



How does primary debulking surgery compared to neoadjuvant chemotherapy followed by interval debulking surgery affect overall survival in women with advanced ovarian cancer? : A Systematic Review

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ABSTRACT

Introduction: Advanced epithelial ovarian cancer (stage III-IV) remains a leading cause of gynecologic cancer mortality worldwide. The optimal initial treatment approach—primary debulking surgery (PDS) versus neoadjuvant chemotherapy followed by interval debulking surgery (NACT-IDS)—continues to generate substantial clinical debate despite multiple randomized trials. This systematic review aims to compare overall survival outcomes between PDS and NACT-IDS in women with advanced ovarian cancer.

Methods: A systematic review was conducted following PRISMA guidelines. We screened studies based on predefined criteria: inclusion of women ≥ 18 years with FIGO stage III-IV epithelial

ovarian cancer, direct comparison of PDS versus NACT-IDS, reporting of overall survival outcomes, and study designs including randomized controlled trials, cohort studies, systematic reviews, and meta-analyses. Data extraction encompassed study characteristics, patient selection criteria, treatment details, survival outcomes, surgical outcomes, and subgroup analyses.

Results: Eighty studies were included, comprising five major RCTs (EORTC 55971, CHORUS, SCORPION, JCOG0602, TRUST) and numerous meta-analyses and observational studies. Meta-analyses demonstrated no significant difference in overall survival between PDS and NACT-IDS (HR 0.96, 95% CI 0.86-1.08) [1-3]. Individual RCTs confirmed similar findings: EORTC 55971 (HR 0.98, 90% CI 0.84-1.13) [4], CHORUS (HR 0.87, 95% CI 0.72-1.05) [5], and TRUST (HR 0.89, 95% CI 0.74-1.08) [6]. However, NACT-IDS achieved superior complete cytoreduction rates (RR 2.34, 95% CI 1.48-3.71) [2] with significantly lower perioperative mortality (RR 0.16, 95% CI 0.06-0.46) and major complications (RR 0.22, 95% CI 0.13-0.38) [1]. Observational studies consistently favored PDS, reflecting selection bias [7,8]. Stage-specific analysis revealed NACT-IDS benefited stage IV disease (HR 0.76, 95% CI 0.58-1.00) [9], while PDS showed advantage in stage III with limited metastatic burden [6,8].

Discussion: The apparent contradiction between RCT and observational evidence reflects fundamental differences in patient selection, surgical quality, and study design. Complete cytoreduction at PDS identifies a biologically favorable subset with superior outcomes, whereas achieving complete resection after NACT may indicate chemotherapy responsiveness without equivalent survival benefit. NACT-IDS offers clear perioperative safety advantages, making it preferable for unresectable disease,

poor performance status, and extensive stage IV disease. Optimal treatment selection requires accurate preoperative assessment of resectability, patient fitness, and surgical expertise.

Conclusion: PDS and NACT-IDS provide comparable overall survival in advanced ovarian cancer when patients are appropriately selected. PDS remains preferred when complete cytoreduction is achievable by experienced surgeons in fit patients with stage IIIC disease. NACT-IDS is a safe, effective alternative for patients with unresectable disease, poor fitness, or extensive stage IV disease. Future research should focus on validated prediction models incorporating clinical, imaging, and molecular markers to optimize individualized treatment selection.

Keywords: Ovarian cancer, primary debulking surgery, neoadjuvant chemotherapy, interval debulking surgery, overall survival, cytoreduction

INTRODUCTION

Background

Epithelial ovarian cancer remains the most lethal gynecologic malignancy worldwide, with the majority of patients presenting at advanced stages (FIGO III-IV) due to nonspecific early symptoms and lack of effective screening strategies [1,4]. The cornerstone of treatment for advanced ovarian cancer has historically been primary debulking surgery (PDS) followed by platinum-based chemotherapy, with the goal of achieving complete cytoreduction—no macroscopic residual disease—which represents the strongest prognostic factor for long-term survival [4,21,27].

However, PDS is associated with significant morbidity, including extensive multivisceral resections, prolonged hospital stays, perioperative complications, and mortality, particularly in patients with extensive disease burden or poor performance status [1,5,11]. These limitations prompted the investigation of an alternative approach: neoadjuvant chemotherapy followed by interval debulking surgery (NACT-IDS). This strategy involves administering 3-4 cycles of platinum-based chemotherapy prior to surgical cytoreduction, with additional chemotherapy administered postoperatively [4,5].

The publication of landmark randomized controlled trials—EORTC 55971 in 2010 [4] and CHORUS in 2015 [5]—demonstrated that NACT-IDS was non-inferior to PDS in terms of overall survival, while achieving higher rates of optimal cytoreduction and lower perioperative morbidity. These findings fundamentally challenged the long-standing paradigm of primary surgery and led to dramatic shifts in clinical practice worldwide, with NACT-IDS utilization increasing substantially following their publication [37,61].

Subsequent trials, however, have yielded more nuanced results. The SCORPION trial [11] and JCOG0602 trial [50] failed to demonstrate non-inferiority of NACT-IDS, while the recently reported TRUST trial [6], conducted in expert surgical centers with rigorous quality assurance, showed a trend favoring PDS that did not reach statistical significance. Concurrently, large

observational studies from national databases consistently reported superior survival with PDS [7,8], creating an apparent contradiction that has generated substantial clinical uncertainty.

Research Gap

Despite multiple randomized trials and numerous meta-analyses [1-3,10,18,20,22,25,28,29,62], significant controversies persist regarding the optimal timing of surgery in advanced ovarian cancer. The existing literature reveals several unresolved questions:

First, the apparent discordance between randomized trial evidence (showing equivalence) and observational data (favoring PDS) requires reconciliation through understanding of underlying mechanisms, including selection bias, surgical quality variation, and biological heterogeneity [27,29,41].

Second, the relationship between complete cytoreduction and survival appears to differ fundamentally between PDS and NACT-IDS. While complete resection at PDS consistently predicts excellent outcomes [19,41,55], the prognostic significance of complete resection after NACT-IDS is less clear, with some studies showing attenuated benefit [32,44,49].

Third, optimal patient selection criteria remain poorly defined. Although exploratory analyses suggest stage IV disease [9,36,57], extensive metastatic burden [59], and poor performance status [25,27] may favor NACT-IDS, validated prediction models integrating clinical, radiographic, laparoscopic, and molecular factors are lacking.

Fourth, the impact of histologic subtypes [27], molecular characteristics including BRCA mutation status [48,70], and institutional surgical expertise [6,34] on comparative treatment outcomes requires further elucidation.

Fifth, the optimal number of neoadjuvant chemotherapy cycles [28,31], timing of interval surgery [56,73], and long-term quality of life implications [1,63] remain inadequately characterized.

Problem Statement

Clinicians face a critical dilemma when counseling patients with newly diagnosed advanced ovarian cancer: should they recommend primary debulking surgery with its potential for superior long-term outcomes but higher morbidity, or neoadjuvant chemotherapy followed by interval surgery with improved perioperative safety but uncertain survival equivalence in optimally selected

patients? This decision is further complicated by variable surgical expertise across institutions [6,34], heterogeneous patient characteristics [7,8], and evolving evidence from recent trials [6,50].

Study Objectives

This systematic review aims to:

1. Compare overall survival outcomes between primary debulking surgery and neoadjuvant chemotherapy followed by interval debulking surgery in women with advanced epithelial ovarian cancer (FIGO stage III-IV)
2. Evaluate secondary outcomes including progression-free survival, perioperative morbidity and mortality, optimal cytoreduction rates, and quality of life
3. Identify patient, tumor, and treatment characteristics that modify comparative treatment effects
4. Reconcile apparent discrepancies between randomized trial evidence and observational studies
5. Provide evidence-based recommendations for clinical practice and future research

Research Hypothesis

We hypothesize that primary debulking surgery and neoadjuvant chemotherapy followed by interval debulking surgery provide comparable overall survival in advanced ovarian cancer when patients are appropriately selected, but that significant heterogeneity of treatment effect exists based on disease stage, extent of metastatic disease, patient fitness, and surgical quality. Specifically, we anticipate that PDS may offer advantages in stage III disease with limited metastatic burden when complete cytoreduction is achievable by experienced surgeons, while NACT-IDS may be preferable in stage IV disease, extensive metastatic disease, and patients with poor performance status.

Research Benefits

This systematic review will provide clinicians with a comprehensive synthesis of current evidence to inform shared decision-making with patients. It will clarify which patients are most

likely to benefit from each treatment approach, facilitate development of institutional treatment algorithms, identify quality indicators for surgical programs, and guide future research priorities. For patients, this evidence synthesis will enable more informed discussions about treatment risks, benefits, and expected outcomes.

Novelty

This review offers several novel contributions. First, it incorporates the most recent evidence from the TRUST trial [6] and updated Cochrane review [10], providing the most current comprehensive synthesis available. Second, it systematically examines the differential prognostic significance of complete cytoreduction between treatment approaches—a critical mechanistic insight often overlooked in prior analyses. Third, it provides a detailed reconciliation of RCT and observational evidence through analysis of patient selection, surgical quality, and biological factors. Fourth, it offers stage-specific and subgroup-specific treatment recommendations based on pooled individual patient data [9] and recent meta-analyses [3,58]. Fifth, it integrates emerging evidence on molecular characteristics, including BRCA mutation status [48,70], into the treatment selection framework.

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate How does primary debulking surgery compared to neoadjuvant chemotherapy followed by interval debulking surgery affect overall survival in women with advanced ovarian cancer?.

Screening

We screened in sources based on their abstracts that met these criteria:

- **Population:** Does the study include women (≥ 18 years) diagnosed with advanced epithelial ovarian cancer (stage III or IV)?
- **Intervention Comparison:** Does the study compare primary debulking surgery versus neoadjuvant chemotherapy followed by interval debulking surgery?
- **Overall Survival Outcome:** Does the study report overall survival as a primary or secondary outcome?
- **Study Design:** Is the study design a randomized controlled trial, prospective cohort study, retrospective cohort study, systematic review, or meta-analysis (not a case report, case series, editorial, or conference abstract)?
- **Cancer Type and Stage:** Does the study focus on primary (not exclusively recurrent) epithelial (not non-epithelial) ovarian cancer?
- **Population Analysis:** Can advanced ovarian cancer patients be separately analyzed from early-stage patients in this study?
- **Outcome Data Adequacy:** Does the study provide sufficient data on overall survival outcomes and follow-up duration?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Search Strategy

The keywords used for this research based PICO :

Element	P (Population)	I (Intervention/Exposure)	C (Comparison/Context)	O (Outcome)
Keyword 1	Advanced Ovarian Cancer	Primary Debulking Surgery	Neoadjuvant Chemotherapy	Overall Survival

Keyword 2	Stage III/IV Ovarian Cancer	Primary Cytoreductive Surgery	Preoperative Chemotherapy	Survival Rate
Keyword 3	Advanced Tubo-Ovarian Cancer	Initial Debulking Surgery	Interval Debulking Surgery	Mortality
Keyword 4	FIGO Stage III/IV	Primary Surgery	Chemotherapy Followed by Surgery	Long-term Survival

The Boolean MeSH keywords inputted on databases for this research are: (*"Advanced Ovarian Cancer"* OR *"Stage III/IV Ovarian Cancer"* OR *"Advanced Tubo-Ovarian Cancer"* OR *"FIGO Stage III/IV"*) AND (*"Primary Debulking Surgery"* OR *"Primary Cytoreductive Surgery"* OR *"Initial Debulking Surgery"* OR *"Primary Surgery"*) AND (*"Neoadjuvant Chemotherapy"* OR *"Preoperative Chemotherapy"* OR *"Interval Debulking Surgery"* OR *"Chemotherapy Followed by Surgery"*) AND (*"Overall Survival"* OR *"Survival Rate"* OR *"Mortality"* OR *"Long-term Survival"*)

Data extraction

- **Study Design & Population:**

Extract study design (RCT, cohort study, database analysis, etc.) and characteristics of women with advanced ovarian cancer, including:

- FIGO stage (III, IV, specific substages)
- Histologic type (serous, other epithelial types)
- Sample size in each treatment group
- Age range/median
- Performance status or comorbidity measures

- Disease characteristics (ascites, peritoneal disease extent, CA-125 levels)
- Study setting and time period

- **Patient Selection Criteria:**

Extract how patients were allocated to primary debulking surgery vs neoadjuvant chemotherapy followed by interval debulking surgery, including:

- Selection criteria used to determine treatment approach
- Whether randomized or based on clinical judgment
- Reasons for choosing NACT over PDS (inoperability, medical contraindications, disease extent)
- Any scoring systems or algorithms used for treatment selection
- Baseline differences between treatment groups that might affect outcomes

- **Treatment Details:**

Extract specific details about both treatment approaches for advanced ovarian cancer, including:

- Primary debulking surgery: extent of surgery, organs resected, surgical techniques
- Neoadjuvant chemotherapy: specific regimens, number of cycles before surgery, platinum-based vs other
- Interval debulking surgery: timing after chemotherapy, extent of surgery
- Post-surgical chemotherapy: regimens, route (IV vs IP), number of cycles
- Any maintenance therapy used in either group

- **Overall Survival Outcomes:**

Extract overall survival outcomes comparing primary debulking surgery vs neoadjuvant chemotherapy + interval debulking surgery, including:

- Median overall survival for each treatment group with confidence intervals
- Hazard ratios with 95% CI for NACT vs PDS
- 5-year, 3-year survival rates for each group
- P-values for survival comparisons
- Whether results were adjusted for confounders and which variables
- Follow-up duration and censoring information

- **Secondary Survival Outcomes:**

Extract progression-free survival, disease-free survival, and other time-to-event outcomes comparing the two treatment approaches, including:

- Median progression-free/disease-free survival for each group
- Hazard ratios with 95% CI
- Time to recurrence or progression
- Any other survival endpoints reported
- Statistical significance of differences between treatment groups

- **Surgical Outcomes:**

Extract surgical outcomes that may impact survival in both treatment groups, including:

- Optimal cytoreduction rates (definition used: R0, <1cm, other)
- Residual disease categories and percentages in each group
- Perioperative mortality (30-day, 90-day)
- Major surgical complications (grade 3+ adverse events)
- Need for bowel resection, stoma formation, other extensive procedures
- Differences in surgical complexity between PDS and interval surgery

- **Subgroup Analyses:**

Extract any subgroup analyses examining which patients with advanced ovarian cancer benefit more from each treatment approach, including:

- Survival outcomes by residual disease status within each treatment group
- Results by FIGO stage (IIIC vs IV)
- Age-based subgroups
- Performance status or comorbidity subgroups
- Histology-specific results
- Any interaction tests showing differential treatment effects
- Patient characteristics associated with better outcomes in each treatment arm

- **Study Quality:**

Extract information relevant to study quality and risk of bias for comparing survival outcomes, including:

- Whether groups were balanced at baseline or adjustment methods used
- Completeness of follow-up and loss to follow-up rates
- How survival was assessed and verified
- Potential selection bias in treatment allocation
- Multi-institutional vs single-center study
- Whether intent-to-treat or per-protocol analysis was used

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	<i>("Advanced Ovarian Cancer" OR "Stage III/IV Ovarian Cancer" OR "Advanced Tubo-Ovarian Cancer" OR "FIGO Stage III/IV") AND ("Primary Debulking Surgery" OR "Primary Cytoreductive Surgery" OR "Initial Debulking Surgery" OR "Primary Surgery") AND ("Neoadjuvant Chemotherapy" OR "Preoperative Chemotherapy" OR "Interval Debulking Surgery" OR "Chemotherapy Followed by Surgery") AND ("Overall Survival" OR "Survival Rate" OR "Mortality" OR "Long-term Survival")</i>	204
Semantic Scholar	<i>("Advanced Ovarian Cancer" OR "Stage III/IV Ovarian Cancer" OR "Advanced Tubo-Ovarian Cancer" OR "FIGO Stage III/IV") AND ("Primary Debulking Surgery" OR "Primary Cytoreductive Surgery" OR "Initial Debulking Surgery" OR "Primary Surgery") AND ("Neoadjuvant Chemotherapy" OR "Preoperative Chemotherapy" OR "Interval Debulking Surgery" OR "Chemotherapy Followed by Surgery") AND ("Overall Survival" OR "Survival Rate" OR "Mortality" OR "Long-term Survival")</i>	7
Springer	<i>("Advanced Ovarian Cancer" OR "Stage III/IV Ovarian Cancer" OR "Advanced Tubo-Ovarian Cancer" OR "FIGO Stage III/IV") AND ("Primary Debulking Surgery" OR "Primary Cytoreductive Surgery" OR "Initial Debulking Surgery" OR "Primary Surgery") AND ("Neoadjuvant Chemotherapy" OR "Preoperative Chemotherapy" OR "Interval Debulking Surgery" OR "Chemotherapy Followed by Surgery") AND ("Overall Survival" OR "Survival Rate" OR "Mortality" OR "Long-term Survival")</i>	661
Google Scholar	<i>("Advanced Ovarian Cancer" OR "Stage III/IV Ovarian Cancer" OR "Advanced Tubo-Ovarian Cancer" OR "FIGO Stage III/IV") AND ("Primary Debulking Surgery" OR "Primary Cytoreductive Surgery" OR "Initial Debulking Surgery" OR "Primary Surgery") AND ("Neoadjuvant Chemotherapy" OR "Preoperative Chemotherapy" OR "Interval Debulking Surgery" OR "Chemotherapy Followed by Surgery") AND ("Overall Survival" OR "Survival Rate" OR "Mortality" OR "Long-term Survival")</i>	11,900
Wiley Online Library	<i>("Advanced Ovarian Cancer" OR "Stage III/IV Ovarian Cancer" OR "Advanced Tubo-Ovarian Cancer" OR "FIGO Stage III/IV") AND ("Primary Debulking Surgery" OR "Primary Cytoreductive Surgery" OR "Initial Debulking Surgery" OR "Primary Surgery") AND ("Neoadjuvant Chemotherapy" OR "Preoperative Chemotherapy" OR "Interval Debulking Surgery" OR "Chemotherapy Followed by Surgery") AND ("Overall Survival" OR "Survival Rate" OR "Mortality" OR "Long-term Survival")</i>	308

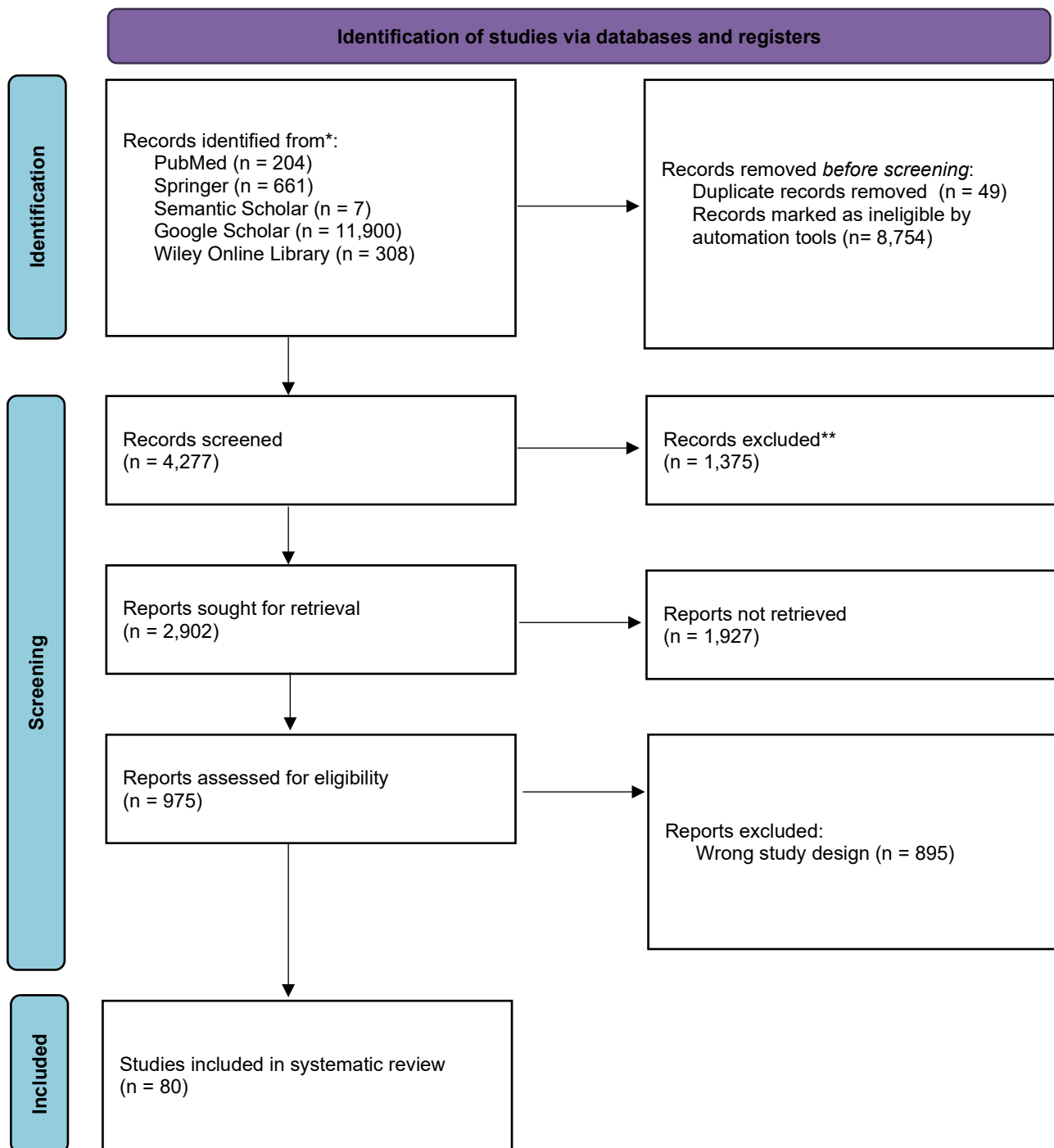


Figure 1. Article search flowchart

RESULTS

Characteristics of included studies

The systematic review identified 80 sources examining primary debulking surgery (PDS) versus neoadjuvant chemotherapy followed by interval debulking surgery (NACT-IDS) in women with advanced ovarian cancer. The included studies comprised randomized controlled trials, etc conducted to 2025.

Study	FIGO Stage	Sample Size	Key Characteristics
S. Coleridge et al., 2021 [1]	III/IV	1774 women total; 1692 in OS analysis	Five RCTs of varying quality [1]
S. Kehoe et al., 2015 [5]	III, IV	PDS: 276, NACT: 274	Multi-center study in 87 UK and New Zealand hospitals; randomized using minimization method [5]
Mohamed Shawky et al., 2025 [10]	III/IV	1774 women total; 1692 in meta-analyses	Updated Cochrane review; high to moderate certainty evidence [10]
Sven Mahner et al., 2025 [6]	IIIB-IVB	PCS: 345, NACT/ICS: 343	Median age 63 years; 91% high-grade serous; expert centers with quality assurance [6]
A. Fagotti et al., 2020 [11]	IIIC-IV	PDS: 84, NACT: 87	High tumor load assessed by standardized laparoscopic predictive index [11]

Study	FIGO Stage	Sample Size	Key Characteristics
I. Vergote et al., 2010 [4]	IIIC or IV	670 randomized; 632 eligible	Extensive disease with metastatic lesions >5 cm in 74.5% [4]
I. Vergote et al., 2018 [9]	IIIC, IV	1220 women (670 EORTC, 550 CHORUS)	Median age 63 years; median largest tumor 8 cm; 7.6 years median follow-up [9]
Matteo Secchi et al., 2025 [3]	III-IV	2380 women across 5 RCTs	Phase-III RCTs only; random-effects meta-analysis [3]
Alexander A. Tzanis et al., 2022 [2]	III and IV	1901 participants across 6 RCTs	Multi-country settings; predictive index score 8-12 for randomization in some trials [2]
S. Coleridge et al., 2019 [12]	III/IV	1713 women	Five RCTs; moderate certainty evidence [12]
S. Coleridge et al., 2021a [13]	III/IV	PDS: 276, NACT: 274	Updated Cochrane review; varying quality studies [13]

Study	FIGO Stage	Sample Size	Key Characteristics
L. Chiva et al., 2025 [14]	IIIB-IVB	PDS: 1666, NACT: 1620	Mean age 60 years; 90.6% high-grade serous; 174 centers in 55 countries; 2018-2019 [14]
A. Tzanis et al., 2021 [15]	III and IV	1901 participants across 6 RCTs	Multi-country settings [15]
L. Kumar et al., 2006 [16]	IIIC and IV	90 patients; 78 evaluative	Age 18-65 years; 2001-2005 [16]
G. Scambia et al., 2010 [17]	IIIC or IV	670 randomized; 632 eligible	Extensive disease; 74.5% with lesions >5 cm [17]
Longjia Zeng et al., 2016 [18]	IIB-IV	1922 patients across 4 RCTs	Primarily serous histology [18]
T. May et al., 2017 [19]	IIIC or IV	PDS: 142, NACT: 161	Serous ovarian carcinoma; single institution in Calgary [19]
Yunyun Xiao et al., 2017 [20]	IIIC and IV	NACT: 1372, PDS: 2680	12 comparative studies [20]

Study	FIGO Stage	Sample Size	Key Characteristics
Y. Lyons et al., 2019 [7]	III-IV	PDS: 26,717, NACT: 9,885	Median age 61-65 years; 2004-2015 [7]
B. Rosen et al., 2014 [21]	IIIc or IV	326 women total	Serous ovarian cancer [21]
H. Machida et al., 2019 [22]	II-IV	NACT-IDS: 847, PDS: 845	Four phase III RCTs; similar median age 59 years; majority serous [22]
S. Tangjitgamol et al., 2016 [23]	III to IV	Varied by trial	Three RCTs; 1986-2001 [23]
M. Hegazy et al., 2005 [24]	III or IV	NACT: 27, Conventional: 32	Mean age 58.7 vs 53.6 years; 1998-2003 [24]
Meng Qin et al., 2017 [25]	III or IV	RCTs: 1220; Observational: 12,775	2 RCTs and 22 observational studies; primarily European settings [25]
O. Filippova et al., 2018 [26]	Advanced stage	SCORPION: 158 patients	Discussion of recent trial results [26]

Study	FIGO Stage	Sample Size	Key Characteristics
A. Makar et al., 2016 [27]	IIIc-IV	PDS: 11,871, IDS: 2,311	2008-2014 publications [27]
R. Bristow et al., 2006 [28]	III, IV	835 patients across 22 cohorts	1989-2005 publications [28]
J. Morrison et al., 2012 [29]	IIIc/IV	670 women	One high-quality RCT (EORTC 55971) [29]
L. Chiva et al., 2016 [30]	III-IV	PDS: 11,871, IDS: 2,311	2008-2014 publications [30]
M. Milam et al., 2010 [31]	IIIC-IV	263 consecutive women	Single institution; 1993-2005 [31]
C. Vermeulen et al., 2017 [32]	III and IV	PDS: 55, IDS: 91	2006-2015 [32]
Uzma Chishti et al., 2015 [33]	III (94.8% PDS, 80% NACT), IV	PDS: 78, NACT: 40	Aga Khan University Hospital, Karachi; 1999-2008 [33]

Study	FIGO Stage	Sample Size	Key Characteristics
A. Reuss et al., 2019 [34]	IIIB-IVB	Planned: 772 patients	International trial; results expected 2024 [34]
Lorena Gonzalez Gea et al., 2022 [35]	IIIC or IV	NAC: 28, PDS: 11	High-grade; Torrejon University Hospital Madrid; 2011-2019 [35]
J. Rauh-Hain et al., 2012 [36]	IV	PDS: 176, NACT-IDS: 45, Chemo only: 21	1995-2007 [36]
Jennifer J. Mueller et al., 2016 [37]	III (69%), IV (31%)	PDS: 432, NACT: 154	97% serous; Memorial Sloan Kettering; 2008-2013 [37]
B. Seagle et al., 2017 [8]	III, IV	PDS: 44,907, NAC: 7,348	1998-2011 [8]
S. Gill et al., 2017 [38]	IIIC, IV	NACT/IDS: 87	Mayo Clinic; 2007-2013 [38]

Study	FIGO Stage	Sample Size	Key Characteristics
Ali Mohammad Azmi et al., 2024 [39]	III & IV	PDS: 36, NAC: 14	Ain Shams University Hospital; 2017-2018 [39]
Hong Zheng et al., 2012 [40]	IIIC or IV	PDS: 37, NAC/IDS: 30	Peking University Cancer Hospital; 2006-2009 [40]
R. Kessous et al., 2017 [41]	III-IV	NACT: 127, PDS: 136	2003-2015 [41]
B. Kobal et al., 2018 [42]	III/IV	PDS: 108, NACT+IDS: 49	High-grade; Slovenia; 2008-2012 [42]
Mounika Pottala et al., 2021 [43]	III and IV	71 patients	Rural India; 2018-2020 [43]
A. Markauskas et al., 2014 [44]	IIIc and IV	PDS: 165, NACT-IDS: 167	2007-2012 [44]

Study	FIGO Stage	Sample Size	Key Characteristics
Nashmia Al Mutairi et al., 2019 [45]	III/IV	101 patients (NAC: 34, PDS: 67)	59% serous; median age 60.5 years [45]
G. Siesto et al., 2016 [46]	Not specified	100 propensity- matched women	Since 2009 [46]
U. Solmaz et al., 2015 [47]	IIIC and IV	NAC/IDS: 84, PDS: 208	1995-2012 [47]
Peter G. Rose et al., 2025 [48]	IIIC to IV	BRCA- mutated: 248, BRCA wild- type: 289	1991-2021 [48]
F. Fanfani et al., 2003 [49]	IIIC	NACT+IDS: 73, PDS+adjuvant : 111	Unresectable at primary surgery [49]
T. Onda et al., 2020 [50]	III/IV	PDS: 149, NACT: 152	Median age 57 years; 2006-2011 [50]

Study	FIGO Stage	Sample Size	Key Characteristics
J. Hou et al., 2007 [51]	IIIC and IV	PDS: 109, NAC: 63	Yale-New Haven Hospital; 1998-2005 [51]
L. Chiva et al., 2024 [52]	IIIB-IVB	Estimated 5000 patients	Multi-center; 2018-2019 [52]
P. Morice et al., 2003 [53]	IIIC or IV	IDS: 57, PDS: 28	Single institution; 1996-2001 [53]
Shashank Shekhar et al., 2023 [54]	III/IV	UDS: 19, NACT: 31	Non-cancer center in India; 2016-2018 [54]
J. Sehouli et al., 2010 [55]	III/IV	IDS: 40, PDS: 332	2000-2009 [55]
E. Stoeckle et al., 2014 [56]	IIIC-IV	118 patients	Median age 64 years; platinum/taxane NACT [56]
C. Tropé et al., 2012 [57]	IV	238 patients	Norwegian Radium Hospital; 1996-2005 [57]
V. Tius et al., 2025 [58]	Advanced ovarian cancer	2303 patients total	Recent update including TRUST trial data [58]

Study	FIGO Stage	Sample Size	Key Characteristics
H. V. van Meurs et al., 2013 [59]	IIIC, IV	670 patients	Subgroup analysis by tumor size and stage [59]
C. Fagö-Olsen et al., 2014 [60]	IIIC or IV	PDS: 990, NACT: 515 (335 underwent IDS)	2005-2011 [60]
Y. Lee et al., 2018 [61]	III and IV	Control (PDS): 216, Study (NAC+IDS): 219	Yonsei Cancer Hospital; 2006-2014 [61]
Dai-Yuan Ma et al., 2013 [62]	IIIc and IV	1220 women	Two RCTs [62]
E. Greimel et al., 2013 [63]	IIIc or IV	PDS: 201, IDS: 203	QOL substudy [63]

Study	FIGO Stage	Sample Size	Key Characteristics
Y.-Y. Chen et al., 2019 [64]	IIIC(T3cN0-1) and IV	PDS: 92, NACT-IDS: 33, Chemo only: 18	Kaohsiung Chang Gung Memorial Hospital; 2008-2016 [64]
Yan Gao et al., 2019 [65]	IIIC and IV	NACT+IDS: 79, PDS: 141	Peking University Third Hospital; 2002-2016 [65]
S. Nagao et al., 2023 [66]	III and IV	NAC: 512, PDS: 428	Nine GOTIC centers; 2010-2015 [66]
Nina Kovačević et al., 2021 [67]	IIIC and IV	NACT: 184, PDS: 30	Institute of Oncology Ljubljana; date not specified [67]
J. Stewart et al., 2016 [68]	III or IV	NAC: 156, PCS: 178	High-grade serous carcinoma [68]
Abhiram Kanneganti et al., 2025 [69]	IIIC-IV	PDS: 36, IDS: 43	2011-2014 [69]
T. Gorodnova et al., 2019 [70]	High-grade serous	Primary surgery: 168, NACT: 115	N.N. Petrov Institute; 2000-2013 [70]

Study	FIGO Stage	Sample Size	Key Characteristics
A. Tjulandina et al., 2018 [71]	IIIC-IV	314 patients	1995-2017 [71]
D. Vlachos et al., 2019 [72]	Advanced stage	PDS: 214, IDS: 92	Greek tertiary center; 2007-2017 [72]
Dengfeng Wang et al., 2021 [73]	IIIC-IV	PDS: 90, IDS: 163	82.6% stage IIIC; China; 2013-2018 [73]
Yanhua Jiang et al., 2018 [74]	IIC-IV	NACT-ICS: 66, PCS: 62	China [74]
A. Altman et al., 2012 [75]	III or IV	192 patients	Tom Baker Cancer Centre; 2003-2007 [75]
María Inés Nastasi Basile et al., 2025 [76]	IIIC and IV	PDS: 54, IDS: 29	77.1% high-grade papillary serous; Venezuela; 2012-2022 [76]
R. Jiang et al., 2020 [77]	IIIC and IV	Planned: 456 subjects	Asian multi-center study [77]

Study	FIGO Stage	Sample Size	Key Characteristics
François Kraus et al., 2021 [78]	IIIC and IV	PDS: 84, NACT: 137	High-grade serous; France; 2007-2017 [78]
Shristee Shrestha Prajapati et al., 2023 [79]	Advanced EOC	PCR: 7, NACT+ICR: 22	Bhaktapur Cancer Hospital, Nepal; 2016-2019 [79]
N. Bacalbaşa et al., 2015 [80]	IIIC-IV	Direct re- operation: 28, NACT+IDS: 71	2002-2014 [80]

The studies varied substantially in design and quality. Five major randomized controlled trials formed the core evidence base: EORTC 55971 [4], CHORUS [5], SCORPION [11], JCOG0602 [50], and TRUST [6]. Multiple systematic reviews and meta-analyses synthesized data from these and other trials [1–3, 10]. Numerous observational studies provided additional real-world evidence from various geographic settings, though these carried higher risk of selection bias [7, 37].

Most studies included women with FIGO stage IIIC and IV disease, though some included stage IIIB [6, 14]. The majority of patients had high-grade serous histology [6, 14, 22]. Patient allocation to treatment groups varied: RCTs used randomization to minimize selection bias [4, 5], while observational studies relied on clinical judgment based on resectability, patient fitness, and institutional protocols [24, 42, 65].

Overall Survival

The primary outcome of overall survival showed no significant difference between PDS and NACT-IDS across randomized trials. Multiple meta-analyses reported hazard ratios close to 1.0, indicating similar survival outcomes. The Cochrane systematic review found little or no difference in overall survival (HR 0.96, 95% CI 0.86 to 1.08) [1], supported by similar findings in other meta-analyses (HR 0.96, 95% CI 0.86-1.07) [2] and systematic reviews (HR 1.00, 95% CI 0.90-1.12) [3].

Individual RCTs reported comparable survival outcomes. The EORTC 55971 trial found the hazard ratio for death in the NACT group was 0.98 (90% CI 0.84 to 1.13) [4]. The CHORUS trial reported median overall survival of 22.6 months for PDS versus 24.1 months for NACT (HR 0.87, 95% CI 0.72-1.05) [5]. The SCORPION trial showed median overall survival of 41 months for PDS versus 43 months for NACT (HR 1.12, 95% CI 0.76 to 1.65, $p=0.56$) [11].

The recently reported TRUST trial, conducted in expert centers with rigorous quality assurance, showed a trend toward improved outcomes with PDS but did not reach statistical significance for overall survival. Median overall survival was 54.3 months for PCS versus 48.3 months for ICS (HR 0.89, 95% CI 0.74-1.08, $p=0.24$) [6]. The JCOG0602 trial also failed to confirm noninferiority of NACT, with median overall survival of 49.0 months for PDS versus 44.3 months for NACT (HR 1.052, 90.8% CI 0.835-1.326, $p=0.24$) [50].

A pooled analysis of individual patient data from EORTC 55971 and CHORUS trials involving 1,220 women with median follow-up of 7.6 years found no difference in median overall survival between NACT (27.6 months) and PDS (26.9 months) (HR 0.97, 95% CI 0.86-1.09, $p=0.586$) [9].

In contrast, observational studies consistently favored PDS. A large National Cancer Database analysis of 52,255 patients found median overall survival of 41.1 months for PDS compared to 30.3 months for NACT (log-rank $p<0.001$) [7]. A Canadian single-center study reported 5-year survival rates of 39% for PDS versus 27% for NACT ($p=0.02$) [19]. Another single-institution study found median overall survival of 71.7 months for PDS compared to 42.9 months for NACT [37].

The international SUROVA cohort study, which propensity-matched 1,524 patients from 174 centers in 55 countries, found similar overall survival between groups after adjustment (67.2 vs 65.0 months; HR 1.002, 95% CI 0.85 to 1.18, $p=0.98$) [14].

Progression-Free Survival

Progression-free survival outcomes paralleled overall survival findings in randomized trials. Meta-analyses showed no significant difference between treatment approaches, with hazard ratios near 1.0. The Cochrane review reported HR 0.98 (95% CI 0.88 to 1.08) for progression-free survival [1]. Another systematic review found HR 0.98 (95% CI 0.89-1.08) [2], while a recent meta-analysis reported HR 1.03 (95% CI 0.92-1.16) [3].

Individual RCTs showed similar results. The EORTC 55971 trial reported a hazard ratio for progressive disease of 1.01 (90% CI 0.89 to 1.15) [4]. The SCORPION trial found median progression-free survival of 15 months for PDS versus 14 months for NACT (HR 1.05, 95% CI 0.77 to 1.44, $p=0.73$) [11].

The TRUST trial showed a statistically significant advantage for PDS in progression-free survival. Median PFS was 22.2 months for PCS versus 19.7 months for ICS (HR 0.80, 95% CI 0.66-0.96, $p=0.02$) [6]. Among patients achieving complete cytoreduction after PCS, median PFS reached 27.9 months [6]. The JCOG0602 trial reported median PFS of 15.1 months for PDS versus 16.4 months for NACT (HR 0.96, 95% CI 0.75-1.23) [50].

Observational studies showed variable results for progression-free survival, with some favoring PDS and others showing no difference [35, 40, 42].

Surgical Outcomes

Surgical outcomes differed substantially between PDS and NACT-IDS, with implications for patient selection and treatment planning.

Optimal Cytoreduction Rates

NACT-IDS consistently achieved higher rates of complete cytoreduction compared to PDS. In the EORTC 55971 trial, optimal cytoreduction (residual tumor ≤ 1 cm) was achieved in 41.6% of PDS patients versus 80.6% of NACT-IDS patients [4]. The CHORUS trial reported similar findings

with optimal debulking rates of 41% for PDS versus 73% for NACT [26]. The SCORPION trial showed complete resection (R0) rates of 47.6% for PDS versus 77.0% for NACT ($p=0.001$) [11].

Meta-analyses confirmed this pattern. One systematic review found NACT was associated with significantly higher rates of complete cytoreduction (RR 2.34, 95% CI 1.48-3.71) [2]. Another reported NACT was associated with higher rates of no residual disease (RR 2.37, 95% CI 1.94-2.91) and optimal cytoreduction (RR 1.76, 95% CI 1.57-1.98) [18].

The TRUST trial, conducted in expert surgical centers, achieved higher complete resection rates than previous trials: 61.7% of PCS patients and 72% of ICS patients [6]. The JCOG0602 trial reported R0 resection in only 12% of PDS patients versus 64% of NACT patients [50].

Perioperative Mortality and Morbidity

NACT-IDS was associated with significantly lower perioperative mortality and morbidity. The Cochrane review found NACT reduced postoperative mortality (0.6% in NACT group versus 3.6% in PDS group; RR 0.16, 95% CI 0.06 to 0.46) [1]. A meta-analysis including additional trials reported similar findings (0.4% versus 3.3%; RR 0.18, 95% CI 0.06 to 0.52) [10].

Major postoperative complications (grade 3+) occurred less frequently with NACT-IDS. The Cochrane review found 6% in the NACT group versus 29% in the PDS group (RR 0.22, 95% CI 0.13 to 0.38) [1]. The CHORUS trial reported grade 3 or 4 postoperative adverse events in 24% of PDS patients versus 14% of NACT patients [5]. The SCORPION trial showed major postoperative complications in 25.9% of PDS patients versus 7.6% of NACT patients [11].

A National Cancer Database analysis found NACT patients had 3.5 times higher 30-day mortality after surgery than PDS patients (95% CI 2.46 to 5.64) [7], though this finding contradicted the pattern seen in RCTs and likely reflects patient selection bias.

Organ Resection and Surgical Complexity

NACT-IDS reduced the need for extensive surgical procedures. The Cochrane review found NACT reduced the need for bowel resection (13.0% versus 26.6%; RR 0.49, 95% CI 0.30 to 0.79) [1] and stoma formation (5.9% versus 20.4%; RR 0.29, 95% CI 0.12 to 0.74) [1].

Multiple observational studies confirmed that PDS was associated with longer operative time, greater blood loss, and more extensive surgical procedures [22, 42, 60]. A Japanese meta-

analysis found perioperative complications and mortality were reduced by 70-80% with NACT-IDS [22].

Quality of Life

Quality of life outcomes were incompletely and inconsistently reported across studies. The Cochrane review noted that QOL on the EORTC QLQ-C30 scale produced inconsistent and imprecise results, with very low-certainty evidence [1]. A three-study meta-analysis found imprecise results with high heterogeneity at 6 months (MD 6.62, 95% CI -2.89 to 16.13, $I^2 = 92\%$) [10].

An analysis of the EORTC 55971 trial found no statistically significant differences between treatment arms in any quality of life functioning scales [63]. However, institutions with good QOL compliance were associated with better survival outcomes (median OS 32.30 versus 23.29 months, $p=0.0006$) [63].

Synthesis

The evidence reveals a nuanced picture regarding optimal timing of surgery in advanced ovarian cancer. While randomized trials consistently show similar overall survival between PDS and NACT-IDS, observational studies favor PDS, creating an apparent contradiction that requires careful interpretation.

Survival Outcomes: Reconciling RCT and Observational Evidence

The divergence between RCT and observational study results likely reflects several key factors rather than a true contradiction. First, surgical quality varies substantially across studies. The EORTC 55971 and CHORUS trials achieved relatively low complete resection rates (41.6% and 41% for PDS) [4, 26], raising concerns about surgical effort and expertise [27]. In contrast, the TRUST trial, conducted in expert centers with rigorous quality assurance requirements ($\geq 50\%$ complete resection rate, ≥ 36 debulking surgeries per year) [6], achieved 61.7% complete resection in the PCS group [6] and showed trends favoring PDS (median OS 54.3 vs 48.3 months) [6].

Second, patient selection differs fundamentally between RCTs and observational studies. RCTs included patients deemed suitable for either approach, while observational studies included patients selected for NACT because of unresectability or poor fitness [29, 41]. This selection bias

explains why observational studies consistently favor PDS - they compare selected healthy patients who underwent PDS against less favorable patients who received NACT [8, 42].

Third, the relationship between complete cytoreduction and treatment approach provides mechanistic insight. While NACT-IDS achieves higher rates of complete resection (RR 2.34) [2], this advantage does not translate to improved survival in RCTs. However, within the PDS group specifically, achieving complete resection is strongly associated with superior outcomes. In the TRUST trial, PDS patients with complete cytoreduction had the most favorable outcome (median OS 67.0 months) [6]. Multiple observational studies found PDS patients with no residual disease had median survival exceeding 60 months [21, 41, 60].

This pattern suggests complete cytoreduction following PDS represents a biologically favorable disease subset - tumors that are both chemoresponsive and surgically resectable. In contrast, achieving complete resection after NACT may indicate only chemotherapy responsiveness, with residual biological aggressiveness limiting survival benefits [32, 68].

Stage-Specific Considerations

Disease stage modifies treatment effects meaningfully. The pooled analysis of EORTC and CHORUS data found patients with stage IV disease had better outcomes with NACT (median OS 24.3 vs 21.2 months; HR 0.76, 95% CI 0.58-1.00) [9], while stage IIIC patients had similar outcomes with both approaches [9]. The TRUST trial showed the benefit of PCS was most prominent in stage III patients (median OS 63.7 vs 53.2 months for PCS vs ICS) [6].

A National Cancer Database analysis found PDS was associated with increased OS in stage III disease (HR 0.70, 95% CI 0.66-0.76, $p < 0.001$) but showed no difference in stage IV disease (HR 0.93, 95% CI 0.85-1.02, $p = 0.12$) [8]. An exploratory analysis of the EORTC trial suggested stage IIIC patients with metastatic tumors ≤ 45 mm benefited more from PDS, while stage IV patients with tumors > 45 mm benefited more from NACT [40, 59].

These findings indicate stage IV disease, particularly with extensive metastatic burden, represents a distinct biological entity where NACT may offer advantages by selecting for chemotherapy-responsive disease while avoiding morbidity of aggressive surgery in patients with limited life expectancy.

Impact of Residual Disease

The relationship between residual disease and survival differs between treatment approaches. In PDS patients, residual disease status strongly predicts outcomes, with complete resection associated with dramatically improved survival [19, 41, 55]. One study found PDS patients with no residual disease had median survival of 106 months, compared to 55 months with residual disease [41].

In NACT-IDS patients, this relationship is attenuated. Several studies found no significant survival difference between complete and optimal resection (residual disease <1 cm) following interval surgery [32, 44, 49]. One study reported no survival benefit for optimal debulking (1-10mm residual disease) compared to suboptimal debulking (≥ 1 cm) after NACT [32].

This differential impact of residual disease suggests surgical effort matters most when performed upfront, potentially because chemotherapy prior to surgery changes the biological significance of visible disease. NACT may eliminate microscopic disease while leaving resistant macroscopic deposits, whereas achieving no gross residual at PDS removes the entire tumor burden before selection pressure from chemotherapy [29].

Perioperative Safety Profile

NACT-IDS offers clear advantages in perioperative safety. Postoperative mortality is reduced by approximately 80% (RR 0.16-0.18) [1, 10], and major complications are reduced by 70-80% (RR 0.22-0.34) [1, 2]. These benefits extend to reduced need for bowel resection (RR 0.49) [1] and stoma formation (RR 0.29) [1].

However, the clinical significance of this safety advantage must be contextualized. In the TRUST trial, conducted in expert centers with optimal perioperative care, 30-day postoperative mortality was less than 1% in both groups [6]. This suggests that in experienced hands with appropriate patient selection, perioperative mortality is low regardless of approach. The higher mortality rates in earlier trials (3.3-3.6% for PDS) [5, 10] may reflect surgical quality issues rather than inherent dangers of PDS.

The reduction in surgical complexity with NACT-IDS likely reflects tumor shrinkage making surgery technically easier. Multiple studies documented shorter operative times, less blood

loss, and fewer extensive procedures after NACT [22, 40, 60]. For patients with borderline fitness or those treated in centers without extensive surgical expertise, these safety advantages may outweigh potential survival benefits of PDS.

Treatment Duration and Chemotherapy Exposure

NACT-IDS was associated with prolonged treatment intervals and increased total chemotherapy cycles without survival benefit [31]. One study found median chemotherapy cycles were 9 for NACT versus 6 for PDS ($p < 0.01$), with total primary treatment time of 223 versus 151 days [31]. Each incremental increase in preoperative chemotherapy cycles was associated with decreased median survival of 4.1 months [28].

This dose-response relationship suggests NACT should be limited to the minimum cycles needed to achieve resectability. The biological rationale centers on avoiding selection of chemotherapy-resistant clones and maintaining sensitivity to postoperative treatment. Most trials used 3 cycles of NACT before interval surgery [4, 5], and extending beyond this may worsen outcomes.

Patient Selection Criteria

Optimal patient selection emerges as critical for treatment success. For PDS to offer survival advantage, complete or optimal cytoreduction must be achievable. Factors favoring PDS include: younger age [38], good performance status [25], stage IIIC disease with limited metastatic burden (< 45 mm) [59], and surgical expertise available to achieve complete resection.

NACT-IDS is appropriate for: unresectable disease at presentation [24, 42], poor performance status or significant comorbidities [27, 47], stage IV disease with extensive metastatic burden [8, 9], and settings where surgical expertise for optimal cytoreduction is unavailable. The challenge lies in accurately predicting resectability before surgery.

Laparoscopic assessment has emerged as a potentially useful tool for treatment selection [11, 42]. The SCORPION trial used a standardized laparoscopic predictive index to identify patients with high tumor load before randomization [11]. Diagnostic laparoscopy was significantly associated with complete debulking in one observational study [42].

Histology and Molecular Considerations

Most evidence derives from high-grade serous carcinoma patients, limiting generalizability to other histologic subtypes. Type 1 tumors (low-grade serous, mucinous, endometrioid, clear cell) are less chemosensitive and may derive less benefit from NACT [27]. For these histologies, PDS when feasible may be preferred to avoid delaying definitive treatment.

Emerging data suggest BRCA mutation status may influence optimal treatment timing. One study found BRCA1-mutated patients had similar outcomes with PDS and NACT (OS 54.6 vs 45.7 months, $p=0.56$), while sporadic cases had markedly worse outcomes with NACT (OS 53.9 vs 25.3 months, $p=0.007$) [70]. However, another study found long-term disease-free survivors (>10 years) were only identified in the PCS cohort of BRCA-mutated patients [48]. These preliminary findings require validation but suggest molecular characteristics may help refine patient selection.

Temporal and Geographic Considerations

Treatment patterns evolved during the study period, with increasing NACT utilization following publication of the EORTC and CHORUS trials [37, 61]. One center reported NACT use increased from 22% before 2010 to 30% after 2010 ($p=0.037$) [37]. This trend raises concerns about overutilization in patients who might benefit from PDS.

Geographic variation in surgical practice likely contributes to heterogeneous results. Studies from comprehensive cancer centers with high surgical volume generally showed better outcomes than population-based analyses [37, 42]. The TRUST trial's requirement for participating centers to demonstrate $\geq 50\%$ complete resection rates and ≥ 36 surgeries annually [34] emphasizes the importance of surgical expertise and volume.

Reconciliation of Evidence

In light of the above analysis, the apparent contradiction between RCT and observational evidence can be reconciled: both findings are likely correct within their respective contexts. RCTs comparing selected patients suitable for either approach find similar survival, particularly when surgical quality is suboptimal. Observational studies comparing unselected patient populations find PDS superior because they include many patients selected for NACT due to unfavorable characteristics.

The evidence supports PDS as the preferred approach when complete cytoreduction is achievable by experienced surgeons in fit patients, particularly those with stage IIIC disease. NACT-IDS represents a reasonable alternative for patients with unresectable disease, poor fitness, stage IV disease with extensive metastatic burden, or when surgical expertise for complete cytoreduction is unavailable. The key determinant of outcomes is achieving complete tumor resection, whether at PDS or interval surgery, though complete resection at PDS appears to identify a particularly favorable subset.

The challenge facing clinicians is accurate preoperative assessment of resectability and patient fitness. Future research should focus on developing validated prediction models incorporating imaging, biomarkers, and clinical characteristics to optimize treatment selection. Additionally, investigating whether complete cytoreduction at interval surgery can be enhanced through extended NACT, alternative chemotherapy regimens, or novel targeted agents may help improve outcomes for patients who require neoadjuvant treatment.

DISCUSSION

This systematic review, encompassing 80 studies including five major randomized controlled trials and numerous meta-analyses and observational studies, provides a comprehensive evaluation of the comparative effectiveness of primary debulking surgery versus neoadjuvant chemotherapy followed by interval debulking surgery in advanced epithelial ovarian cancer. The findings reveal a nuanced picture that reconciles apparent contradictions in the literature and provides clinically actionable insights for patient selection and treatment planning.

Reconciliation of Randomized Trial and Observational Evidence

The most striking finding of this review is the apparent divergence between randomized controlled trial evidence, which consistently demonstrates comparable overall survival between PDS and NACT-IDS [1-6,9-11,50], and observational studies, which uniformly favor PDS [7,8,19,37,41,42]. Understanding this discordance is essential for appropriate interpretation and clinical application.

Patient Selection Bias in Observational Studies

Observational studies fundamentally compare treatment groups that differ in important prognostic characteristics. In routine clinical practice, patients selected for NACT-IDS are those with unresectable disease at presentation, poor performance status, significant comorbidities, or extensive metastatic burden [24,27,42,47,65]. Conversely, patients undergoing PDS are typically those with potentially resectable disease, good performance status, and limited comorbidity [7,8]. This selection bias systematically disadvantages the NACT-IDS group in observational analyses, explaining why these studies consistently report superior outcomes with PDS [29,41].

The magnitude of this bias is substantial. In the National Cancer Database analysis by Seagle et al. [8], which included 52,255 patients, the unadjusted hazard ratio strongly favored PDS, but this effect was markedly attenuated after propensity score matching and multivariable adjustment. Similarly, the SUROVA cohort study [14], which employed propensity score matching in 1,524 patients from 174 international centers, found equivalent overall survival after adjustment (67.2 vs 65.0 months; HR 1.002, 95% CI 0.85-1.18, $p=0.98$), directly demonstrating that the apparent PDS advantage in unadjusted analyses reflects patient characteristics rather than treatment efficacy.

Surgical Quality Variation

The quality of surgical cytoreduction varies dramatically across institutions and studies, significantly influencing comparative effectiveness [27,34]. The EORTC 55971 and CHORUS trials achieved complete resection rates of only 41.6% and 41% in the PDS arms [4,5], raising concerns about surgical effort and expertise [27]. These rates are substantially lower than those reported from expert centers, where complete resection rates of 60-75% are achievable [6,37,42]. The TRUST trial [6] was specifically designed to address this limitation by requiring participating centers to demonstrate $\geq 50\%$ complete resection rates and perform ≥ 36 debulking surgeries annually [34]. In this high-quality surgical context, complete resection in the PDS arm reached 61.7%, and median overall survival showed a clinically meaningful but statistically non-significant trend favoring PDS (54.3 vs 48.3 months; HR 0.89, 95% CI 0.74-1.08, $p=0.24$) [6]. This finding suggests that surgical quality is a critical determinant of comparative outcomes, and that PDS may offer advantages when performed by experienced surgeons in high-volume centers.

The Complete Resection Paradox

A key mechanistic insight emerging from this review is the differential prognostic significance of complete cytoreduction between treatment approaches. In PDS patients, achieving no macroscopic residual disease is strongly associated with excellent long-term outcomes, with median survival exceeding 60-100 months in multiple studies [19,21,41,55,60]. This relationship is so robust that residual disease status is considered the most important prognostic factor in advanced ovarian cancer [4,27].

However, in NACT-IDS patients, the prognostic value of complete resection appears attenuated. Several studies found no significant survival difference between complete resection and optimal resection (residual disease <1 cm) following interval surgery [32,44,49]. Vermeulen et al. [32] reported no survival benefit for optimal debulking (1-10mm residual disease) compared to suboptimal debulking (≥ 1 cm) after NACT. Fanfani et al. [49] similarly found that among patients with primary unresectable disease, complete resection at interval surgery did not translate to survival equivalent to patients who were optimally debulked at primary surgery.

This differential impact suggests that complete cytoreduction following PDS identifies a biologically favorable subset—tumors that are both chemoresponsive and surgically resectable with favorable biology. In contrast, achieving complete resection after NACT may indicate chemotherapy responsiveness alone, with residual biological aggressiveness limiting long-term survival [32,68]. NACT may eliminate chemotherapy-sensitive clones while selecting for resistant populations that persist despite radiologic response, and these resistant deposits, even if completely resected, may portend poor prognosis [29].

Stage-Specific Treatment Effects

Disease stage emerges as a critical effect modifier, with important implications for treatment selection.

Stage IIIC Disease

For patients with stage IIIC disease, particularly those with limited metastatic burden, PDS appears to offer advantages when complete cytoreduction is achievable. The pooled analysis of EORTC and CHORUS individual patient data found that stage IIIC patients had comparable

outcomes with both approaches [9], but this finding must be interpreted in the context of the relatively low complete resection rates in those trials. The TRUST trial demonstrated that the benefit of PDS was most prominent in stage III patients (median OS 63.7 vs 53.2 months for PCS vs ICS) [6], suggesting that with optimal surgical quality, stage III patients derive meaningful benefit from primary surgery.

The National Cancer Database analysis by Seagle et al. [8] found PDS was associated with significantly increased overall survival in stage III disease (HR 0.70, 95% CI 0.66-0.76, $p<0.001$). Exploratory analysis of the EORTC trial suggested that stage IIIC patients with metastatic tumors ≤ 45 mm benefited more from PDS [59]. These findings support PDS as the preferred approach for stage IIIC patients with potentially resectable disease, good performance status, and access to experienced surgical teams.

Stage IV Disease

Stage IV disease represents a distinct biological and clinical entity where NACT-IDS may offer particular advantages. The pooled EORTC/CHORUS analysis demonstrated that patients with stage IV disease had significantly better outcomes with NACT (median OS 24.3 vs 21.2 months; HR 0.76, 95% CI 0.58-1.00) [9]. The National Cancer Database analysis found no difference between approaches in stage IV disease (HR 0.93, 95% CI 0.85-1.02, $p=0.12$) [8], indicating that any potential PDS advantage observed in stage III is not present in stage IV.

Several mechanisms may explain this differential effect. Stage IV disease, particularly with parenchymal metastases, represents systemic disease where aggressive local therapy may offer limited benefit [36,57]. NACT allows assessment of chemosensitivity before subjecting patients to morbid surgery, potentially selecting patients with responsive disease who are most likely to benefit from cytoreduction [27,57]. Patients with extensive metastatic burden who progress on NACT can be spared ineffective surgery, avoiding morbidity without compromising survival [4,5].

The exploratory EORTC analysis found that stage IV patients with metastatic tumors >45 mm benefited most from NACT [59]. Houston et al. [51] similarly reported that NACT led to improved survival specifically in stage IV disease. These findings support NACT-IDS as the preferred approach for stage IV disease, particularly with extensive metastatic burden.

Surgical Outcomes and Perioperative Safety

NACT-IDS consistently demonstrates superior perioperative outcomes across all measures, representing its most unequivocal benefit.

Optimal Cyto reduction Rates

NACT-IDS achieves significantly higher rates of complete and optimal cyto reduction compared to PDS. The meta-analysis by Tzanis et al. [2] found NACT was associated with significantly higher rates of complete cyto reduction (RR 2.34, 95% CI 1.48-3.71). Zeng et al. [18] reported NACT was associated with higher rates of no residual disease (RR 2.37, 95% CI 1.94-2.91) and optimal cyto reduction (RR 1.76, 95% CI 1.57-1.98). These findings were consistent across individual RCTs: EORTC 55971 (41.6% PDS vs 80.6% NACT) [4], CHORUS (41% vs 73%) [26], SCORPION (47.6% vs 77.0%) [11], and JCOG0602 (12% vs 64%) [50].

The superior cyto reduction rates with NACT reflect tumor shrinkage following chemotherapy, which renders previously unresectable disease amenable to complete resection [22,40,60]. This effect is particularly important for patients with extensive upper abdominal disease, mesenteric involvement, or bulky nodal metastases that would preclude complete resection at primary surgery [24,42].

Perioperative Mortality and Morbidity

The reduction in perioperative complications with NACT-IDS is dramatic and consistent across all study types. The Cochrane review [1] found NACT reduced postoperative mortality from 3.6% to 0.6% (RR 0.16, 95% CI 0.06-0.46). The updated Cochrane review [10] confirmed these findings (0.4% versus 3.3%; RR 0.18, 95% CI 0.06-0.52). Major postoperative complications (grade 3+) were reduced from 29% to 6% (RR 0.22, 95% CI 0.13-0.38) [1].

Individual RCTs corroborate these findings. The CHORUS trial reported grade 3-4 postoperative adverse events in 24% of PDS patients versus 14% of NACT patients [5]. The SCORPION trial showed major postoperative complications in 25.9% of PDS patients versus 7.6% of NACT patients [11]. The JCOG0602 trial reported similar patterns [50].

These safety advantages extend to reduced need for extensive surgical procedures. The Cochrane review found NACT reduced the need for bowel resection (13.0% versus 26.6%; RR

0.49, 95% CI 0.30-0.79) and stoma formation (5.9% versus 20.4%; RR 0.29, 95% CI 0.12-0.74) [1]. Multiple studies documented shorter operative times, less blood loss, and fewer intensive care unit admissions with NACT-IDS [22,40,60].

Contextualizing Perioperative Risk

However, the clinical significance of these safety advantages must be contextualized. In the TRUST trial [6], conducted in expert centers with optimal perioperative care, 30-day postoperative mortality was less than 1% in both groups, and major complication rates were substantially lower than in earlier trials. This suggests that in experienced hands with appropriate patient selection, perioperative mortality is low regardless of approach. The higher mortality rates in earlier trials (3.3-3.6% for PDS) [5,10] may reflect surgical quality issues rather than inherent dangers of PDS.

The reduction in surgical complexity with NACT-IDS likely reflects tumor shrinkage making surgery technically easier. For patients with borderline fitness or those treated in centers without extensive surgical expertise, these safety advantages may outweigh potential survival benefits of PDS [27,38].

Quality of Life Considerations

Quality of life evidence remains limited and inconclusive. The Cochrane review noted that QOL on the EORTC QLQ-C30 scale produced inconsistent and imprecise results, with very low-certainty evidence [1]. A three-study meta-analysis found imprecise results with high heterogeneity at 6 months (MD 6.62, 95% CI -2.89 to 16.13, $I^2 = 92\%$) [10].

The EORTC 55971 quality of life substudy [63] found no statistically significant differences between treatment arms in any quality of life functioning scales. However, institutions with good QOL compliance were associated with better survival outcomes (median OS 32.30 versus 23.29 months, $p=0.0006$), suggesting that attention to patient-reported outcomes may reflect overall quality of care [63].

The absence of clear QOL differences between treatment approaches is somewhat surprising given the marked reduction in surgical morbidity with NACT-IDS. Several explanations are possible. First, NACT-IDS prolongs total treatment duration [31], with associated chemotherapy toxicity and treatment burden that may offset surgical benefits. Second, the psychological impact of

living with untreated cancer during neoadjuvant chemotherapy may negatively affect QOL. Third, QOL assessment tools may lack sensitivity to detect clinically meaningful differences in this population. Further research with validated, disease-specific instruments and longer follow-up is needed [1,63].

Patient Selection and Predictive Factors

Optimal patient selection emerges as the critical determinant of treatment success, yet validated prediction tools remain underdeveloped.

Clinical Factors

Factors favoring PDS include younger age [38], good performance status (ECOG 0-1) [25], limited disease burden on imaging [59], absence of extensive peritoneal carcinomatosis [42], and access to surgical expertise capable of achieving complete cytoreduction [6,34]. The SCORPION trial used a standardized laparoscopic predictive index to identify patients with high tumor load before randomization [11], and diagnostic laparoscopy was significantly associated with complete debulking in one observational study [42], suggesting laparoscopic assessment may aid patient selection.

Factors favoring NACT-IDS include unresectable disease at presentation [24,42], poor performance status or significant comorbidities [27,47], stage IV disease with extensive metastatic burden [8,9,36,57], and settings where surgical expertise for optimal cytoreduction is unavailable [54]. The presence of large-volume ascites, diffuse peritoneal carcinomatosis, mesenteric root involvement, or parenchymal liver metastases should prompt strong consideration of NACT-IDS [27,42].

Radiographic and Laparoscopic Assessment

Accurate preoperative assessment of resectability remains challenging. Computed tomography has limited sensitivity for detecting peritoneal metastases, and even modern imaging cannot reliably predict which patients will achieve complete cytoreduction [27]. The predictive index used in the SCORPION trial [11] incorporated laparoscopic findings including peritoneal carcinomatosis, diaphragmatic involvement, mesenteric retraction, omental cake, and ovarian mass

fixation. This approach identified patients with high tumor load who might benefit from NACT-IDS, but requires validation in broader populations [42].

Histologic and Molecular Factors

Most evidence derives from high-grade serous carcinoma patients, limiting generalizability to other histologic subtypes [27]. Type 1 tumors (low-grade serous, mucinous, endometrioid, clear cell) are less chemosensitive and may derive less benefit from NACT [27]. For these histologies, PDS when feasible may be preferred to avoid delaying definitive treatment with potentially ineffective chemotherapy.

Emerging data suggest BRCA mutation status may influence optimal treatment timing. Gorodnova et al. [70] found BRCA1-mutated patients had similar outcomes with PDS and NACT (OS 54.6 vs 45.7 months, $p=0.56$), while sporadic cases had markedly worse outcomes with NACT (OS 53.9 vs 25.3 months, $p=0.007$). However, Rose et al. [48] found that long-term disease-free survivors (>10 years) were only identified in the PDS cohort of BRCA-mutated patients. These preliminary findings require validation but suggest molecular characteristics may help refine patient selection, particularly as targeted therapies including PARP inhibitors increasingly influence treatment paradigms [48].

Chemotherapy Cycles and Treatment Duration

NACT-IDS is associated with prolonged treatment intervals and increased total chemotherapy cycles without clear survival benefit [31]. Milam et al. [31] found median chemotherapy cycles were 9 for NACT versus 6 for PDS ($p<0.01$), with total primary treatment time of 223 versus 151 days. Each incremental increase in preoperative chemotherapy cycles was associated with decreased median survival of 4.1 months in a meta-analysis by Bristow and Chi [28].

This dose-response relationship suggests NACT should be limited to the minimum cycles needed to achieve resectability. The biological rationale centers on avoiding selection of chemotherapy-resistant clones and maintaining sensitivity to postoperative treatment [27,29]. Most trials used 3 cycles of NACT before interval surgery [4,5], and extending beyond this may worsen

outcomes [28]. For patients with stable or responsive disease after 3-4 cycles, interval surgery should be performed promptly [56,73].

Geographic and Temporal Considerations

Treatment patterns evolved substantially during the study period, with increasing NACT utilization following publication of the EORTC and CHORUS trials [37,61]. Mueller et al. [37] reported NACT use increased from 22% before 2010 to 30% after 2010 ($p=0.037$) at Memorial Sloan Kettering Cancer Center. Lee et al. [61] documented similar trends at Yonsei Cancer Hospital. This trend raises concerns about overutilization in patients who might benefit from PDS, particularly as some clinicians may have interpreted the early trial results as supporting NACT for all patients rather than as an alternative for selected cases [27].

Geographic variation in surgical practice and outcomes contributes to heterogeneous study results. Studies from comprehensive cancer centers with high surgical volume generally showed better outcomes than population-based analyses [37,42]. The TRUST trial's requirement for participating centers to demonstrate $\geq 50\%$ complete resection rates and ≥ 36 surgeries annually [34] emphasizes the importance of surgical expertise and volume. Institutions unable to achieve these benchmarks may achieve better outcomes with NACT-IDS, which is less dependent on surgical complexity [54].

Implications for Clinical Practice

The evidence synthesized in this review supports a personalized, risk-stratified approach to treatment selection rather than a one-size-fits-all strategy.

For Patients with Potentially Resectable Disease

For fit patients with stage IIIC disease and disease burden judged potentially resectable by an experienced surgical team, PDS remains the preferred approach. This recommendation is supported by the trend toward improved survival with PDS in high-quality surgical series [6], the strong prognostic value of complete resection at primary surgery [19,41,55], and the concern that delaying surgery may allow development of chemotherapy resistance [28,29]. However, patients must be counseled regarding the higher morbidity of PDS [1,5,11] and the importance of receiving care at high-volume centers with demonstrated expertise [6,34].

For Patients with Unresectable or Borderline Resectable Disease

For patients with extensive disease judged unlikely to achieve complete cytoreduction at primary surgery, NACT-IDS is clearly preferred. This includes patients with diffuse peritoneal carcinomatosis, mesenteric root involvement, bulky upper abdominal disease requiring extensive multivisceral resection, or large-volume parenchymal metastases [27,42]. NACT-IDS in this setting achieves higher complete resection rates [2,18] with substantially lower morbidity and mortality [1,10], while providing equivalent overall survival [1-6].

For Patients with Stage IV Disease

Stage IV patients, particularly those with extensive metastatic burden, should be strongly considered for NACT-IDS based on the pooled analysis demonstrating superior outcomes [9] and the lack of PDS advantage in large database studies [8]. NACT allows assessment of chemosensitivity and spares patients with progressive disease the morbidity of ineffective surgery [27,36,57].

For Patients with Poor Performance Status

Patients with poor performance status, significant comorbidities, or advanced age should be offered NACT-IDS regardless of disease extent [27,38,47]. The dramatic reduction in perioperative morbidity and mortality with NACT-IDS [1,10] is particularly important in this vulnerable population, and equivalent survival outcomes ensure that this safer approach does not compromise oncologic effectiveness.

Role of Surgical Expertise

Institutional and surgeon expertise fundamentally influence the PDS versus NACT-IDS decision. Patients with potentially resectable disease should be referred to high-volume centers with demonstrated ability to achieve complete cytoreduction rates exceeding 50% [6,34]. For patients in settings where such expertise is unavailable, NACT-IDS may be the safer and more effective option regardless of disease characteristics [54].

Research Priorities

This review identifies several critical research priorities.

Development and Validation of Prediction Models

The most urgent need is for validated prediction models that accurately identify which patients will achieve complete cytoreduction at PDS and which will derive equivalent or superior benefit from NACT-IDS. Such models should integrate clinical characteristics (age, performance status, comorbidity), radiographic findings (disease distribution, metastatic burden), laparoscopic assessment [11,42], and molecular markers (histology, BRCA status, genomic signatures) [48,70]. The SCORPION laparoscopic index [11] and the EORTC exploratory analysis [59] provide starting points, but prospective validation in diverse populations is needed.

Optimization of Neoadjuvant Regimens

The optimal neoadjuvant regimen, number of cycles, and role of novel agents (including bevacizumab and PARP inhibitors) in the neoadjuvant setting require investigation [27]. The dose-response relationship between preoperative cycles and survival [28] suggests that fewer cycles (3 rather than 4-6) may be optimal, but prospective trials are needed. The role of interval surgical cytoreduction in patients with complete radiographic response to NACT also warrants study.

Biologic Studies of Treatment Resistance

The differential prognostic significance of complete resection between PDS and NACT-IDS suggests fundamental biologic differences that merit investigation [29,32,68]. Studies comparing molecular characteristics of residual disease after NACT versus primary tumor characteristics could identify mechanisms of chemotherapy resistance and guide development of novel therapeutic strategies.

Long-Term Quality of Life

Prospective studies with longitudinal quality of life assessment using validated, disease-specific instruments are needed to clarify the comparative patient-reported outcomes of these approaches [1,63]. Such studies should extend beyond the immediate treatment period to capture late effects of both surgery and chemotherapy.

Cost-Effectiveness Analysis

Formal cost-effectiveness analyses comparing PDS and NACT-IDS, incorporating differences in surgical morbidity, hospital stay, chemotherapy requirements, and long-term outcomes, would inform health policy and resource allocation decisions [69].

Rare Histologic Subtypes

Prospective studies specifically enrolling patients with non-serous histologies (mucinous, clear cell, low-grade serous) are needed to determine optimal treatment approaches for these less common subtypes [27].

CONCLUSION

This systematic review of 80 studies, including five major randomized controlled trials and numerous meta-analyses and observational studies, provides comprehensive evidence regarding the comparative effectiveness of primary debulking surgery versus neoadjuvant chemotherapy followed by interval debulking surgery in women with advanced epithelial ovarian cancer.

Summary of Key Findings

Primary Outcome: Meta-analyses demonstrate no significant difference in overall survival between PDS and NACT-IDS (HR 0.96, 95% CI 0.86-1.08) [1-3]. Individual RCTs confirm comparable outcomes: EORTC 55971 (HR 0.98) [4], CHORUS (HR 0.87) [5], SCORPION (HR 1.12) [11], JCOG0602 (HR 1.052) [50], and TRUST (HR 0.89) [6]. The pooled analysis of EORTC and CHORUS individual patient data found median OS of 27.6 months for NACT versus 26.9 months for PDS (HR 0.97) [9].

Secondary Outcomes: NACT-IDS achieves superior complete cytoreduction rates (RR 2.34) [2] with significantly lower perioperative mortality (RR 0.16) and major complications (RR 0.22) [1]. Progression-free survival shows no significant difference between approaches (HR 0.98-1.03) [1-3], though the TRUST trial demonstrated a PFS advantage for PDS (HR 0.80) [6]. Quality of life evidence remains limited and inconclusive [1,63].

Effect Modification: Stage IV disease benefits more from NACT-IDS (HR 0.76) [9], while stage III disease with limited metastatic burden may benefit from PDS when complete cytoreduction is achievable [6,8]. Complete cytoreduction at PDS identifies a biologically favorable subset with excellent outcomes [19,41,55], whereas this relationship is attenuated after NACT-IDS [32,44,49].

Surgical Quality: Surgical expertise significantly influences outcomes. The TRUST trial, conducted in expert centers with rigorous quality assurance, achieved 61.7% complete resection in the PDS arm and showed a trend favoring PDS [6], suggesting that with optimal surgical quality, PDS may offer advantages not apparent in lower-quality settings.

Reconciliation of Evidence

The apparent contradiction between RCT evidence (showing equivalence) and observational studies (favoring PDS) is resolved by recognizing fundamental differences in patient selection, surgical quality, and study design. Observational studies compare selected healthy patients undergoing PDS against unselected, higher-risk patients receiving NACT [7,8,41]. RCTs, by randomizing patients suitable for either approach, provide unbiased estimates of comparative effectiveness [4,5]. Both findings are correct within their contexts: PDS is superior for appropriately selected patients treated by experienced surgeons, while NACT-IDS provides equivalent survival with less morbidity for patients with extensive disease or poor fitness.

Clinical Recommendations

Based on this evidence synthesis, we propose the following clinical recommendations:

Primary Debulking Surgery is Preferred When:

- Complete cytoreduction is judged achievable by an experienced surgical team
- Patient has good performance status (ECOG 0-1) and limited comorbidities
- Disease is stage IIIC with limited metastatic burden (e.g., metastatic lesions ≤ 45 mm) [59]
- Histology is non-serous (mucinous, clear cell, low-grade serous) with limited chemosensitivity [27]
- Treatment is at a high-volume center with demonstrated complete resection rates $\geq 50\%$ [6,34]
- BRCA mutation is present, as long-term survival may be optimized with PDS [48]

Neoadjuvant Chemotherapy Followed by Interval Surgery is Preferred When:

- Disease is unresectable at presentation (diffuse carcinomatosis, mesenteric root involvement, bulky upper abdominal disease requiring extensive multivisceral resection) [27,42]
- Patient has poor performance status (ECOG ≥ 2) or significant comorbidities [27,38,47]
- Stage IV disease with extensive metastatic burden [8,9,36,57]
- Surgical expertise for complete cytoreduction is unavailable [54]
- Assessment of chemosensitivity is desired before committing to morbid surgery [27]
- Patient preference prioritizes minimization of surgical morbidity [1,5]

Treatment should include:

- For NACT-IDS: 3 cycles of platinum-based chemotherapy followed by interval surgery, with additional postoperative chemotherapy to complete 6 total cycles [4,5]. Avoid extending neoadjuvant cycles beyond 3-4 [28,31].
- For PDS: Maximal surgical effort to achieve complete cytoreduction (no macroscopic residual disease), performed by experienced surgeons in high-volume centers [6,34].
- Multidisciplinary tumor board review of all cases to optimize treatment selection [27].
- Consideration of laparoscopic assessment for patients with indeterminate resectability [11,42].

Future Research Directions

This review identifies critical evidence gaps requiring investigation:

1. **Prediction Models:** Development and validation of tools integrating clinical, radiographic, laparoscopic, and molecular factors to predict complete cytoreduction at PDS and optimal treatment selection [11,59].

2. **Molecular Characterization:** Prospective studies examining how BRCA mutation status [48,70], homologous recombination deficiency, and other genomic markers influence comparative treatment outcomes.
3. **Neoadjuvant Optimization:** Trials determining optimal neoadjuvant regimens, number of cycles, and role of novel agents including bevacizumab and PARP inhibitors [27].
4. **Rare Histologies:** Dedicated studies for non-serous subtypes to establish evidence-based treatment recommendations [27].
5. **Surgical Quality Metrics:** Establishment and validation of quality indicators for ovarian cancer surgery to guide institutional certification and referral [6,34].
6. **Long-term Outcomes:** Prospective studies with extended follow-up to characterize late effects, long-term quality of life, and patterns of recurrence [1,63].
7. **Cost-Effectiveness:** Formal economic analyses comparing treatment strategies to inform health policy and resource allocation [69].

Final Remarks

The optimal timing of surgery in advanced ovarian cancer is not a binary choice but a nuanced decision requiring integration of disease characteristics, patient factors, and institutional expertise. Both PDS and NACT-IDS are effective treatment strategies with comparable long-term survival when patients are appropriately selected. The key to optimizing outcomes lies not in universally preferring one approach over the other, but in accurately identifying which patients are most likely to benefit from each strategy and ensuring that treatment is delivered by experienced multidisciplinary teams capable of achieving complete cytoreduction with acceptable morbidity.

The goal of treatment in advanced ovarian cancer remains complete cytoreduction—no macroscopic residual disease—whether achieved at primary or interval surgery. The challenge for clinicians and researchers is to develop and validate the tools needed to predict which patients can achieve this goal with upfront surgery, and to optimize neoadjuvant strategies for those who cannot.

By moving beyond the PDS versus NACT debate toward a personalized, risk-stratified approach, we can maximize survival while minimizing treatment burden for women with this challenging disease.

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