European Journal of Surgical Oncology 52 (2026) 111355

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Review Article

Surgical timing in advanced ovarian cancer during the TRUST trial era: A systematic review, meta-analysis and study-level meta-regression of randomized controlled trials

Veronica Tius [a], Cristina Taliento [b], Martina Arcieri [c], Sara Filippin [a], Miriam Isola [d], Maria De Martino [d], Nicolò Bizzarri [e], Matteo Pavone [e], Mauro Signorelli [f], Domenica Lorusso [f], Paolo Scollo [g,h], Sandro Pignata [i], Vito Chiantera [i], Giorgio Bogani [j], Jvan Casarin [k], Anna Fagotti [e], Stefano Restaino [c,l], Giuseppe Vizzielli [a,c,*]

[a] Department of Medicine (DMED), University of Udine, Udine, Italy
[b] Department of Obstetrics and Gynecology, University Hospital "Sant'Anna", Ferrara, Italy
[c] Clinic of Obstetrics and Gynecology, "S. Maria della Misericordia" University Hospital, Azienda Sanitaria Universitaria Friuli Centrale (ASUFC), Udine, Italy
[d] Department of Medicine, Institute of Statistics, University of Udine, Udine, Italy
[e] Gynecologic Oncology Unit, Fondazione Policlinico Universitario A Gemelli IRCCS, Rome, Italy
[f] Unit of Gynecologic Oncology, IRCCS Humanitas Research Hospital, Rozzano, Milan, 20089, Italy
[g] Cannizzaro Hospital, Division of Gynecology and Obstetrics, Catania, Italy
[h] Kore University, Enna, Italy
[i] Department of Urology and Gynecology, National Cancer Institute IRCCS Fondazione G Pascale, Naples, Italy
[j] Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Department of Surgery, Milan, Italy
[k] University of Insubria, 'Filippo Del Ponte' Hospital, Department of Obstetrics and Gynecology, Varese, Italy
[l] School in Biomedical Sciences, Gender Medicine, Child and Women Health, University of Sassari, Sassari, Italy

ARTICLE INFO

Keywords:
Ovarian cancer
Primary debulking surgery
Interval debulking surgery
Neoadjuvant chemotherapy
Overall survival
Surgical complications

ABSTRACT

The best surgical timing for advanced epithelial ovarian cancer, whether primary debulking surgery or interval debulking surgery, remains debated. Recent data, including the preliminary ones from TRUST trial, necessitates an updated critical evaluation. A systematic search of PubMed identified only randomized controlled trials comparing interval debulking surgery versus primary debulking surgery in patients with newly diagnosed advanced ovarian cancer. Primary outcomes included overall survival (OS) and progression-free survival (PFS). A random-effects meta-analysis, meta-regression, cumulative synthesis, and leave-one-out influence analysis were performed. A total of 2303 patients were included. Compared to primary debulking surgery, interval debulking surgery was associated with lower rates of postoperative complications (OR = 0.37; 95 % CI: 0.18–0.79; P = 0.01) and mortality (OR = 0.23; 95 % CI: 0.09–0.57; P = 0.002). Meta-analysis showed higher rates of complete cytoreduction with interval debulking surgery (OR = 3.84; 95 % CI: 2.14–6.91; P < 0.00001) and lower rates of macroscopic residual disease (OR = 0.20; 95 % CI: 0.13–0.30; P < 0.00001). Pooled data revealed no significant difference in OS (HR = 0.95; 95 % CI: 0.87–1.04; P = 0.26) or PFS (HR = 0.94; 95 % CI: 0.85–1.03; P = 0.16). Subgroup analyses by stage and residual disease confirmed similar survival outcomes. The meta-regression results suggested that even in trials with very high complete cytoreduction rates, no clinically meaningful OS benefit was observed for upfront surgery. In conclusion, interval debulking surgery offers comparable survival outcomes to primary debulking, with reduced perioperative morbidity and mortality, supporting its role as a valid surgical alternative.
Prospero registration number: CRD420251105308.

* Corresponding author. Department of Medicine (DMED), University of Udine, piazzale S. Maria della Misericordia 15, Udine, Italy.
E-mail addresses: giuseppevizzielli@yahoo.it, giuseppe.vizzielli@uniud.it (G. Vizzielli).

https://doi.org/10.1016/j.ejso.2025.111355
Received 29 September 2025; Received in revised form 7 December 2025; Accepted 9 December 2025
Available online 18 December 2025

1. Introduction

The surgical management of patients diagnosed with epithelial ovarian cancer remains a major challenge in gynecologic oncology. Traditionally, primary debulking surgery (PDS) has been the preferred treatment choice. However, neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) has become a viable alternative strategy. The main goal of cytoreductive surgery is to achieve optimal debulking, defined as no visible disease or residual tumor less than 10 mm, which is strongly linked to better survival outcomes [1,2]. Several meta-analyses and a Cochrane Review [3–6] have shown that neoadjuvant chemotherapy followed by interval debulking surgery provides similar progression-free survival and overall survival compared to primary debulking surgery, while significantly decreasing perioperative morbidity and mortality. Nevertheless, these findings should be interpreted with caution, as important methodological heterogeneities among the included studies—such as differences in study design and internal validity, patient selection criteria and surgical quality,—could not be fully mitigated, even with rigorous pooled analysis.

This systematic review and meta-analysis synthesizes current evidence comparing these two surgical timings based on survival outcomes, rates of optimal cytoreduction, and surgical morbidity incorporating recently published preliminary data from the TRUST trial [7], presented at the 2025 American Society of Clinical Oncology (ASCO) Meeting [8], that was specifically designed to ensure high surgical proficiency and standardized radical debulking criteria. In addition to updating the evidence base by incorporating the recently presented TRUST trial, our revised analysis integrates a more extensive and structured set of subgroup analyses and advanced methodological tools—study-level meta-regression, cumulative meta-analysis, and leave-one-out influence analysis. These procedures allow us to explore heterogeneity across trials, assess the temporal stability of the treatment effect, and evaluate whether surgical completeness at PDS modifies survival outcomes. Such analyses have not been systematically performed in previous meta-analyses and provide a more granular understanding of factors influencing the apparent equivalence between PDS and IDS.

The aim is to provide comprehensive quantitative analysis and up-to-date evidence in the context of quality-certified surgery. Furthermore, data from present meta-analysis will help multidisciplinary gynecologic oncology teams make informed clinical decisions and personalized treatment planning.

2. Materials and methods

1. Search strategy

A systematic search of PubMed (MEDLINE) was conducted from inception to June 7th, 2025, using MeSH terms such as “ovarian neoplasm,” “ovarian cancer,” “chemotherapy,” “adjuvant,” “neo-adjuvant,” “surgery,” “primary,” and “interval.” The full search string is available in Supplemental materials S1. References from relevant articles were also manually checked. Preliminary data from TRUST trial were retrieved from 2025 ASCO abstracts online publications [8]. The review protocol was registered in PROSPERO (Registration number: CRD420251105308). In addition, some authors (GV, SR, DL, MS) contributed to a separate meta-analysis on the same overarching topic [9], which was conducted under a distinct PROSPERO registration and with different methodological aims. The present study was conceived independently and includes additional analyses (meta-regression, cumulative synthesis, influence analysis) not performed in the previous work; therefore, it represents a complementary, non-duplicative effort.

2. Eligibility criteria and study selection

Study selection was based on predefined criteria. Population: adult women with newly diagnosed advanced (International Federation of Gynecology and Obstretics (FIGO) stages III and IV) epithelial ovarian, tubal, or peritoneal cancer. Studies with non-epithelial types or recurrent disease were excluded. Intervention: neoadjuvant platinum-based chemotherapy followed by interval debulking surgery. Comparison: primary debulking surgery followed by adjuvant chemotherapy. Outcomes: primary survival measures. Secondary outcomes included complete cytoreduction, residual disease, surgical data, complications, operative time, blood loss, hospital stay, and follow-up data like quality of life, re-laparotomy, and mortality. At least one primary outcome was required eligibility.

We excluded non-human studies and non-RCTs. Both published and unpublished sources underwent detailed assessment. Exclusions included case reports, meta-analyses, book chapters. No restrictions on language, date, or location. Two reviewers (TV, FS) independently screened titles and abstracts; full texts of eligible studies were obtained, and disagreements were resolved through discussion until consensus was reached.

3. Data extraction

Data extraction was done independently by two authors (VT, SF), who reviewed main and supplemental manuscripts. They extracted data for each study: first author, publication year, country, study period, sample size and patients’ characteristics like mean age and Performance Status. General data such as histotype, grading, and FIGO stage were also included. Information on tumor load and chemotherapy protocols was gathered as well. Additionally, the following operative data was retrieved: operative time, surgical complexity score, number of chest procedures (pericardiophrenic nodes, pleurectomy, intraoperative thoracic drainage), number of upper abdominal procedures, and specific advanced abdominal procedures (bowel resection, lymph node dissection, and splenectomy). Residual disease after cytoreductive surgery was also documented. Perioperative data included intraoperative and postoperative complications, blood loss, re-laparotomy rate, surgery-related mortality, average hospital stay. Data related to quality of life were obtained. Finally, overall survival and progression free survival were recorded (median months, events/total, hazard ratio (HR), and confidence intervals (CIs)).

4. Quality assessment

Risk of bias of the included RCTs are extensively discussed in literature [6,10,11]. However, we performed the quality assessment for each trial using Cochrane RoB2 [12] tool, which evaluates bias in selection, performance, detection, attrition, and reporting. For TRUST trial, risk of bias was assessed based on available data and the protocol (NCT02828618).

5. Statistical analysis

Meta-analysis was performed with a random effect using Review Manager Web v7.9.0, with $p < 0.05$ as significant. For continuous variables, mean difference with 95 % CIs and for dichotomous outcomes Odds Ratios (OR) with 95 % CIs were computed, then pooled using the Mantel-Haenszel method. Time-to-event data were analyzed with a generic inverse variance method, reporting summary HRs and 95 % CIs. 95 % CIs were constructed using the Wald-type method. Variability in effect estimates due to heterogeneity was assessed using the I-squared (I^2) statistic, with an I^2 value over 75 % indicating high heterogeneity. Between study variance in the random-effects model was estimated using DerSimonian-Laird approach. Sensitivity analyses were conducted to evaluate the impact of each individual dataset on the overall results by sequentially omitting one trial at a time. Lastly, subgroup analysis was performed by evaluating overall survival by FIGO stage and residual tumor post-surgery, categorizing into no residual tumor, microscopic (1–10 mm), and macroscopic (>10 mm). Moreover, we performed

additional exploratory analyses to assess effect modification and robustness. A study-level meta-regression evaluated whether completeness of cytoreduction at PDS (proportion of CC-0 resections) modified the log(HR) for OS. Weighted least squares were applied using inverse-variance plus τ^2 weights. To assess temporal stability, we conducted a cumulative random-effects meta-analysis ordered by year of publication. A leave-one-out influence analysis was also performed to evaluate whether any single trial disproportionately affected the pooled effect estimates. These analyses were implemented in Python using custom scripts, following CONSORT and PRISMA-2020 guidelines [13,14]. All statistical scripts used for meta-regression, cumulative synthesis, and influence analysis were implemented in Python (v3.11) and are provided in the Supplementary Appendix.

3. Results

1. Studies selection and characteristics

The search strategy covered 856 articles. After removing duplicates and applying criteria, 9 reports of 5 RCTs were identified. Vergote et al. [15], Greimel et al. [16], and Prescott et al. [17] refer to the EORTC 55971 trial. Fagotti et al. [18] and Marchetti et al. [19] are part of the SCORPION trial. Onda et al., 2016 [20] and Onda et al., 2020 [21] belong to JCOG0602 trial. Two additional studies, Kehoe et al. – CHORUS trial [22]- and Mahner et al. – TRUST trial [7]-, were also included. The PRISMA flow diagram details the inclusion process (Fig. S1).

EORTC 55971 was a multicenter trial (1998–2006) with 670 ovarian cancer patients diagnosed via biopsy, randomized to primary debulking surgery with six chemo cycles or neoadjuvant chemotherapy followed by interval debulking surgery within six weeks and at least three post-operative chemo cycles. Platinum regimens were most common; other agents were used in 5.9 % of interval debulking surgery and 6.8 % of primary debulking surgery groups. Median follow-up was 56.4 months.

The CHORUS trial was a multicenter study enrolling 550 patients from 2004 to 2010. Histological confirmation before surgery was obtained via biopsy or aspiration. At final analysis, 255 women had primary debulking surgery and 219 had interval debulking surgery; the median interval from surgery to postoperative chemotherapy was 29 days and 32 days, respectively. Interval debulking in the primary debulking surgery group was allowed after three chemotherapy cycles in women with residual disease post-surgery. The median follow-up was 52.8 months.

The JCOG0602 trial was a non-inferiority study conducted in Japan that enrolled 301 patients between 2006 and 2011 with advanced ovarian cancer confirmed by imaging or cytology. Histologic confirmation was not required at trial entry. Patients in the primary debulking surgery arm underwent debulking surgery followed by 8 cycles of adjuvant chemotherapy; interval debulking surgery was performed if residual tumor after primary surgery was greater than 1 cm and was mandatory if the uterus, adnexa, or omentum were not removed during primary debulking surgery. Patients assigned to the interval debulking surgery group received 4 cycles of chemotherapy and was performed 28–49 days after the last cycle; adjuvant chemotherapy started within 21 days of surgery (35 days if extensive surgical procedures were performed). The median follow-up was 60 months.

The SCORPION trial, a single-institution study in Italy (2011–2016), involved 171 patients with stage IIIC or IV ovarian cancer. Patients were randomized into arms after staging laparoscopy if they had high tumor load based on Predictive Index (PI) score [23]. In the primary debulking surgery group, secondary cytoreduction was not allowed after chemotherapy if residual tumor exceeded 1 cm. The interval debulking surgery group received 3–4 cycles of carboplatin-paclitaxel before surgery. Bevacizumab was used in 48.8 % in the interval debulking surgery group and 39.7 % in the primary debulking surgery patients. Of 171, 143 received treatment. Median follow-up was 59 months.

The TRUST trial is an international RCT, involving patients with advanced ovarian cancer who were deemed suitable for radical surgery and underwent surgical debulking at quality-certified gynecologic cancer centers. Between 2019 and 2024, 343 patients were assigned to the interval debulking surgery group and 345 to the primary debulking surgery group. A carboplatin-paclitaxel regimen was used; Bevacizumab was given to 59 % and 65 % of patients in the interval debulking surgery and primary debulking surgery groups, respectively, and Poly (ADP-ribose) polymerases (PARP) inhibitors were used as maintenance therapy when appropriate. Median follow-up was 74.6 months.

2. Quality assessment

The bias risk, main concerns, and limitations of the EORTC 55971, CHORUS, SCORPION, and JCOG0602 trials are detailed elsewhere [6,10,11]. The overall bias risk for the TRUST trial was 'moderate,' mainly due to reporting shortcomings of key methodological details. Only attrition and reporting bias were judged low, with complete follow-up and thorough reporting. More details are in Supplemental Materials S1 and Fig. S2.

3. Patients general characteristics

Table S2 summarizes the main demographic and clinical characteristics of the enrolled patients. Serous histotype was the most frequent, accounting for 80 % in the interval debulking surgery group and 83.4 % in the primary debulking surgery group, respectively ($p = 0.03$). Stage III and IV disease was diagnosed in 73.7 % and 23.7 % in the interval debulking surgery group, and in 68.2 % and 24.8 % in the primary debulking surgery group, showing no statistical differences ($p = 0.16$ and $p = 0.47$). Regarding FIGO staging inclusion criteria: two studies [15,18] included patients diagnosed with stage IIIC or higher disease; Kehoe et al. [22] also included IIIA and IIIB disease, and Mahner et al. [7] included stage IIIB or higher disease, whereas Onda et al. [20] did not provide further specifics. Tumor load was assessed differently across studies: Fagotti et al. [18] used PI at diagnostic laparoscopy enrolling cases with PI score between 8 and 12, Kehoe et al. [22] provided median tumor size, Onda et al. [20] reported the median size of upper abdominal tumors, and Vergote et al. [15] provided the largest metastatic tumor at randomization.

4. Peri-operative data

Operative data are in Tables S3 and S4. Interval debulking surgery had shorter average operative time (227.84 vs. 263.2 min), but data heterogeneity prevented a meta-analysis. Interval debulking surgery involved less advanced procedures like splenectomy [OR = 0.23; CI 95 % (0.08, 0.84); $I^2 = 89$ %; $P = 0.02$] and bowel resection [OR = 0.29; CI 95 % (0.11, 0.73); $I^2 = 92$ %; $P = 0.008$] (Fig. S3). Surgical complexity was only assessed by one study [18] using the Aletti score [24]. Chest procedures were performed more in the primary debulking surgery group [7,18]. Intraoperative complications were described by two studies [18,20] and were less common in interval debulking surgery. Meta-analysis showed that neoadjuvant chemotherapy followed by interval debulking surgery significantly reduced the risk of post-operative complications [OR = 0.37, CI 95 % (0.18, 0.79); $I^2 = 81$ %; $P = 0.01$]; in particular, infection and gastrointestinal fistula were less frequent in patients undergoing interval debulking surgery (p value = 0.003 and p value = 0.05). Pooled data demonstrated that neoadjuvant chemotherapy followed by interval debulking surgery significantly decreases the risk of postsurgical mortality compared to primary debulking surgery [OR = 0.23, CI 95 % (0.09, 0.57); $I^2 = 0$ %; $P = 0.002$] (Fig. S4).

5. Cytoreduction rates

All included studies reported data on residual disease after

cytoreductive surgery (Table 1). Meta-analysis indicated that interval debulking surgery achieved higher rates of complete cytoreduction with no residual disease [OR = 3.84; CI 95 % (2.14, 6.91); I^2 = 88 %; P < 0.00001] and lower rates of macroscopic residual disease after surgery [OR = 0.20; CI 95 % (0.13, 0.30); P < 0.00001]. The risk of microscopic residual disease (0–10 mm) did not differ significantly between groups [OR = 0.78; CI 95 % (0.46, 1.32); P = 0.35] (Fig. 1). Substantial heterogeneity was detected for complete cytoreduction (I^2 = 88 %) and microscopic residual disease (I^2 = 84 %), while heterogeneity was moderate for macroscopic residual disease (I^2 = 62 %).

6. Survival outcomes

All studies reported survival data (Table 2). As shown in Fig. 2, no significant survival difference was found between interval debulking and primary debulking surgery, with overall survival [HR = 0.95; CI 95 % (0.87, 1.04); I^2 = 0 %; P = 0.26] and progression free survival [HR = 0.94; CI 95 % (0.85, 1.03); I^2 = 17 %; P = 0.16] indicating similar survival rates. Low heterogeneity was observed for both outcomes.

7. Quality of life

Quality-of-life (QoL) assessments varied among the included trials in terms of definition, assessment methods, and questionnaires used; details and findings are summarized in Table S7. The EORTC QLQ-C30 was the most used tool to assess patients' quality of life.

The SCORPION trial [18] found lower global health scores for primary debulking surgery compared to interval debulking surgery over 12 months, but the difference (6.27) was not clinically meaningful. The CHORUS trial [22] saw slightly higher QoL scores at 6 months for interval debulking surgery (−7.6). Overall, 61 % in the interval debulking surgery group improved by at least 5 points in global quality of life at 12 months, versus 44 % in primary debulking surgery group. EORTC 55971 [15] reported significant differences at 12 months in pain and dyspnea domains, higher in primary and interval debulking surgery groups, respectively, with no other significant differences reported.

Data from Onda et al. [20] were not reported and detailed TRUST trial findings [7] could not be retrieved. However, Mahner et al. revealed at ASCO no significant QoL differences between groups at any time.

8. Subgroup analyses

We conducted an overall survival subgroup analysis based on disease stage and residual tumor after cytoreductive surgery; such data were available from four studies [7,15,20,22] (Fig. 3). Patients with stage III disease showed no better overall survival with either timing [HR = 0.94; CI 95 % (0.83, 1.07); I^2 = 15 %; P = 0.37] and similar results were observed in the stage IV subgroup [HR = 1.03; CI 95 % (0.87, 1.23); I^2 = 0 %; P = 0.71]. For overall survival according to residual tumor, subgroup analysis was limited to no residual disease and macroscopic residual disease, as data for these groups were available from three studies [7,15,18]. Our analysis did not reveal a significant survival benefit for patients undergoing interval debulking with no residual disease or macroscopic residual disease after surgery, with pooled HR = 0.94 [CI 95 % (0.74, 1.21); I^2 = 38 %; P = 0.65] and 1.20 [CI 95 % (0.61, 2.39); I^2 = 87 %; P = 0.60], respectively.

9. Sensitivity analysis

High heterogeneity was observed across trials for complete cytoreduction with no residual disease. Onda et al. [20] likely contributed to this heterogeneity. Removing this trial, pooled estimates remained significant [OR 2.84, 95 % CI (1.93, 4.18), P < 0.00001; I^2 = 69 %]. Heterogeneity was also high for postoperative complications and splenectomy rates; removing Fagotti et al. [18], estimates stayed significant, with OR 0.57 [95 % CI (0.41, 0.78), P = 0.0005; I^2 = 0 %] and OR 0.47 [95 % CI (0.28, 0.80), P = 0.005; I^2 = 43 %]. Cytoreduction with microscopic residual disease and bowel resection rates remained highly heterogeneous (I^2 > 75 %) even after removing individual trials.

10. Meta-regression

Study-level meta-regression showed that higher complete cytoreduction (CC-0) rates in the PDS arm were associated with a non-significant trend toward improved OS with upfront surgery (β = 0.31; 95 % CI –0.21 to 0.83; p = 0.15) (Fig. 4). This corresponds to a negligible shift in log(HR) (~0.03) for each 10 % absolute increase in PDS CC-0 rate, indicating that surgical completeness at PDS did not meaningfully modify the treatment effect.

11. Cumulative meta-analysis

Cumulative random-effects meta-analysis, ordered chronologically (EORTC → CHORUS → JCOG → SCORPION → TRUST), showed a remarkably stable HR for OS consistently approximating 1.0 (Fig. S9). Introduction of the TRUST data narrowed confidence intervals but did not alter the direction of effect, supporting the temporal robustness of the equivalence between PDS and IDS.

12. Leave-one-out influence analysis

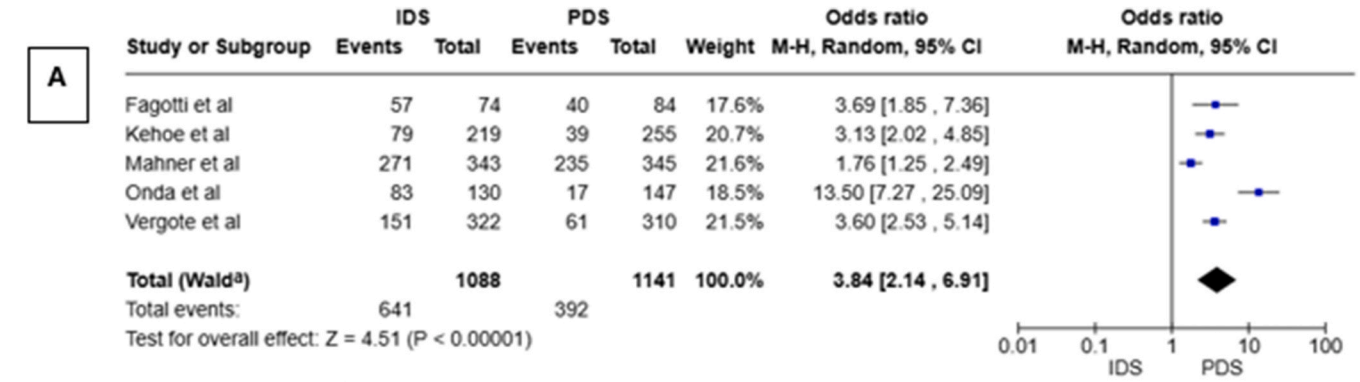
Leave-one-out analysis demonstrated that removal of any individual RCT—including CHORUS, SCORPION, or TRUST—did not materially change the pooled HR (range: 0.97–1.04) (Fig. S10). These findings indicate that no single study disproportionately influenced the observed

Table 1
Cytoreduction rates.

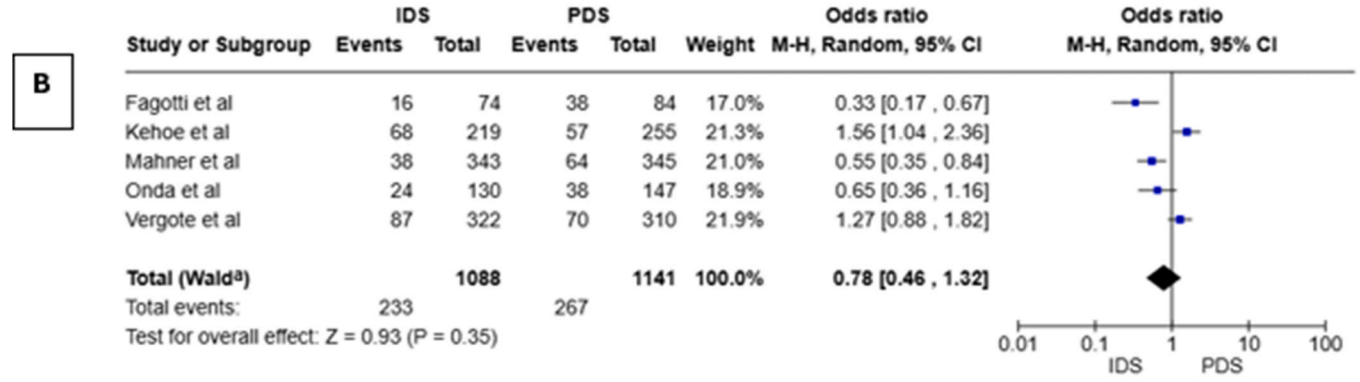
Authors	Residual disease (no gross/1–10 mm/> 10 mm)		Complete resection (RT = 0)	
	NACT	PDS	NACT	PDS
Fagotti et al. (SCORPION trial)	no gross: 57/74 (77 %) 1–10 mm: 16/74 (21.6 %) >10 mm: 1/74 (1.4 %), no cytoreduction for progressive disease: 13/87 (14.9 %)	no gross: 40/84 (47.6 %) 1–10 mm: 38/84 (45.2 %) >10 mm: 16/84 (7.1 %) no cytoreduction for progressive disease: 0/84 (0 %)	77 %	47.6 %
Kehoe et al. (CHORUS trial)	no gross: 79/219 (36 %) 1–10 mm: 68/219 (31 %) >10 mm: 54/219 (24 %) misisng data: 18	no gross: 39/255 (15 %) 1–10 mm: 57/255 (22.3 %) >10 mm: 137/255 (53.7 %) missing data: 22	36 %	15 %
Mahner et al. (TRUST trial)	no gross: 271/343 (79 %) 1–10 mm: 38/343 (11 %) >10 mm: 13/343 (3.8 %)	no gross: 235/345 (68 %) 1–10 mm: 64/345 (18.5 %) >10 mm: 35/345 (10 %)	79 %	68 %
Onda et al. (JCOG0602 trial)	no gross: 83/130 (63.8 %) 1–10 mm: 24/130 (18.5 %) >10 mm: 23/130 (17.7 %)	no gross: 17/147 (11.6 %) 1–10 mm: 38/147 (25.9 %) >10 mm: 92/147 (62.6 %)	63.8 %	11.6 %
Vergote et al. (EORTC 55971 trial)	no gross: 151/322 (51.2 %) 1–10 mm: 87/322 (29.5 %) >10 mm: 52/322 (16.1 %) missing data: 5/322 (1.7 %)	no gross: 61/310 (19.4 %) 1–10 mm: 70/310 (22.2 %) >10 mm: 167/310 (53.8 %) missing data: 17/310 (5.4 %)	51.2 %	19.4 %

NACT = neoadjuvant chemotherapy; PDS = primary debulking surgery; RT = residual tumor.

A



B



C

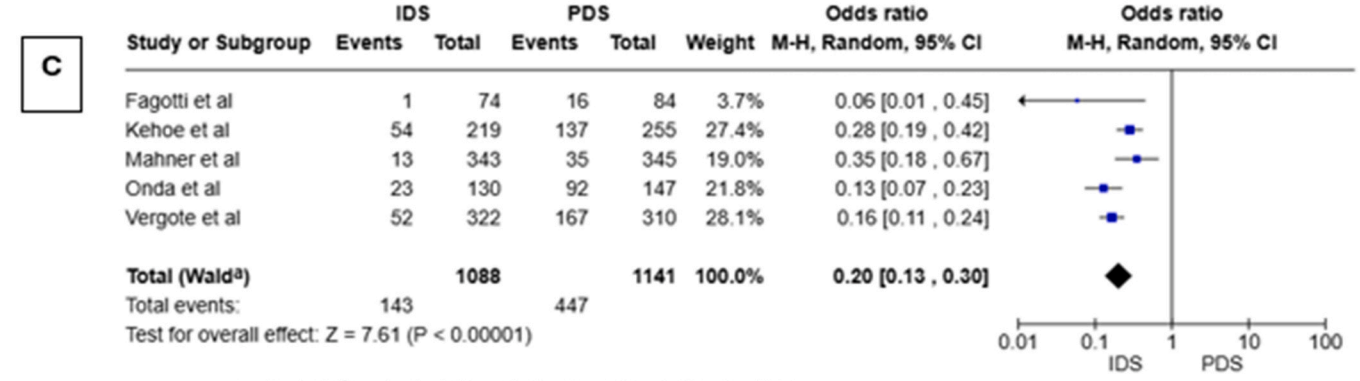


Fig. 1. Forest plot of a) no residual disease rate b) microscopical (1–10 mm) residual disease rate c) macroscopical (>10 mm) residual disease rate in primary versus interval debulking surgery among stage III-IV ovarian cancer patients.

Table 2
Survival outcomes.

Authors	Overall survival		Progression free survival	
	NACT	PDS	NACT	PDS
Fagotti et al. (SCORPION trial)	43 months HR 1.12 (0.76,1.65)	41 months	14 months HR 1.05 (0.77,1.44)	15 months
Kehoe et al. (CHORUS trial)	24.1 months (21.0–28.7) HR 0.87 (0.72,1.05) OS events: 220/274 (80.2 %)	22.6 months (18.6–25.9) OS events: 231/276 (83.6 %)	12 months (10.6–13.1) HR 0.90 (0.76,1.08) PFS events: 248/274 (90.5 %)	10.7 months (9.7–11.9) PFS events: 248/276 (89.8 %)
Mahner et al. (TRUST trial)	48.3 months (43.6–55.9) HR 0.89 (0.74,1.08) OS events: 223/343 (65 %)	54.3 months (49.1–63.3) OS events: 209/345 (60.6 %)	19.7 months (17.9–21.9) HR 0.80 (0.66,0.96) PFS events: 253/343 (73.8 %)	22.1 months (20.4–24.5) HR 0.80 (0.66,0.96) PFS events: 219/345 (63.5 %)
Onda et al. (JCOG0602 trial)	44.3 months HR 1.05 (0.83, 1.32)	49 months	16.4 months HR 0.96 (0.75,1.23)	15.1 months
Vergote et al. (EORTC 55971 trial)	30 months HR 0.98 (0.84, 1.13) OS events: 235/322 (72.9 %)	29 months OS events: 230/310 (74.1 %)	12 months HR 1.01 (0.89,1.15) PFS events: 313/334 (93.7 %)	12 months PFS events: 310/336 (92.2 %)

NACT = neoadjuvant chemotherapy; PDS = primary debulking surgery; OS = overall survival; PFS = progression free survival; HR = hazard ratio.

survival equivalence.

4. Discussion

1. Summary of Main Results

This systematic review and meta-analysis confirms that neoadjuvant chemotherapy followed by interval debulking surgery reduces extensive procedures, postoperative complications, and perioperative mortality, while increasing complete cytoreduction rates compared with primary debulking surgery. Despite these differences in morbidity and surgical complexity, overall and progression-free survival remained similar between the two strategies. The subgroup and sensitivity analyses, the newly added study-level meta-regression, cumulative meta-analysis, and leave-one-out influence analysis strengthen the robustness of our findings. The cumulative meta-analysis demonstrated that the hazard ratio for overall survival has remained consistently close to unity over 15 years of randomized evidence, independently of the study added. The leave-one-out analysis confirmed that no individual RCT—including CHORUS, SCORPION or the preliminary TRUST data—substantially affected the pooled estimate.

2. Results in the Context of Published Literature

A key question is whether variation in surgical quality, especially the completeness of cytoreduction at PDS, might explain the absence of a survival advantage. Our meta-regression directly addresses this: higher CC-0 rates at PDS did not meaningfully alter the OS effect, suggesting that surgical expertise alone is insufficient to change the overall equivalence seen across trials. This finding, along with the reduced morbidity profile of IDS, highlights the central role of tumor biology, disease burden, and perioperative risk—factors that may outweigh the potential benefits of upfront radical cytoreduction even in quality-certified centers. These results are consistent with current evidence indicating that extensive upfront surgery can carry significant morbidity that may negate potential survival gains. The TRUST trial, designed with strict surgical quality standards, did not show PDS superiority, reinforcing the importance of patient selection and biological factors over surgical timing. Therefore, personalized triage models—considering tumor burden, performance status, and the likelihood of achieving safe, complete cytoreduction—are becoming more vital for guiding clinical decisions. While additional trial-level features (e.g., laparoscopy-based scoring systems [23,24], BRCA/HRD status [25], variations in chemotherapy regimens, or Peritoneal Cancer Index - PCI [26]) contribute to clinical heterogeneity, inconsistent reporting of these factors across included RCTs limits definitive comparisons. Still, their importance emphasizes the need for more standardized reporting in future trials.

3. Strengths and weaknesses

The major strengths of this review include its comprehensive synthesis of all available randomized evidence, the integration of TRUST preliminary data, and the addition of advanced analytical techniques—meta-regression, cumulative synthesis, and leave-one-out influence analysis—that provide a more nuanced understanding of heterogeneity and evidence stability. Long follow-up periods and a sample of more than 2300 patients further enhance the reliability of the findings. However, significant limitations remain. Several included trials were underpowered, used diverse eligibility criteria, or lacked standardized surgical quality assurance (Tables S8 and S9). Data on tumor burden, surgical complexity, and quality-of-life outcomes were inconsistently reported. TRUST is only available in abstract form, precluding complete risk-of-bias evaluation. Persistent heterogeneity in cytoreduction outcomes highlights the influence of unmeasured clinical factors. These limitations require cautious interpretation and reinforce the need for high-quality, adequately powered RCTs with strict surgical standardization.

4. Implications for Practice and Future Research

The overall evidence supports a personalized, biology-informed approach to surgical timing.

Since the TRUST trial failed to demonstrate the superiority of PDS despite certified surgical expertise, PDS may be suitable for patients with low-intermediate tumor burden, good performance status and high likelihood of achieving safe CC-0 cytoreduction. IDS appears advantageous in patients with extensive disease, high predicted surgical complexity or increased perioperative risk.Future research should focus on integrating validated triage models (e.g., Fagotti score, Vizzielli score, Aletti score), molecular stratification, and standardized measures of tumor burden with artificial intelligence playing a role in this context [27].

Further analyses on disease-free survival and recurrence patterns, especially site and timing, would also be valuable. Emerging evidence suggests distinct recurrence dynamics between primary and interval debulking strategies, which could help tailor treatment more effectively.

We await data from two ongoing randomized trials—FOCUS (NCT04515602) and the SUNNY study (NCT02859038): the first will assess the efficacy and safety of surgical strategies across different tumor burdens, the latter will provide data from high-volume and high surgical experienced centers.

5. Conclusion

Data from five clinical trials and meta-analyses show that neoadjuvant chemotherapy followed by interval debulking surgery reduces perioperative morbidity and lowers postoperative mortality without harming quality of life. Our findings, including preliminary data from the TRUST trial, suggest that interval debulking surgery is not inferior to primary debulking surgery in terms of survival, even when considering FIGO stage and residual disease. The lack of significant differences in overall survival among patients with complete cytoreduction—despite

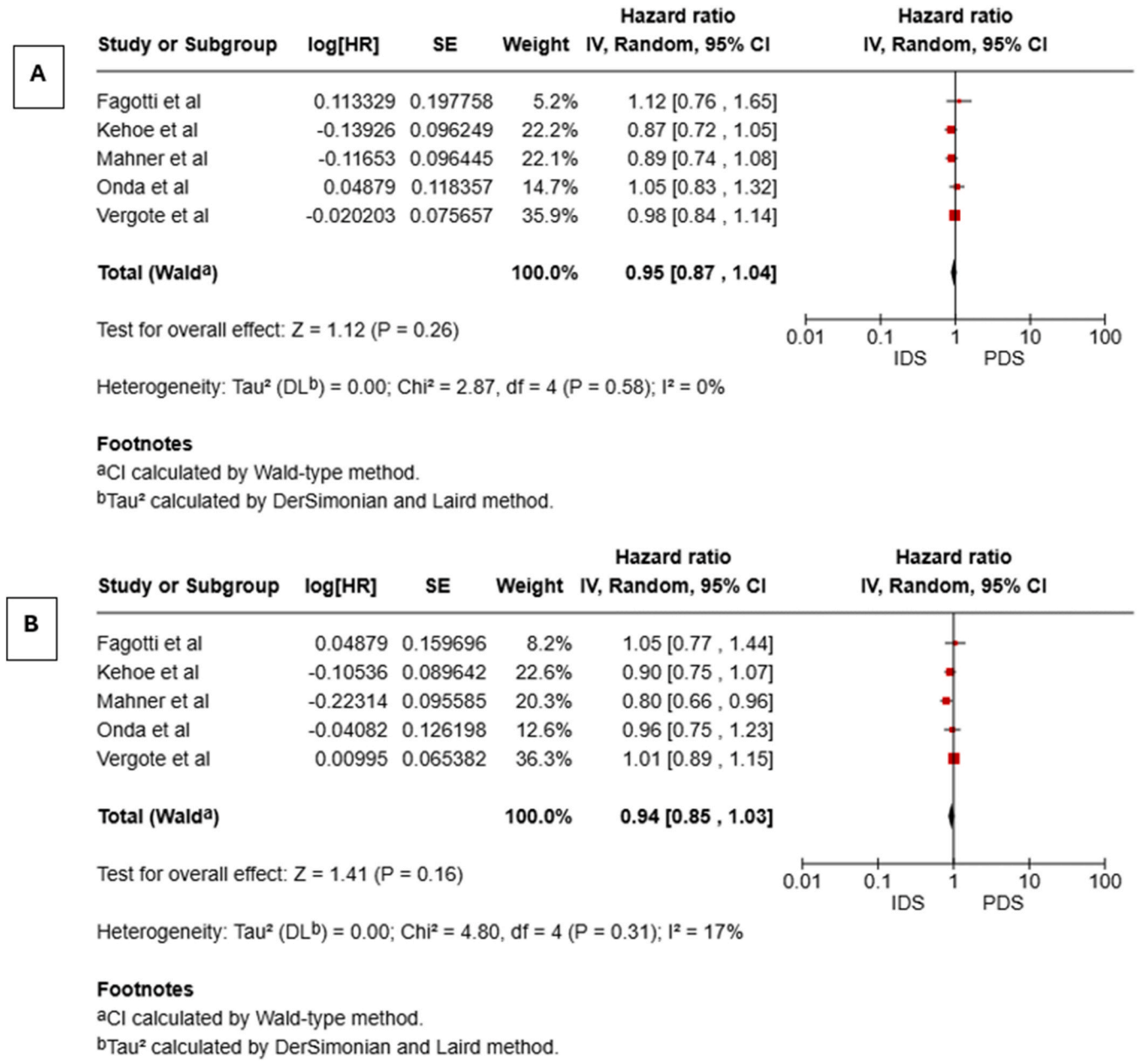


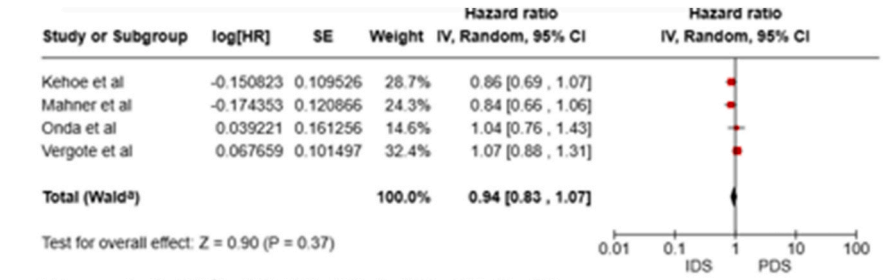
Fig. 2. Forest plot of a) overall survival b) progression free survival in primary versus interval debulking surgery among stage III-IV ovarian cancer patients.

small sample sizes—indicates that factors like tumor burden and surgical complexity also affect long-term outcomes and treatment choices. The cumulative meta-analysis shows that the OS equivalence between PDS and IDS is not a recent artifact caused by TRUST but has remained consistent over 15 years of randomized evidence. The meta-regression results suggest that even in trials with very high PDS CC-0 rates, no clinically meaningful OS benefit was observed for upfront surgery, emphasizing the dominant roles of tumor biology and perioperative morbidity rather than surgical timing alone. Finally, the leave-one-out analysis confirms that the pooled results are reliable and not influenced by any single RCT. Therefore, future trials need to be methodologically strong, sufficiently powered, and conducted within certified surgical networks to determine whether specific patient groups may benefit more from one surgical timing over another. Only carefully standardized designs will allow the field to move beyond apparent equivalence toward a genuinely individualized approach.

Author contributions

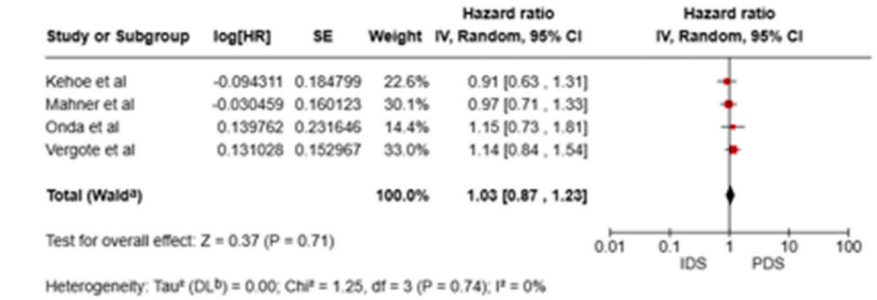
Veronica Tius: Conceptualization, Supervision, Writing – Original Draft, Project Administration, Data Acquisition; Cristina Taliento: Writing – Original Draft, Project Administration, Data Acquisition; Martina Arcieri: Conceptualization, Supervision, Writing – Review & Editing, Project Administration; Sara Filippin: Writing – Original Draft, Data Acquisition; Miriam Isola: Writing – Review & Editing; Maria De Martino: Writing – Review & Editing; Nicolò Bizzarri: Writing – Review & Editing; Matteo Pavone: Supervision; Mauro Signorelli: Supervision; Domenica Lorusso: Supervision; Paolo Scollo: Supervision; Sandro Pignata: Writing – Review & Editing; Vito Chiantera: Supervision; Giorgio Bogani: Supervision; Jvan Casarin: Supervision; Anna Fagotti: Supervision; Stefano Restaino: Conceptualization, Supervision, Writing – Review & Editing, Project Administration; Giuseppe Vizzielli: Conceptualization, Supervision, Project AdministrationAll authors have read and agreed to the published version of the manuscript.

A



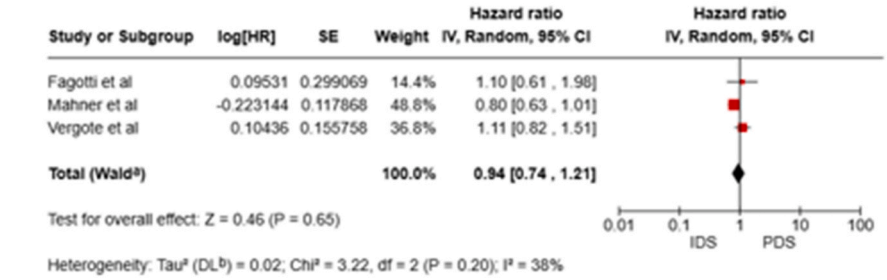
Footnotes
[a]CI calculated by Wald-type method.
[b]Tau² calculated by DerSimonian and Laird method.

B



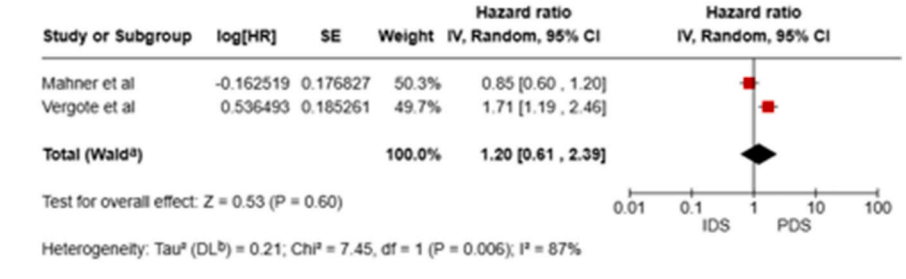
Footnotes
[a]CI calculated by Wald-type method.
[b]Tau² calculated by DerSimonian and Laird method.

C



Footnotes
[a]CI calculated by Wald-type method.
[b]Tau² calculated by DerSimonian and Laird method.

D



Footnotes
[a]CI calculated by Wald-type method.
[b]Tau² calculated by DerSimonian and Laird method.

Fig. 3. Forest plot of a) overall survival in FIGO stage III ovarian cancer subgroup b) overall survival in FIGO stage IV ovarian cancer subgroup; c) overall survival in no residual disease after surgery subgroup d) overall survival in macroscopical disease after surgery subgroup in primary versus interval debulking surgery among stage III-IV ovarian cancer patients.

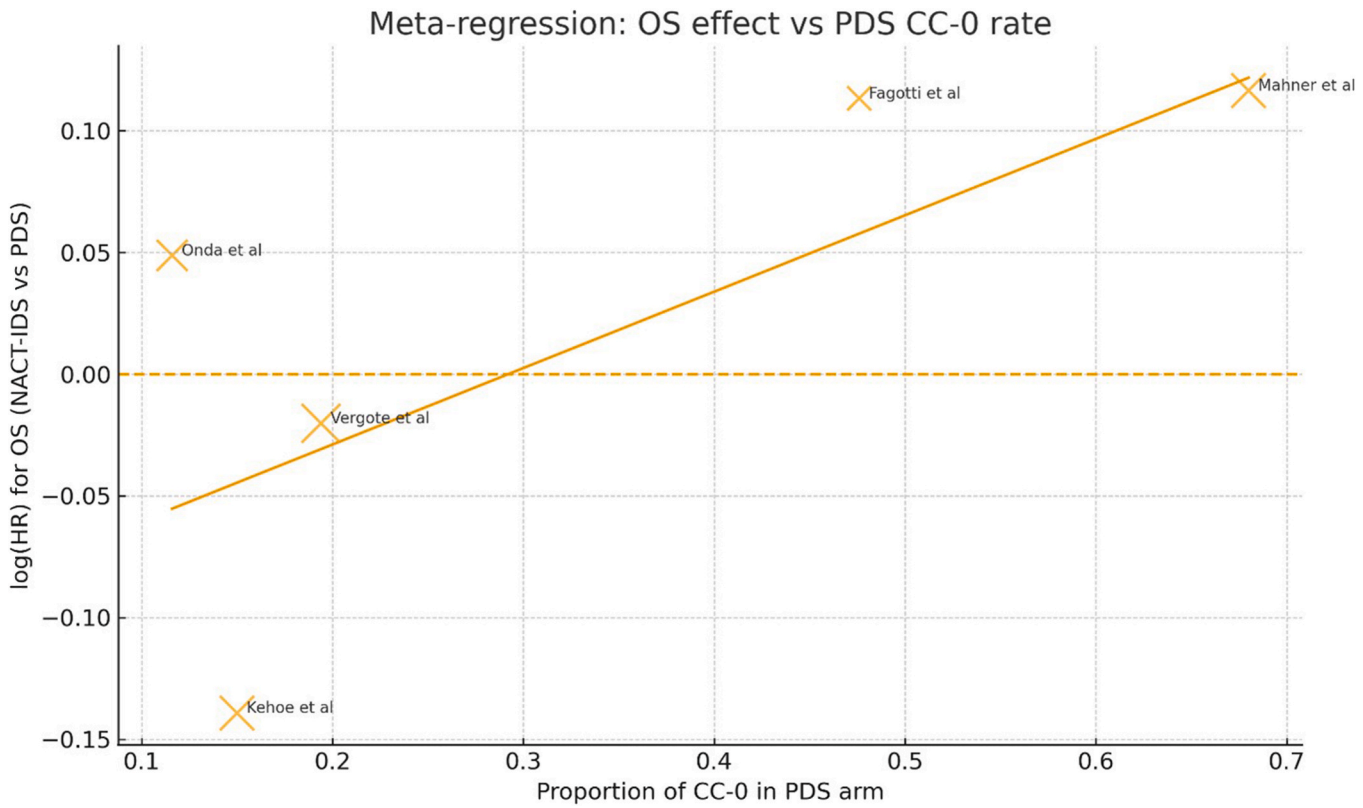


Fig. 4. Study-level meta-regression (bubble plot) of Overall Survival. Bubble plot depicting the relationship between proportion of complete cytoreduction (CC-0) at primary debulking surgery (PDS) and log(HR) for OS. Bubble size is proportional to study precision. The regression line and 95 % CI indicate no significant effect modification.

Ethics statement

The authors have nothing to report.

Disclosure

The authors GV, SR, DL, MS, acknowledge contributing to a separate meta-analysis on the same general topic [9], conducted under a different PROSPERO registration and with distinct methodological aims. No overlap in data extraction, analyses, or manuscript text occurred.

Data availability statement

All data relevant to the study are included in the article or uploaded as supplementary information. All data were extracted from previously published studies; thus, they are publicly available.

Funding

The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2025.111355.

References

[1] Bryant A, Hiu S, Kunonga PT, Gajjar K, Craig D, Vale L, et al. Impact of residual disease as a prognostic factor for survival in women with advanced epithelial ovarian cancer after primary surgery. Cochrane Database Syst Rev 2022;9(9). CD015048.
[2] Kim JH, Kim SI, Park EY, Ha HI, Kim JW, Coleman RL, et al. Impact of postoperative residual disease on survival in epithelial ovarian cancer with consideration of recent frontline treatment advances: a systematic review and meta-analysis. Gynecol Oncol 2023;179:24–32.
[3] Tzanis AA, Iavazzo C, Hadjivasilis A, Tsouvali H, Antoniou GA, Antoniou SA. Neoadjuvant chemotherapy versus primary debulking surgery in FIGO stage III and IV Epithelial ovarian, tubal or peritoneal cancer: a systematic review and meta-analysis. Oncol Rev 27 September 2022;16:10605.
[4] Lv X, Cui S, Zhang X, Ren C. Efficacy and safety of neoadjuvant chemotherapy versus primary debulking surgery in patients with ovarian cancer: a meta-analysis. J Gynecol Oncol 2020;31(2):e12.
[5] Yang L, Zhang B, Xing G, Du J, Yang B, Yuan Q, et al. Neoadjuvant chemotherapy versus primary debulking surgery in advanced epithelial ovarian cancer: a meta-analysis of peri-operative outcome. Zhou S, curatore. PLoS One 23 October 2017; 12(10):e0186725.
[6] Coleridge SL, Bryant A, Kehoe S, Morrison J. Chemotherapy versus surgery for initial treatment in advanced ovarian epithelial cancer. Cochrane Database Syst Rev 5 February 2021;2(2):CD005343.
[7] Mahner S, Heitz F, Salehi S, Reuss A, Guyon F, Fotopoulou C, et al. TRUST: trial of Radical upfront surgical therapy in advanced ovarian cancer.
[8] Mahner S, Heitz F, Salehi S, Reuss A, Guyon F, Du Bois A, et al. TRUST: trial of radical upfront surgical therapy in advanced ovarian cancer (ENGOT ov33/AGO-OVAR OP7). J Clin Oncol 2025;43(17_suppl). LBA5500–LBA5500.
[9] Secchi M, Signorelli M, Rulli E, Maruccio M, Di Martino G, Spadaro D, et al. Neoadjuvant chemotherapy followed by interval surgery versus primary debulking surgery in FIGO stage III-IV epithelial ovarian cancer: a systematic review and meta-analysis. Eur J Cancer Oxf Engl 1990. 15 November 2025;232:116116.
[10] Wright AA, Bohlke K, Armstrong DK, Bookman MA, Cliby WA, Coleman RL, et al. Neoadjuvant chemotherapy for newly diagnosed, advanced ovarian cancer: society

of gynecologic oncology and American society of clinical oncology clinical practice guideline. J Clin Oncol Off J Am Soc Clin Oncol 2016;34(28):3460–73.
[11] Gaillard S, Lacchetti C, Armstrong DK, Cliby WA, Edelson MI, Garcia AA, et al. Neoadjuvant chemotherapy for newly diagnosed, advanced ovarian cancer: ASCO guideline update. J Clin Oncol March 2025;43(7):868–91.
[12] Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. Br Med J 28 August 2019;366:l4898.
[13] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Br Med J 29 March 2021;372:n71.
[14] Hopewell S, Chan AW, Collins GS, Hróbjartsson A, Moher D, Schulz KF, et al. CONSORT 2025 statement: updated guideline for reporting randomised trials. Lancet 3 May 2025;405(10489):1633–40.
[15] Vergote I, Amant F, Ehlen T. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. N Engl J Med 2010.
[16] Greimel E, Kristensen GB, Van Der Burg MEL, Coronado P, Rustin G, Del Rio AS, et al. Quality of life of advanced ovarian cancer patients in the randomized phase III study comparing primary debulking surgery versus neo-adjuvant chemotherapy. Gynecol Oncol November 2013;131(2):437–44.
[17] Prescott LS, Vergote I, Sun CC, Bodurka DC, Coleman RL. Transfusion use and effect on progression-free, overall survival, and quality of life in upfront treatment of advanced epithelial ovarian cancer: evaluation of the european organization for research and treatment EORTC-55971 cohort. Int J Gynecol Cancer January 2023; 33(1):1–9.
[18] Fagotti A, Ferrandina MG, Vizzielli G, Pasciuto T, Fanfani F, Gallotta V, et al. Randomized trial of primary debulking surgery versus neoadjuvant chemotherapy for advanced epithelial ovarian cancer (SCORPION-NCT01461850). Int J Gynecol Cancer November 2020;30(11):1657–64.
[19] Marchetti C, Giannarelli D, Vizzielli G, Ferrandina GabriellaM, Tortorella L, Fanfani F, et al. Quality of life in patients with advanced ovarian cancer after primary debulking surgery versus neoadjuvant chemotherapy: results from the randomised SCORPION trial (NCT01461850). BJOG Int J Obstet Gynaecol December 2023;130(13):1579–88.
[20] Onda T, Satoh T, Saito T, Kasamatsu T, Nakanishi T, Nakamura K, et al. Comparison of treatment invasiveness between upfront debulking surgery versus interval debulking surgery following neoadjuvant chemotherapy for stage III/IV ovarian, tubal, and peritoneal cancers in a phase III randomised trial: Japan clinical oncology group study JCOG0602. Eur J Cancer September 2016;64:22–31.
[21] Onda T, Satoh T, Ogawa G, Saito T, Kasamatsu T, Nakanishi T, et al. Comparison of survival between primary debulking surgery and neoadjuvant chemotherapy for stage III/IV ovarian, tubal and peritoneal cancers in phase III randomised trial. Eur J Cancer May 2020;130:114–25.
[22] Kehoe S, Hook J, Nankivell M, Jayson GC, Kitchener H, Lopes T, et al. Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial. Lancet July 2015;386(9990):249–57.
[23] Fagotti A, Ferrandina G, Fanfani F, Garganese G, Vizzielli G, Carone V, et al. Prospective validation of a laparoscopic predictive model for optimal cytoreduction in advanced ovarian carcinoma. Am J Obstet Gynecol December 2008;199(6):642.e1–6.
[24] Aletti GD, Dowdy SC, Podratz KC, Cliby WA. Relationship among surgical complexity, short-term morbidity, and overall survival in primary surgery for advanced ovarian cancer. Am J Obstet Gynecol 2007;197(6):676.e1–7.
[25] Arcieri M, Tius V, Andreetta C, Restaino S, Biasioli A, Poletto E, et al. How BRCA and homologous recombination deficiency change therapeutic strategies in ovarian cancer: a review of literature. Front Oncol 2024;14:1335196.
[26] Jacquet P, Sugarbaker PH. Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. In: Sugarbaker PH, editor. Curatore. Peritoneal carcinomatosis: principles of management [internet]. Boston, MA: Springer US; 1996. p. 359–74. https://doi.org/10.1007/978-1-4613-1247-5_23.
[27] Restaino S, De Giorgio MR, Pellecchia G, Arcieri M, Vasta FM, Fedele C, et al. Artificial intelligence in gynecological oncology from diagnosis to surgery. Cancers 21 March 2025;17(7):1060.