard analysis, the reported values were inserted into the pooled analysis. However, in case of absence of such data, indirect estimation was performed by extracting the time-to-event data from the Kaplan-Meier curves provided in each paper. Graphical points were obtained by manual digitalization using ScanIt Software by AmsterCHEM (https://www.amsterchem.com/scanit.html) and the curves were reconstructed using the KMtoIPD R package [11]. Hazard ratios (HRs) were estimated using the resulting patients summary statistics [12]. A p-value of 0.05 was established as the

threshold for significance. The study heterogeneity was quantified using Tau^2, Cochran's Q and the Higgins & Thompson's I^2 statistic. Tau^2 >0.1 and a 95% confidence interval (CI) not including 0 were considered to indicate substantial heterogeneity. I^2 values above 40% were considered to represent moderate heterogeneity while values above 75% were considered an indication of considerable heterogeneity. The presence of substantial between-study heterogeneity was considered for a $p<0.1$. Outlier analysis was performed and studies with CIs not overlapping with the pooled CIs were considered potential outliers. Funnel plots were used to inspect publication bias while Egger's regression test was used to test for asymmetry in the funnel plot.

RESULTS

1. Description of the included studies

The results of the literature research are shown in the PRISMA flowchart (**Fig. 1**). After removing duplicates, 1,497 studies were selected for title and abstract screening, with 1,156 being removed due to irrelevance toward the topic under investigation. An additional 341

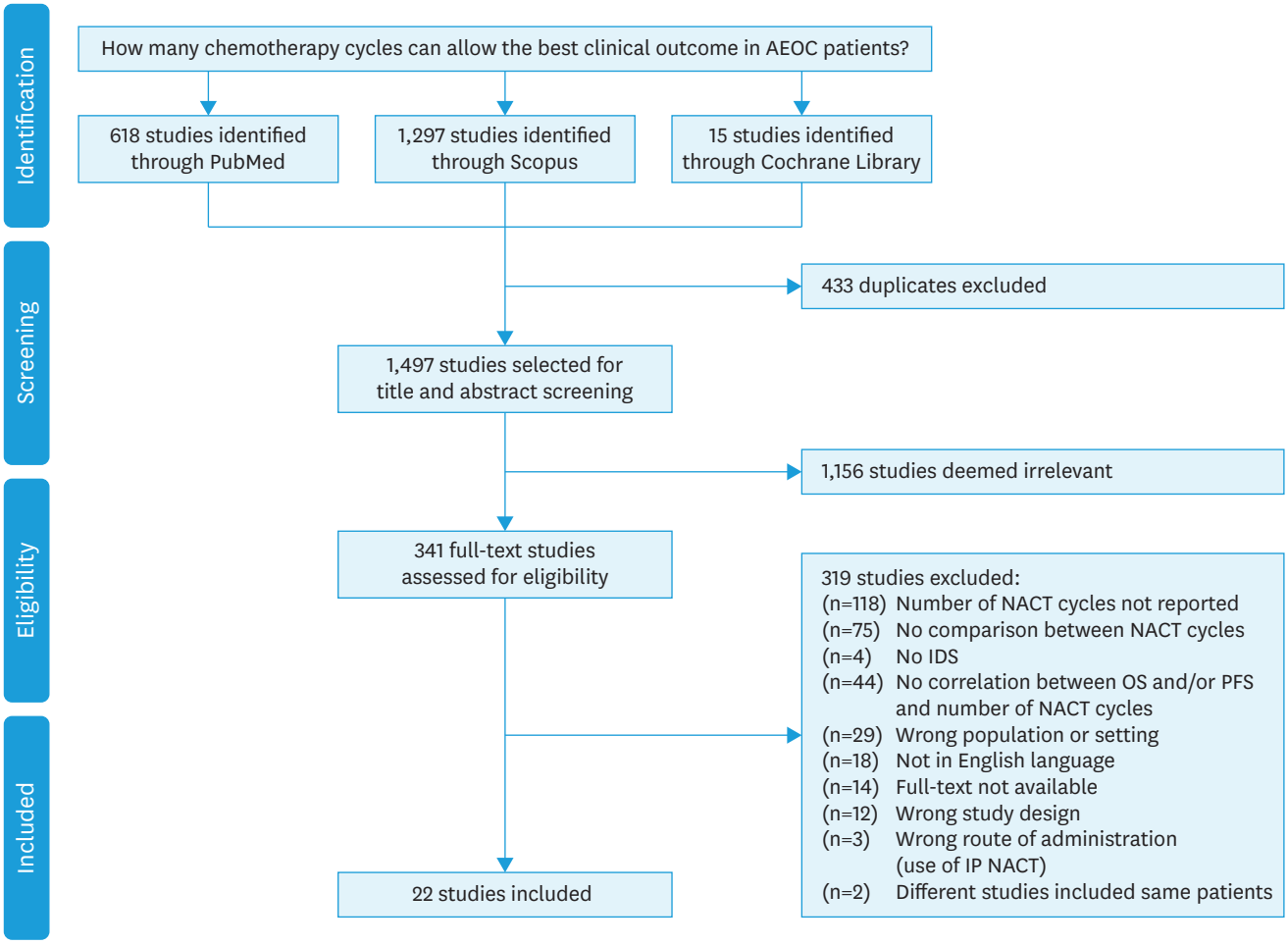

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart showing the selection of studies for the systematic review and meta-analysis and the stepwise exclusion.
AEOC, advanced epithelial ovarian cancer; IDS, interval debulking surgery; IP, intraperitoneal; NACT, neoadjuvant chemotherapy; OS, overall survival; PFS, progression-free survival.

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full text articles were evaluated, but 319 were excluded due to a lack of correlation between survival outcomes and number of NACT cycles or no reporting of the number of NACT cycles (**Fig. 1**). Finally, 22 articles met the inclusion criteria and were analyzed in the systematic review (**Table 1**).

Table 1. Summary of the studies included in the meta-analysis

Author, year, country	Study design	No. of patients	Age (yr)	No. of NACT cycles	FIGO stage	Hystology	Surgery	Chemotherapy	Results
Akladios et al. (2016), France [13]	Retrospective multicenter	n=204 ≤4 cycles n=75 ≥5 cycles n=129	≤4 cycles: ≤55 n=23; 56–69 n=36; ≥70 n=16 ≥5 cycles: ≤55 n=32; 56–69 n=62; ≥70 n=35	≤4 vs. ≥5	≤4 cycles: III n=53; IV n=22 ≥5 cycles: III n=92; IV n=37	≤4 cycles: HGSOC n=67; other n=8 ≥5 cycles: HGSOC n=110; other n=16; missing n=3	≤4 cycles: R0 n=42 (56%) ≥5 cycles: R0 n=78 (60.5%) Aletti score ≥2: ≤4 cycles n=46; ≥5 cycles n=53 (41.1%)	Platinum and taxane n=187 Other platinum-based n=17	No differences in OS and PFS
Altman et al. (2017), Canada [31]	Retrospective	n=403 0–3 cycles n=263 ≥4 cycles n=139	Mean=63	≤3 vs. ≥4	Stage IIIC n=272; stage IV n=79; missing n=52	HGSOC n=403	R0=46% R1=38% R2=15%	Platinum and taxane n=403	Patients that had received ≥4 cycles of neoadjuvant treatment had a worse prognosis than those treated with 0–3 cycles
Bacry et al. (2022), France [23]	Retrospective	n=140 NACT cycles ≤3 n=45 NACT cycles >3 n=95	Mean=62.6 (SD 10.4)	≤3 vs. ≥4	≤3 cycles: stage III n=40; stage IV n=5 >3 cycles: stage III n=61; stage IV n=34	≤3 cycles: HGSOC n=44; endometrioid n=1 >3 cycles: HGSOC n=82; endometrioid n=3; clear cells n=1; mucinous n=1; other n=5; missing=3	≤3 cycles: R0 n=40 (88.8%); R1 n=1 (2.2%); R2 n=1 (2.2%) ≥4 cycles R0 n=73 (76.8%); R1 n=9 (9.4%); R2 n=4 (4.2%) Complication grade III (Clavien-Dindo): ≤3 cycles n=1 (2.2%); ≥4 cycles n=4 (4.2%)	Paclitaxel 175 mg/m^2 and carboplatin AUC5 n=140	No differences in OS and PFS
Betrian et al. (2022), France [33]	Retrospective multicenter	n=365 3–4 NACT cycles n=219 6 NACT cycles n=146	Median=62 (range 21–88)	≤4 vs. ≥5	Stage IIIC n=282; stage IV n=83	Serous n=275; low grade serous n=18; serous grade N/A n=48; mucinous n=1; endometrioid n=10; clear cell n=2; carcinosarcoma n=6; others n=2; missing n=3	PCI median (range) n=9 (0–39) R0 n=318 (87.1%); R1 n=47 (12.9%) Aletti score: <8 n=213 (58.4%); ≥8 n=152 (41.6%)	Carboplatin AUC 5–6 and paclitaxel 175 mg/m^2, once every 3 weeks n=365	No differences in OS and PFS
Bogani et al. (2017), Italy [15]	Retrospective multicenter	n=193 3 cycles n=77 4 cycles n=74 ≥5 cycles n=43	Mean= 57.8±10.3	≤3 vs. ≥4	Stage IIIC n=30; stage IV n=163	HGSOC n=158; low-grade serous n=17; clear cell n=6; high-grade endometrioid n=1; low-grade endometrioid n=1; undifferentiated n=10	≤3 cycles: R0 n=53 (68.8%) ≥4 cycles: R0 n=64 (55%)	NR	Patients undergoing 3 cycles experienced a similar PFS but an improved OS in comparison to patients receiving at least 4 cycles
Chung et al. (2017), South Korea [27]	Retrospective	n=197 <4 cycles n=152 ≥4 cycles n=45	Median=57 (range 27–80)	≤3 vs. ≥4	Stage IIIB n=7; stage IIIC n=45; stage IVA n=89; stage IVB n=56	Serous n=180; mucinous n=4; endometrioid n=3; clear cell n=7; others n=3	R0 n=72 (37%); R=0.5 cm n=63 (32%); R=1 cm n=27 (14%); R=2 cm n=5 (3%); R >2 cm n=8 (4%); unknown n=22 (11%)	Platinum and taxane n=197	No differences in OS and PFS

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Table 1. (Continued) Summary of the studies included in the meta-analysis

Author, year, country	Study design	No. of patients	Age (yr)	No. of NACT cycles	FIGO stage	Hystology	Surgery	Chemotherapy	Results
Colombo et al. (2014), France [14]	Retrospective	IDS group n=147 ≤4 cycles n=110 >4 cycles n=37	≤4 cycles: <60 n=49; ≥60 n=61 >4 cycles: <60 n=17; ≥60 n=20	≤4 vs. ≥5	≤4 cycles: stage IIIC n=86; stage IV n=24 >5 cycles: stage IIIC n=21; stage IV n=16	≤4 cycles: serous n=102; clear cell n=3; endometrioid n=2; mucinous n=2; other: n=1. >5 cycles: serous n=31; clear cell n=2; endometrioid n=1; mucinous n=2; other n=1	PCI before surgery <17: ≤3 cycles n=77 (75.5%); ≥4 cycles n=29 (82.9%) PCI before surgery >17: ≤3 cycles n=25 (24.5%); ≥4 cycles n=6 (17.1%) R0: ≤3 cycles n=67 (61.5%); ≥4 cycles n=24 (64.9%)	Platinum based and paclitaxel n=147	Patients receiving >4 cycles NACT had worse OS
Ferron et al. (2009), France [28]	Retrospective	n=58 3–4 cycles n=47 5–6 cycles n=11	Median=57 (39–76)	≤4 vs. ≥5	Stage IIIC n=49; stage IV n=9	Serous: n=42; mixed: n=9; Undifferentiated: n=6; endometrioid n=1	R0 n=58	Platinum based and paclitaxel n=58	No differences in OS and PFS
Gupta et al. (2020), India [22]	Retrospective	n=100 2 NACT cycles n=2 3 NACT cycles n=12 4 NACT cycles n=14 5 NACT cycles n=3 6 NACT cycles n=69	Median=50	≤3 vs. ≥4	Stage IIIC n=60; stage IV n=40	HGSOC n=100	R0 n=28; R1 n=6; R2 n=66 CRS 1 n=25; CRS 2 n=35; CRS 3 n=40	Paclitaxel (175 mg/m^2) and carboplatin (5/6 AUC) n=97; others n=3	No significant difference in PFS, although a trend was observed in favor of <4 cycles of NACT
Iwase et al. (2015), Japan [29]	Retrospective	n=124 <5 cycles n=32 ≥5 cycles n=92	Median=58 (29–83)	≤4 vs. ≥5	Stage IIIB n=6; stage IIIC n=77; stage IV n=41; missing n=1	Serous n=105; non serous n=19	R0 n=98; R1 n=15; R2 n=11	Before 2005: ifosfamide, epirubicin, and cisplatin After 2005: paclitaxel and carboplatin	No differences in OS
Lecointre et al. (2020), France [19]	Retrospective	n=501 ≤4 cycles n=236 >5 cycles n=265	≤4 cycles: median=60.7 >5 cycles: median=62.6	≤4 vs. ≥5	≤4 cycles: stage III n=202; stage IV n=34 >5 cycles: stage III n=207; stage IV n=58	≤4 cycles: serous n=123; other n=101; missing n=12 >5 cycles: serous n=151; other n=103; missing n=11	≤4 cycles: R0 n=169 (75.8%); R1–2 n=54 (24.2 %); missing n=13 ≥5 cycles: R0 n=177 (71.4%); R1–2 n=71 (28.6 %); missing n=17 No difference in complications	≤4 cycles: platinum and taxane n=224; other platinum-based n=12 >5 cycles: n=240; other platinum-based n=25	No differences in OS and PFS
Liu et al. (2020), USA [20]	Prospective observational study	n=199 3 cycles n=73 4 cycles n=70 ≥5 cycles n=56	3 cycles: median=66 (range 43.1–86.4) 4 cycles: median=65 (range 43.2–87.2) ≥5 cycles: median=68.6 (range 45.1–87.9)	≤4 vs. ≥5	3 cycles: stage III n=29; stage IV n=44 4 cycles: stage III n=23; stage IV n=47 ≥5 cycles: stage III n=14; stage IV n=42	3 cycles: HGSOC n=65; other n=8 4 cycles: HGSOC n=66; other n=4 ≥5 cycles: HGSOC n=52; other: n=4	3 cycles: R0 n=50 (68.5%) 4 cycles: R0 n=49 (70%) >5 cycles: R0 n=40 (71.4%)	Weekly paclitaxel/ carboplatin n=134; other n=53	Patients receiving ≥5 NACT cycles may have a worse prognosis in comparison to 3 or 4 cycles, despite maximal cytoreduction

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Table 1. (Continued) Summary of the studies included in the meta-analysis

Author, year, country	Study design	No. of patients	Age (yr)	No. of NACT cycles	FIGO stage	Hystology	Surgery	Chemotherapy	Results
Marchetti et al. (2021), Italy [26]	Retrospective	n=315 ≤4 NACT cycles n=245 >4 NACT cycles n=70	Mean=60.5 (SD 11.7)	≤4 vs. ≥5	Stage III n=225 ; stage IV n=90	HGSOC n=290; others n=25	≤4 cycles: RT0 n=213 (86.9%); RT ≥1 mm n=32 (13.1%) ≥5 cycles: RT0 n=54 (77.1%); RT ≥1 mm n=16 (22.9%) No difference in Clavien-Dindo and Vizzielli's score	3-weekly carboplatin AUC5–6 plus paclitaxel 175 mg/m^2 n=83 Weekly carboplatin AUC2 plus paclitaxel 60–80 mg/m^2 n=232	No differences in OS and PFS
Minareci et al. (2022), Turkey [25]	Retrospective	n=221 3 cycles of NACT n=67; 4–5 cycles of NACT n=70 6 cycles of NACT n=84	≤55 n=80 56–69 n=102 ≥70 n=39	≤3 vs. ≥4	Stage IIIC n=191; stage IV n=30	HGSOC n=221	NACT=3 cycles: R0 n=40 (59.7%); R1 n=27 (40.3%) NACT=4 or 5 cycles: R0 n=42 (60%); R1 n=28 (40%) NACT=6 cycles: R0 n=51 (60.7%); R1 n=33 (39.3%) No difference in surgical procedures	Platinum based chemotherapy plus paclitaxel n=221	Patients receiving >3 NACT cycles had worse OS than patients who received 3 NACT cycles No differences in PFS
Nitecki et al. (2021), USA [16]	Retrospective	n=265 3–4 cycles/ CGR n=162 3–4 cycles/ incomplete resection n=31 >4/CGR n=50 >4/incomplete resection n=18	Median=65	≤4 vs. ≥5	Stage III: n=114; stage IV: n=150; missing n=1	HGSOC n=237; other n=28	SCC Low: 3–4 cycles/CGR n=93 (57%); 3–4 cycles/incomplete resection n=19 (61%); >4 cycles/CGR n=32 (64%); >4 cycles/ incomplete resection n=14 (78%) Intermediate: 3–4 cycles/CGR n=56 (35%); 3–4 cycles/ incomplete resection n=11 (36%); >4 cycles/ CGR n=15 (30%); >4 cycles/incomplete resection n=3 (17%) High: 3–4 cycles/CGR n=13 (8%) 3–4 cycles/ incomplete resection n=1 (3%); >4 cycles/ CGR n=3 (6%); >4 cycles/incomplete resection n=1 (5%)	Taxane/ platinum based NACT in one of 2 regimens: every 3 weeks or weekly n=265	No differences in OS and PFS
Phillips et al. (2018), UK [18]	Retrospective	n=398 ≤4 cycles n=231 >5 cycles n=167	Median=63.9 (42.2–85.6)	≤4 vs. ≥5	Stage III n=273; stage IV n=125	Serous n=370; other n=24; missing n=4	≤4 cycles: R0 n=165 (71.4%); R1: n=27 (11.7%); R2: n=39 (16.9%) ≥5 cycles: R0 n=90 (53.9%); R1 n=28 (16.8%); R2 n=49 (29.3%) SCC ≤4 cycles: low n=145 (62.8%); intermediate n=49 (21.2%); high n=37 (16.0%)	Carboplatin: n=194 Carboplatin taxane: n=304 Additional bevacizumab: n=124	No differences in OS

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Table 1. (Continued) Summary of the studies included in the meta-analysis

Author, year, country	Study design	No. of patients	Age (yr)	No. of NACT cycles	FIGO stage	Hystology	Surgery	Chemotherapy	Results
Stewart et al. (2016), Canada [32]	Retrospective	NACT group n=156 3 cycles n=48 4 cycles n=76 ≥5 cycles n=32	Median=60 (NACT group)	≤3 vs. ≥4	Stage IIIA n=8; stage IIIB n=5; stage IIIC n=115; stage IV n=28 (NACT group)	HGSOC n=156	R0 n=124 (79%); R1 n=32 (21%)	Platinum based chemotherapy n=156	No differences in OS and PFS
Stoeckle et al. (2011), France [30]	Retrospective	NACT group n=137 ≤4 cycles n=33 ≥5 cycles n=104	Median=60 (17–88)	≤4 vs. ≥5	≤4 cycles: stage IIIB n=1; stage IIIC n=23; stage IV n=9 ≥5 cycles: stage IIIB n=7; stage IIIC n=65; stage IV: n=32	≤4 cycles: serous n=29; endometrioid n=1; undifferentiated n=1; mucinous n=1; clear cell n=1 ≥5 cycles: serous n=90; endometrioid n=6; undifferentiated n=3; mucinous n=4; other n=1	Bowel resection: ≤4 cycles n=6 (18%); ≥5 cycles n=15 (14%) Significant morbidity: ≤4 cycles n=5 (15%); ≥5 cycles n=13 (13%) R0: ≤4 cycles n=12 (36%); ≥5 cycles n=60 (58%)	Platine based chemotherapy n=137	Trend to better survival in delayed IDS patients (>5 cycles of NACT) compared to early IDS patients (<4 cycles of NACT) without reaching significance
Thomas et al. (2022), France [24]	Retrospective multicenter	n=2,059 <4 NACT cycles n=1,120 ≥5 NACT cycles n=939	Median <4 cycles 63.0 (range 20–88) Median ≥5 cycles=63.0 (range 22–87)	≤4 vs. ≥5	<4 cycles: stage III n=850; stage IV n=270 ≥5 cycles: stage III n=564; stage IV n=375	<4 cycles: serous n=802; endometrioid n=18; others n=226; missing n=74 ≥5 cycles: serous n=599; endometrioid n=12; others n=247; missing n=81	Complete gross resection ≤4 cycles: yes n=599 (84.7%); no n=108 (15.3%); missing n=413 ≥5 cycles: yes n=398 (79.1%); no n=105 (20.9%); missing n=436	<4 cycles: carboplatin + paclitaxel n=1,073; carboplatin alone n=20; others n=26; missing n=1 ≥5 cycles: carboplatin + paclitaxel n=871; carboplatin alone n=38; others n=30	Standard IDS was associated with better PFS but not significantly associated with better OS Carrying IDS after ≥5 NACT cycles seems to have a negative effect on patients' survival
Yao et al. (2020), Australia [21]	Retrospective	n=572 2–4 cycles n=498 ≥5 cycles n=74	Median=67 (range 20–91)	≤4 vs ≥5	≤4 cycles: stage III n=323; stage IV n=175; ≥5 cycles: stage III n=43; IV n=31	Serous n=446; endometrioid n=7; clear cell n=10; mucinous n=2; other n=99; missing n=8	≤4 cycles: R0 n=337 (67.7%); R <1 cm n=108 (21.7%); R ≥1 cm n=10 (13.5%) ≥5 cycles: R0 n=46 (62.2%); R <1 cm n=18 (24.3%); R ≥1 cm n=53 (10.6%)	NR	No differences in OS
Yoneoka et al. (2019), Japan [17]	Retrospective	n=143 3–4 cycles n=117 6 cycles n=26	3–4 cycles: median=61 (36–87) 6 cycles: median=62 (41–78)	≤4 vs. ≥5	3–4 cycles: stage III n=69, stageIV n=48 6 cycles: stage III n=9, stageIV n=17	3–4 cycles: serous n=113; endometrioid n=1; clear cell n=3 6 cycles: serous n=25; clear cell: n=1	R0: 3–4 cycles n=82 (70.1%); 6 cycles n=18 (69.2%)	NR	No differences in OS and PFS
Zorzato et al. (2019), Italy [35]	Retrospective	n=108 3–4 cycles n=84 ≥5 cycles n=24	Median=65.0 (range 36–85)	≤4 vs. ≥5	Stage IIIC n=91; stage IV n=17	HGSOC n=108	SCC: low n=104 (96.3%); intermediate n=4 (3.7%); high n=0 CRS: CRS 1 n=24; CRS 2 n=18; CRS 3 n=66	Carboplatin/ paclitaxel every 3 weeks n=90 Carbotaxol and bevacizumab n=18	No differences in OS and PFS

AUC, area under the curve; CRS, chemotherapy response score; FIGO, International Federation of Gynecology and Obstetrics; HGSOC, high-grade serous ovarian carcinoma; IDS, interval debulking surgery; NACT, neoadjuvant chemotherapy; N/A, not available; NR, not reported; OS, overall survival; PCI, peritoneal cancer index; PFS, progression-free survival; R, macroscopic residual disease; SCC, surgical complexity score; SD, standard deviation.

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Most of the included studies were conducted in Europe (12 studies; 54.5%), followed by North America (4 studies; 18.2%), Asia (5 studies; 22.7%) and Australia (1 study; 4.5%). In terms of study design, one was prospective, while the other 21 were retrospective, 4 were multicenter, and 18 were single center. The enrollment period was estimated to be around 20 years, from 1980 to 2020, and the studies were published between 2009 and 2022, with 45.5% in the last 3 years (**Fig. S1A**). Funnel plots of the studies showed a symmetric distribution and the Egger's test indicated the lack of funnel plot asymmetry suggesting the absence of publication biases both in case of PFS as well as OS (**Fig. S1B**).

The primary objective of 15 studies was the investigation of PFS and OS with respect to the number of NACT cycles [13-27], while in the remaining studies this result was reported but not as the primary outcome [28-33].

The NACT regimens reported in 18 studies were 3-weekly or weekly administration of platinum and taxane, while 3 studies did not specify the regimens [15,17,21]. One study reported the administration of cyclophosphamide and cisplatin until 2005 and a combination of carboplatin and taxol after 2005 [29].

A total of 7,005 AEOC patients treated with NACT followed by IDS were analyzed, with 4,766 being in FIGO stage III and 2,285 in stage IV (**Table S1**). When considering only the studies comparing patients receiving ≤3 NACT cycles and ≥4 NACT cycles, no significant difference in the distribution of stages III and IV was detected (p=0.36) (**Table S2**). However, when considering only the studies comparing patients receiving ≤4 NACT cycles and ≥5 NACT cycles, an increased proportion of stage IV patients was observed in the patients receiving ≥5 NACT cycles (37.4% vs. 30.1%, respectively) (**Table S3**). Serous EOC was the main diagnosis in 5,725 (84.12%) patients, while the remaining 1,081 (15.88%) were diagnosed with other histotypes such as clear cell, endometrioid, mucinous and undifferentiated (**Table S1**).

Only 3 studies [13,19,30] reported the response to NACT using the Response Evaluation Criteria in Solid Tumors criteria [34] and no significant differences were found between the early and delayed IDS groups. In terms of surgical details, there are only a few studies that have reported important information such as peritoneal cancer index, complications from surgical procedures, and complexity score. However, all studies have reported the completeness of cytoreduction (R0) that was achieved in 57.5% of 4,228 patients.

Regarding the relationship between the number of NACT cycles and surgical parameters, most studies included in the systematic review did not find significant differences. Only Bacry et al. [23] found a meaningful difference between early and delayed IDS, reporting a higher number of posterior pelvectomies in patients undergoing IDS after ≤3 cycles of NACT without a noticeable increase in complications. When it comes to the completeness of cytoreduction (R0), Marchetti et al. [26] and Stoeckle et al. [30] were the only authors to find that a higher number of NACT cycles led to an increased rate of R0. However, this significant trend was opposite when pooling all studies together. Namely, when confronting patients receiving ≤3 NACT cycles and ≥4 NACT cycles, a lower proportion of R0 was observed in the case of NACT ≥4 (56%) vs. NACT ≤3 (71%) (**Table S4**). Same result was seen also when pooling the studies confronting patients receiving ≤4 NACT cycles and ≥5 NACT cycles (76.9% R0 vs. 70.9% R0, respectively) (**Table S5**).

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As far as the *BRCA* status is concerned, only 4 studies comparing patients receiving ≤4 NACT cycles and ≥5 NACT cycles reported this parameter. When pooling these results, no significant difference was seen between the groups (p=0.11) (**Table S6**).

Regarding survival outcomes, 16 studies [13,16-19,21-23,26-30,32,33,35] showed no significant differences in PFS and OS when comparing patients undergoing delayed or early IDS. In 6 studies [14,15,20,24,25,31], an unfavorable outcome was linked to an increase in the number of NACT cycles prior to IDS. Interestingly, Stoeckle et al. [30] discovered a trend towards improved survival in patients undergoing delayed IDS (≥5 cycles of NACT), although the results were not statistically significant.

2. Quality assessment

The risk of bias in the papers included is reported in **Table 2**. Of the 22 studies, 15 (68.2%) were rated as "fair" out of which 12 (80%) with a score of 10/14, 1 (6.7%) with a score of 9/14, 2 (13.3%) with a score of 8/14; the remaining 7 (31.8%) were rated as "good." with a score of 11/14. The low scores in the evaluation were largely the result of problems with the study design, particularly the absence of a sample size estimate and the lack of reporting on patients who were lost to follow-up. This information was only assessed in 2 studies [15,23].

3. Meta-analysis

The criteria used to distinguish "early," and "delayed" IDS varied across studies. In some, patients who underwent 4 cycles of NACT were considered "early," while in others they were considered "delayed." To prevent the introduction of potential bias, we chose to analyze these studies separately, given the alternating categorization of the 4-cycle group as both "early" and "delayed."

Out of the 22 studies, 15 [13,14,16-21,24,26,28-30,33,35] established 4 cycles as the threshold for "early" IDS and compared surgery after ≤4 cycles to surgery ≥5 or more cycles of NACT. The other 7 studies [15,22,23,25,27,31,32] established 3 cycles as the threshold for "early" IDS and compared surgery after ≤3 NACT cycles with surgery after ≥4 NACT cycles. Four studies did not have PFS analysis data, while all had OS data.

4. Survival analysis in the 7 studies comparing ≤3 vs. ≥4 NACT cycles

PFS

Out of all the 22 articles included in our study, 7 (31.8%) had the NACT threshold set at 3 comprising 1,410 patients. Almost all studies [15,22,23,25,27,32] (6; 85.7%) reported PFS data while the work by Altman et al. [31] did not provide any such data. No statistically significant difference in PFS was observed between patients who received 3 or fewer cycles and those who received 4 or more cycles prior to IDS (random effects model: HR=1.13; 95% CI=0.99–1.29; p=0.07) (**Fig. 2A**). The between-study heterogeneity variance was estimated at a Tau^2<0.001; 95% CI=0–0.35 and I^2=21.8%; 95% CI=0–66.2, suggesting that inconsistency between studies was minimal. The prediction interval ranged from g=0.94 to 1.36.

OS

All 7 studies dividing patients into early and delayed IDS with a threshold of 3 NACT cycles reported OS data. The meta-analysis showed a statistically significant difference in survival between the 2 groups of patients, in favor of the patients receiving fewer NACT cycles (random effects model: HR=1.31; 95% CI=1.08–1.59; p=0.006) (**Fig. 2B**). The heterogeneity measured for this result was also low with a Tau^2=0.01; 95% CI=0–0.26 and I^2=16.1%; 95%

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Table 2. Quality assessment of the selected studies

Item	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total score
Akladios et al. [13]	☺	☺	☺	☺	☹	☺	☺	☺	☺	☺	☺	☹	😐	☺	11
Colombo et al. [14]	☺	☺	☺	☺	☹	☺	☺	☺	☺	☹	☺	☹	😐	☺	10
Ferron et al. [28]	☺	☺	☺	☺	☹	☺	☺	☺	☺	☹	☺	☹	😐	☹	9
Bogani et al. [15]	☺	☺	☺	☺	☹	☺	☺	☺	☺	☹	☺	☹	☺	☺	11
Nitecki et al. [16]	☺	☺	☺	☺	☹	☺	☺	☺	☺	☹	☺	☹	😐	☺	10
Stoeckle et al. [30]	☹	☺	☺	☺	☹	☺	☺	☺	☺	☹	☺	☹	😐	☹	8
Yoneoka et al. [17]	☺	☺	☺	☺	☹	☺	☺	☺	☺	☹	☺	☹	😐	☺	10
Phillips et al. [18]	☺	☺	☺	☺	☹	☺	☺	☺	☺	☺	☺	☹	😐	☺	11
Lecointre et al. [19]	☺	☺	☺	☺	☹	☺	☺	☺	☺	☺	☺	☹	😐	☺	11
Liu et al. [20]	☺	☺	☺	☺	☹	☺	☺	☺	☺	☺	☺	☹	😐	☺	11
Altman et al. [31]	☺	☺	☺	☺	☹	☺	☺	☺	☺	☹	☺	☹	😐	☺	10
Zorzato et al. [35]	☺	☺	☺	☺	☹	☺	☺	☺	☺	☹	☺	☹	😐	☺	10
Yao et al. [21]	☺	☺	☺	☺	☹	☺	☺	☺	☺	☺	☺	☹	😐	☺	11
Steward et al. [32]	☺	☺	☺	☺	☹	☺	☺	☺	☺	☹	☺	☹	😐	☺	10
Gupta et al. [22]	☹	☺	☺	☺	☹	☺	☺	☺	☺	☹	☺	☹	😐	☹	8
Chung et al. [27]	☺	☺	☺	☺	☹	☺	☺	☺	☺	☹	☺	☹	😐	☺	10
Bacry et al. [23]	☺	☺	☺	☺	☹	☺	☺	☺	☺	☹	☺	☹	☺	☺	11
Thomas et al. [24]	☺	☺	☺	☺	☹	☺	☺	☺	☺	☹	☺	☹	😐	☺	10
Betrian et al. [33]	☺	☺	☺	☺	☹	☺	☺	☺	☺	☹	☺	☹	😐	☺	10
Minareci et al. [25]	☺	☺	☺	☺	☹	☺	☺	☺	☺	☹	☺	☹	😐	☺	10
Iwase et al. [29]	☺	☺	☺	☺	☹	☺	☺	☺	☺	☹	☺	☹	😐	☺	10
Marchetti et al. [26]	☺	☺	☺	☺	☹	☺	☺	☺	☺	☹	☺	☹	😐	☺	10

☺: yes (1 point); ☹: no (0 points); 😐: information not available. The assigned quality rating was good, fair, or poor for each study. Quality was rated based on the sum of positive responses as poor (0–4 out of 14 questions), fair (5–10 out of 14 questions), or good (11–14 out of 14 questions).

CI=0–60.0, suggesting a minimal inconsistency between the included studies. The prediction interval ranged from g=0.89 to 1.92.

5. Survival analysis in 15 studies comparing ≤4 vs. ≥5 NACT cycles

PFS

Fifteen studies (68.2%) comprising 5,595 patients had the NACT threshold set at 4 cycles. Out of these 15 studies, 11 (73.3%) [13,14,17,19-21,24,26,28,33,35] provided data on PFS. When pooling their results, a statistically significant difference in PFS was observed between patients who underwent ≤4 and ≥5 NACT cycles, with favorable outcomes in patients who received early IDS (random effects model: HR=1.22; 95% CI=1.08–1.36; p<0.001) (**Fig. 3A**). This corresponds to a 54.9% likelihood that the patients who receive more NACT cycles will experience recurrence first. The heterogeneity for this comparison was significant (p=0.03) Tau^2=0.02; 95% CI=0–0.12 and I^2=48.1%; 95% CI=0–73.4, suggesting moderate heterogeneity between studies. The prediction interval ranged from g=0.88 to 1.68. Outlier identification analysis revealed that the study by Liu et al. [20] could potentially be classified as an outlier as determined by the lack of overlap between the CI of their findings and the CI of the pooled

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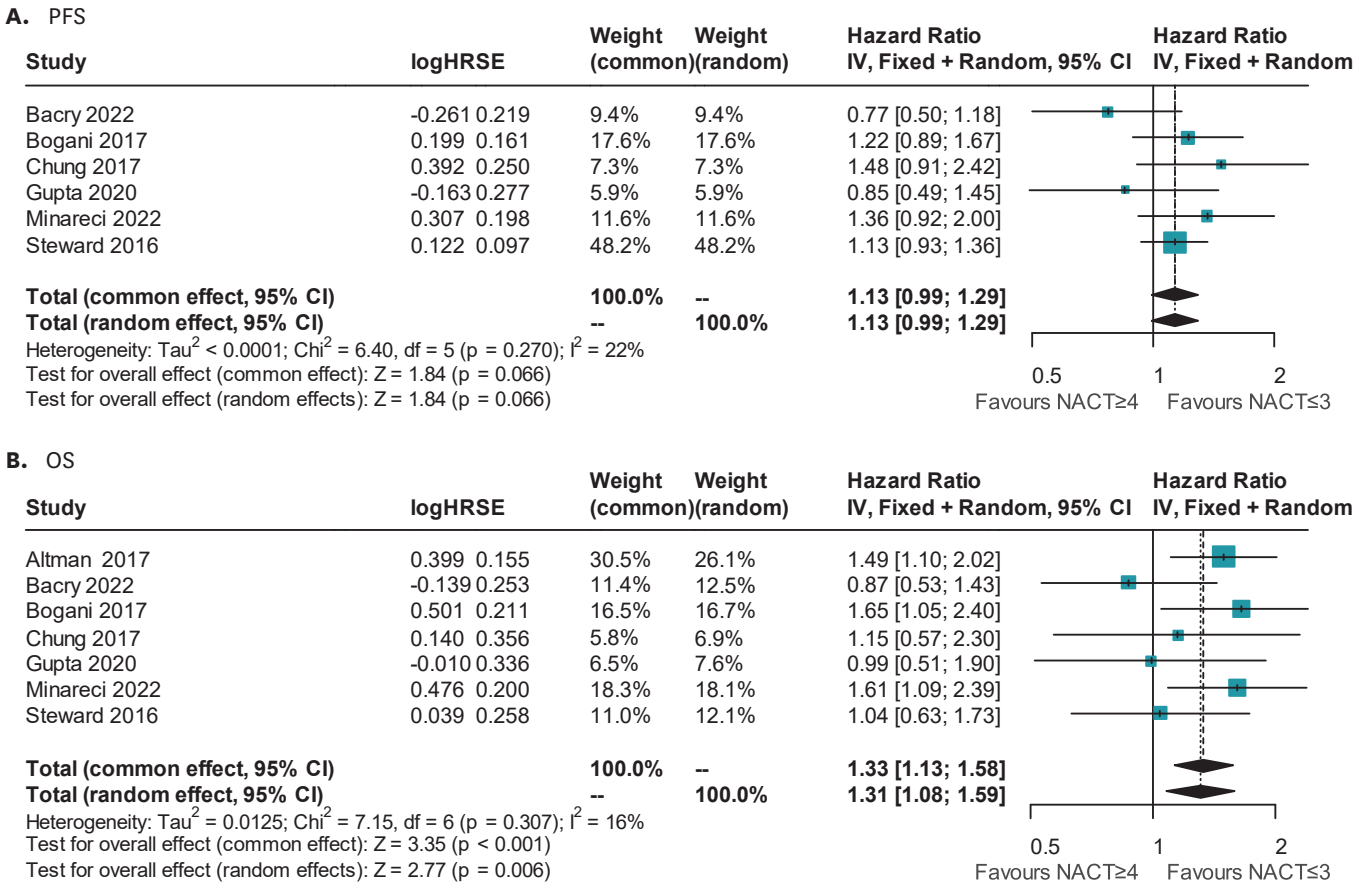

Fig. 2. The forest plot for PFS (A) and OS (B) in studies with a NACT threshold of 3 shows a trend towards a poorer prognosis for patients undergoing delayed IDS, but this did not reach statistical significance. HRs are for NACT ≥4/NACT ≤3 and 95% CI.
CI, confidence interval; HR, hazard ratio IDS, interval debulking surgery; NACT, neoadjuvant chemotherapy; OS, overall survival; PFS, progression-free survival; SE, standard error.

effect. The reanalysis of the data excluding this study obtained similar results (random effects model: HR=1.17; 95% CI=1.06–1.31; p=0.002) with a reduction in heterogeneity (Tau^2=0.01; 95% CI=0–0.07 and I^2=32.2%; 95% CI=0–66.7, p=0.14). This indicates that the overall pooled effect was not heavily biased by outliers.

OS

All 15 studies (100%) with the NACT threshold set at 4 reported data on OS. The pooled analysis showed a 54.3% increased risk of death in patients who underwent ≥5 NACT cycles (random effects model: HR=1.19; 95% CI=1.07–1.32; p=0.002) (**Fig. 3B**). The heterogeneity for this comparison was bellow the significance level (p=0.12) estimated at a Tau^2=0.01; 95% CI=0–0.13]; I^2=30.5%; 95% CI=0%–62.6%. The prediction interval ranged from *g*=0.93 to 1.52. The same potential outlier study was identified and removed, and similar results were obtained (random effects model: HR=1.16; 95% CI=1.05–1.28; p=0.004), with an associated reduction in heterogeneity values (Tau^2=0.006; 95% CI=0–0.05 and I^2=4.4%; 95% CI=0–57], p=0.4).

Given that paclitaxel was added to the standard chemotherapy regimen of OC patients after the GOG111 and OV10 trials, we excluded the studies enrolling patients before 1996 or not reporting paclitaxel as part of the patients treatments and report similar results (PFS: HR=1.2; 95% CI=1.06–1.35; p=0.003; and OS: HR=1.19; 95% CI=1.06–1.33; p=0.003) (**Fig. S2**).

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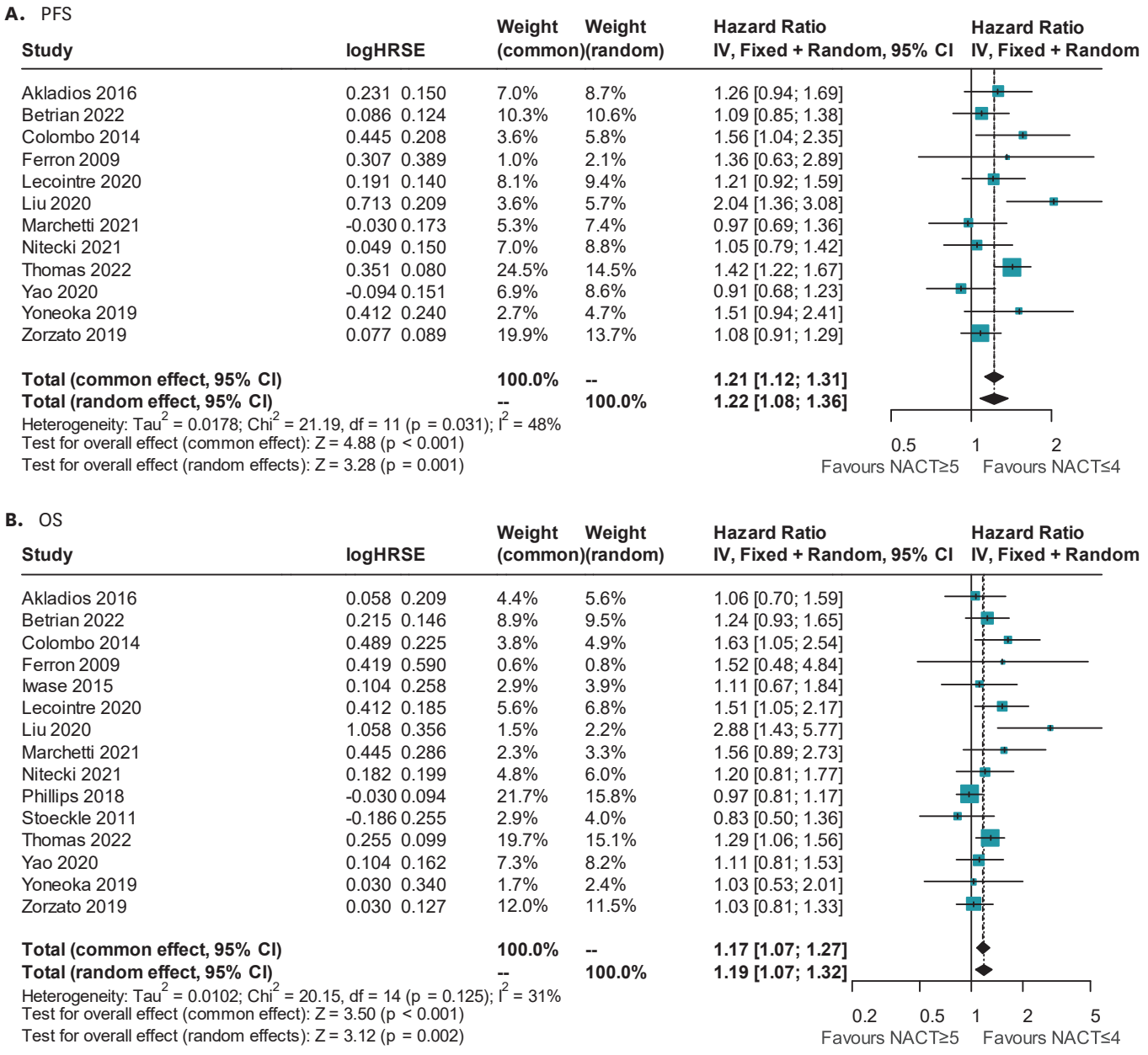

Fig. 3. Forest plot for PFS (A) and OS (B) of studies with a NACT threshold set at 4 shows a significant decline in PFS for patients who underwent delayed IDS. However, only a tendency towards a worse OS was noted. HRs are for NACT ≥5/NACT ≤4 and 95% CI.
CI, confidence interval; HR, hazard ratio IDS, interval debulking surgery; NACT, neoadjuvant chemotherapy; OS, overall survival; PFS, progression-free survival; SE, standard error.

DISCUSSION

To the best of our knowledge, the current systematic review and meta-analysis is the largest available analysis of women undergoing IDS after various cycles of NACT for AEOC. Our analysis revealed a lack of consensus about the optimal number of NACT cycles for the best survival outcomes. Most of the studies were retrospective with only one observational prospective study, and no prospective RCTs have been published to date. The studies analyzed were highly heterogeneous with respect to tumor characteristics, such as

tumor histology (**Table S1**), number of NACT cycles before IDS and the reported surgical parameters (**Table 1**).

Based on the years of publication data, it can be said that the debate on IDS timing has expanded in recent years, as approximately 45.5% of the studies were published in the last 3 years. Although there was an agreement regarding platinum based NACT, a standardized approach to determining the optimal number of NACT cycles prior to IDS has yet to be established.

International guidelines recommend surgery at the earliest opportunity, ideally after 3 cycles. However, our analysis found that early IDS was usually performed after 4 cycles instead of 3 cycles in nearly twice as many studies (15 compared to 7). This result may be due to the multitude of factors that need to be considered when determining a patient's suitability for surgery, considering general health, response to chemotherapy, histotypes with different intrinsic response to therapy, surgical expertise and, availability of facilities [36].

Data about surgery was lacking in some studies and it was highly variable. The works of Thomas et al. [24] and Marchetti et al. [26] had established that the number of cycles of NACT does not simplify the procedure or reduce the associated complications. This contradicts the notion that an increased number of NACT cycles would result in less aggressive surgery, as seen in gastrointestinal and breast cancer [37,38].

The completeness of cytoreduction is widely recognized as one of the most important prognostic factors for ovarian cancer but studies about IDS lack to stress this issue. Only the study by Yao et al. [21] reported that the number of NACT cycles did not affect survival, but complete cytoreduction was associated with a survival benefit [21]. Therefore, it is hypothesized that complete cytoreduction at the time of IDS, rather than the number of NACT cycles, may be associated with longer survival.

In terms of the impact of NACT cycles number on survival outcomes, only a few studies showed a significant result [14,15,20,24,25,31], while the remaining ones reported only a trend towards a worse outcome in patients receiving more NACT cycles. When all studies were pooled in the meta-analysis, a trend toward a decline in PFS and a significant decrease of OS with increasing number of NACT cycles was observed. In any case, when analyzing studies comparing only ≤3 vs. ≥4 cycles of NACT, the number of patients included in the studies was small, which could explain the borderline statistical significance in case of PFS. Conversely, a significant difference in terms of PFS was found in patients who received ≤4 cycles compared to those who received ≥5 NACT cycles, with a negative impact in the case of delayed IDS. This significance was also maintained in the OS analysis.

Our meta-analysis showed a worse prognosis in patients undergoing IDS after a higher number of NACT cycles. However, the decision-making process behind extending the number of NACT cycles is seldom clearly specified. The reasons for this decision can vary based on factors such as advanced age, the overall health condition of the patient which may hinder their ability to undergo major surgery and necessitate additional treatment cycles, as well as a diminished response to chemotherapy leading to the selection of patients with platinum-resistant clones [39]. Therefore, multiple contributing factors can lead to a worse prognosis independent of the number of chemotherapy cycles [23,24]. Given that the decision to increase the number of cycles depends on the clinical evaluation of the patient and the individual tumoral response (usually an interim evaluation after 3–4 cycles by CA-125 and CT scan), the strength of these

significant results is limited to concluding that a higher number of cycles is associated with a detrimental outcome, but the putative causative effect can be demonstrated solely in the setting of a RCT. The 2 ongoing RCTs: the CHRONO trial (NCT03579394) and the GOGER trial (NCT02125513) should provide more consistent proof in this regard.

Our systematic review and meta-analysis have several strengths. Firstly, it included a large number of reports, pooling together data from 7,005 AEOC patients. This represents a significant cohort, given the rarity of the disease and the advanced stage of the tumor. Secondly, separate analyses were conducted to account for differences in the threshold for NACT cycles (3 or 4 cycles), as heterogeneity was observed in this aspect due to inconsistent inclusion of patients receiving 4 cycles in early and delayed IDS.

However, our work has some limitations. Firstly, the heterogeneity of the studies limited the evaluation to only PFS and OS as clinical outcomes, excluding other potentially important variables. Secondly, patient enrollment took place over a long period of time (in some cases over 10 years), during which diagnosis and treatment schemes may have slightly varied. Although almost all patients in the meta-analysis received platinum-based chemotherapy, one study included a combination of other drugs such as ifosfamide, epirubicin, and cisplatin in patients treated before 2005 [29]. However, this potential bias is expected to have a minimum impact due to the relatively small number of patients from this single study compared to the entire population included in this meta-analysis.

In conclusion, our investigation highlights the need to further evaluate the ideal number of NACT cycles, as this aspect has yet to be determined based on the currently available body of research. Despite evidence suggesting a possible relationship between NACT cycles and progression, the correlation with survival outcomes requires cautious interpretation considering the presence of various confounding factors. To establish a clear understanding, it is imperative to undertake additional rigorous research in the form of RCTs as chemotherapy schemes can impact both the overall success of the treatment and the patient's quality of life. A clear understanding of the optimal number of cycles is crucial for clinicians to ensure the best possible outcomes for their patients.

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SUPPLEMENTARY MATERIALS

Table S1

Overall distribution of OC histotypes and stages of the patients from the studies included in the meta-analysis

Click here to view

Table S2
Analysis of the distribution of International Federation of Gynecology and Obstetrics ovarian cancer stages between patients receiving ≤3 NACT cycles and ≥4 NACT cycles

Click here to view

Table S3
Analysis of the distribution of International Federation of Gynecology and Obstetrics ovarian cancer stages between patients receiving ≤4 NACT cycles and ≥5 NACT cycles

Click here to view

Table S4
Analysis of the distribution of residual disease after surgery between patients receiving ≤3 NACT cycles and ≥4 NACT cycles

Click here to view

Table S5
Analysis of the distribution of residual disease after surgery between patients receiving ≤4 NACT cycles and ≥5 NACT cycles

Click here to view

Table S6
Analysis of the distribution of *BRCA* genotypes between patients receiving ≤4 NACT cycles and ≥5 NACT cycles

Click here to view

Fig. S1
Distribution of the published studies included in our systematic review and meta-analysis by year. Funnel plots evaluating the publication bias of the studies. Egger's test for funnel plot asymmetry is reported above each graph.

Click here to view

Fig. S2
Forest plot for PFS (A) and OS (B) of studies with a NACT threshold set at 4 (excluding those without paclitaxel) shows a significant decline in PFS for patients who underwent delayed IDS. However, only a tendency towards a worse OS was noted. HRs are for NACT ≥5/NACT ≤4 and 95% CI.

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