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Prehabilitation during neoadjuvant chemotherapy in advanced ovarian cancer is associated with improved surgical candidacy and chemotherapy outcomes

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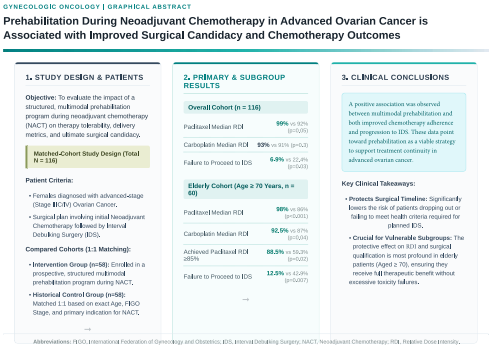
HIGHLIGHTS

- Prehabilitation during NACT was associated with improved chemotherapy delivery in OC.
- Higher IDS rates observed with prehabilitation vs matched controls.
- Benefits most pronounced in patients aged ≥70 years.
- Prehab reduced dose delays and reductions during NACT.
- Supports prehabilitation as a perioperative optimization strategy in OC.

GRAPHICAL ABSTRACT



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ABSTRACT

Objective. To evaluate the association between of a structured, multimodal prehabilitation program during neoadjuvant chemotherapy (NACT) on chemotherapy delivery, treatment tolerability, and surgical candidacy in patients with advanced-stage ovarian cancer (OC).

Methods. This was a matched-cohort study of patients with stage IIIC/IV OC receiving NACT at a single tertiary center. The intervention group participated in a prospective multimodal prehabilitation trial during NACT, and a historical control group was matched 1:1 based on age, FIGO stage, and indication for NACT. Primary endpoints included relative dose intensity (RDI) for carboplatin and paclitaxel and surgical outcomes.

Results. A total of 116 patients were included. In the overall cohort, median RDI was higher in the prehabilitation group for paclitaxel (99% vs. 92%, $p = 0.05$) and similar for carboplatin (93% vs. 91%, $p = 0.3$). The proportion achieving RDI ≥85% was 84.0% vs. 75.4% for paclitaxel ($p = 0.3$) and 74.1% vs. 65.5% for carboplatin ($p = 0.3$). Failure to proceed to interval debulking surgery (IDS) was lower in the prehabilitation group (6.9% vs. 22.4%, $p = 0.03$).

In patients aged ≥70 years ($n = 60$), prehabilitation was associated with higher median RDI for paclitaxel (98% vs. 86%, $p < 0.001$) and carboplatin (92.5% vs. 87%, $p = 0.04$), as well as a higher proportion achieving RDI ≥85% for paclitaxel (88.5% vs. 59.3%, $p = 0.02$). Failure to proceed to IDS was also lower (12.5% vs. 42.9%, $p = 0.007$).

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Conclusion. Multimodal prehabilitation during NACT was associated with improved chemotherapy delivery and higher rates of IDS, particularly in patients aged ≥70 years. These preliminary findings suggest a potential role for prehabilitation as a strategy to enhance treatment adherence in advanced OC.

1. Introduction

Ovarian cancer (OC) is the second most common gynecologic malignancy and the leading cause of gynecologic cancer–related death in the United States [1]. The median age at diagnosis is 63 years [2], with most patients presenting with advanced-stage disease [3]. The prognosis is poor, with five-year survival remaining below 50% [4]. According to current American Society of Clinical Oncology (ASCO) guidelines [5], primary cytoreductive surgery is the preferred initial treatment for patients who are medically fit, with complete cytoreduction being strongly associated with better outcomes [6]. For patients unlikely to achieve complete cytoreduction or at high risk of perioperative morbidity, neoadjuvant chemotherapy (NACT) is recommended prior to interval debulking surgery (IDS) [7]. The ability to proceed to IDS after NACT is itself a critical determinant of outcomes, yet a substantial proportion of patients never reach surgery due to clinical deterioration, treatment intolerance, or inadequate response to chemotherapy [8].

NACT is typically administered for three to four cycles, most commonly using a platinum–taxane doublet. The effectiveness of NACT, however, depends critically on delivering treatment at the planned dose and schedule [9]. Relative dose intensity (RDI), defined as the ratio of the dose intensity delivered compared to the standard recommended dose for a chemotherapy regimen [10], is commonly used to compare dose intensity and compliance, taking into account dose delays and reductions. A robust dose–response relationship has been demonstrated across multiple cancer types, with reduced RDI consistently associated with inferior tumor response and survival [11].

Maintaining an optimal RDI is often challenging, particularly among older, frail, and multimorbid OC patients [12]. These vulnerabilities increase susceptibility to chemotherapy-related toxicities—including hematologic complications, fatigue, and neuropathy—and contribute to functional decline during NACT [13]. In turn, this may further compromise performance status, limit chemotherapy delivery, and reduce surgical fitness. Consequently, a substantial proportion of patients with OC receive less than 85% of the intended chemotherapy dose, with rates approaching 60% in prior studies [14], especially among older or frail populations [15].

Prehabilitation, a structured, multimodal intervention integrating exercise, nutritional optimization, symptom management, and psycho-social support, has emerged as a promising strategy to enhance physiologic reserve prior to major surgeries [16,17]. By targeting modifiable determinants of resilience, including cardiorespiratory fitness, skeletal muscle mass, nutritional status, and psychological well-being, prehabilitation has been shown to improve surgical readiness and postoperative recovery across multiple surgical populations, including OC [18]. Many of these same factors are closely linked to chemotherapy tolerance, raising the question of whether prehabilitation might improve chemotherapy delivery. Although growing evidence supports the positive impact of exercise- and dietary-based interventions on chemotherapy tolerance in various malignancies [19,20], data in the OC population remain limited. Accordingly, the present study evaluates whether structured prehabilitation during NACT is associated with improved treatment tolerability, chemotherapy delivery, and the likelihood of proceeding to IDS in patients with OC.

2. Methods

2.1. Study design and eligibility criteria

This is an observational matched cohort study of OC patients who received NACT prior to IDS at Mayo Clinic. The intervention group consisted of patients who participated in a multimodal prehabilitation program delivered during the NACT period as part of a prospective, single-arm pilot trial between October 2021 and May 2024. The comparison group comprised a matched historical cohort of OC patients treated with NACT without prehabilitation between March 2018 and December 2022. For the current analysis, study outcomes were assessed retrospectively from the electronic health records (EHRs). No major institutional changes occurred during the study period with respect to systemic treatment protocols, surgical approach, or perioperative care pathways.

Eligible patients aged ≥18 years, with stage IIIC or IV epithelial OC, and received NACT. Patients with incomplete medical records, withdrew consent from the prehabilitation trials, or died during the NACT were excluded. These exclusions were applied to ensure complete ascertainment of study outcomes. The study was approved by the Mayo Clinic Institutional Review Board, and written consent was documented.

2.2. Prehabilitation intervention

Patients in the exposure group were identified from one of two prospective clinical trials of prehabilitation in advanced OC patients undergoing NACT (NCT05047926). Participants engaged in a structured prehabilitation program designed to support physical fitness, nutrition, and psychological well-being during NACT. The program combined aerobic exercise (e.g., walking 30 min per day, three days per week) with strength training through the REST program [21], nutrition counseling targeting 1.2–1.5 g/kg/day of protein intake, and psychological support through the Resilient Living Program® [22]. In the first trial, initial exercise and nutrition prescriptions were delivered on-site by clinical staff, with subsequent sessions conducted at home and supported by weekly contact with a study coordinator. In the second parallel trial, all education and prescriptions were delivered remotely, with patients receiving weekly virtual health coaching sessions from a clinical exercise physiologist. Although delivery modalities differed between the two trials, both interventions were standardized with respect to core components. Prehabilitation program was initiated at the start of NACT and continued until the time of IDS.

Patients in the control cohort received standard NACT without structured prehabilitation. Adherence to individual components of the prehabilitation program was recorded within the parent clinical trials but were not included in the current analysis. Reporting of the prehabilitation intervention was guided by the SOS-PREHAB recommendations [23].

2.3. Matching

To reduce baseline confounding, propensity scores were estimated using logistic regression based on age at diagnosis, disease stage (stage III vs. stage IV), and indication for NACT. Indication for NACT was categorized as patient-related factors, disease-related factors, or a combination of both, and was based on institutional algorithms

considering disease extent, albumin and age [8]. Patients in the prehabilitation group were then matched 1:1 to control patients using nearest-neighbor propensity score matching without replacement. All eligible patients from both cohorts were included in the matching pool, and unmatched patients were excluded.

2.4. Data extraction and study variables

Data was extracted from EHRs and included demographic, clinicopathological, and chemotherapy data. Demographic and clinicopathological data included age, race/ethnicity, body mass index (BMI), marital status, comorbidities, performance status (PS) (ECOG), FIGO disease stage, baseline laboratory values, tumor histology and BRCA status. Chemotherapy-related variables included regimen type, planned and delivered doses, scheduled and actual dates of each cycle, and the total number of cycles completed.

NACT regimens were administered according to institutional standards and physician discretion, using one of the following paclitaxel–carboplatin–based protocols:

1. Conventional regimen: carboplatin AUC 6 and paclitaxel 175 mg/m^2 intravenously every 3 weeks.
2. Dose-dense regimen: carboplatin AUC 6 every 3 weeks with paclitaxel 80 mg/m^2 intravenously on days 1, 8, and 15 of a 21-day cycle.
3. Weekly/MITO-7 regimen: carboplatin AUC 2 and paclitaxel 60 mg/m^2 intravenously on a weekly schedule.

Bevacizumab (15 mg/kg intravenously every 3 weeks) was administered at the discretion of the treating oncologist. Paclitaxel's dose calculations were excluded in patients who received carboplatin without paclitaxel as part of a clinical trial (NCT04606914) or who switched to carboplatin-based regimens containing agents other than paclitaxel. For patients transitioned to carboplatin with nab-paclitaxel, paclitaxel doses were considered full unless a reduction was documented. Patients enrolled in clinical trials received standard-of-care carboplatin–paclitaxel–based regimens consistent with institutional practice and were included in pooled analyses of study outcomes.

Cancelled chemotherapy cycles were recorded as both a dose reduction and a treatment delay. Treatment-related toxicities included febrile and severe neutropenia. Healthcare utilization data, including emergency department visits and hospitalizations during NACT, were also captured. Surgical details and outcomes were similarly documented.

2.5. Study objectives and definitions

The primary objective of this study was to evaluate the potential association of structured home-based prehabilitation during NACT on chemotherapy delivery and surgical outcomes. The primary endpoints were RDI over the entire planned NACT course of the carboplatin–paclitaxel regimen and surgical outcomes. RDI was calculated as the ratio of delivered to planned dose intensity (mg/m^2 per week) for each myelosuppressive agent separately. Planned carboplatin doses were determined using the Calvert formula (AUC 6), with an upper cap of 900 mg for weight and a lower cap of 0.7 mg/dL for baseline creatinine [24]. Paclitaxel doses were calculated based on body surface area using the Mosteller formula [25].

Delivered dose intensity for each agent was calculated from the actual administered doses and cycle intervals recorded in the EHRs. For each patient, the total delivered dose of each agent was divided by the total treatment duration (in weeks) to obtain the delivered dose intensity. RDI for each agent was then expressed as:

$$\text{RDI} = \frac{\text{Delivered dose intensity}}{\text{Planned dose intensity}} \times 100$$

An RDI below 85% was considered a clinically meaningful reduction based on prior studies [26]. Surgical outcomes were categorized as no surgery, complete cytoreduction (no gross residual disease), optimal cytoreduction (<1 cm residual disease), or suboptimal/aborted cytoreduction >1 cm residual disease or intraoperative termination due to unresectable disease). Aborted procedures were analyzed separately from the no-surgery group because these patients proceeded to the operating room and underwent intraoperative assessment before termination of the procedure. Additional outcomes included postoperative complications classified by the Clavien–Dindo system (none, minor [grades I–II], or major [grades III–V]) [27], postoperative blood transfusion requirements, unplanned intensive care unit (ICU) admission, length of hospital stay, and 30-day hospital readmission.

Secondary outcomes included chemotherapy tolerability and treatment response. Chemotherapy tolerability outcomes comprised of dose reductions (any decrease from the planned dose) and dose delays (treatments administered ≥7 days later than scheduled). Neutropenia was defined as an absolute neutrophil count (ANC) <1500/μL and graded according to CTCAE v5.0, with severe neutropenia classified as grade 3 (ANC 500–1000/μL), grade 4 (ANC <500/μL), and grade 5 (death) [28]. Febrile neutropenia was defined as neutropenia accompanied by a fever ≥38.3 °C (101 °F) or ≥ 38.0 °C (100.4 °F) sustained for more than 1 h. CA125 normalization was defined as a value below 46 U/mL, based on the institutional reference range. A post hoc subgroup analysis of patients aged ≥70 years was exploratory.

2.6. Statistical analysis

Descriptive statistics summarized patient demographics, clinical characteristics, chemotherapy regimens, and outcomes. Continuous variables were reported as mean ± standard deviation (SD) or median (interquartile range) (IQR) and compared using independent-samples *t*-tests or Mann–Whitney *U* tests. Categorical variables were summarized as counts and percentages and compared using Chi-square or Fisher's exact tests. Baseline covariate balance after propensity score matching was assessed using standardized mean differences (SMDs), with values <0.1 indicating adequate balance. To assess residual confounding, exploratory multivariable logistic regression analyses were performed for achieving an RDI >85% for both carboplatin and paclitaxel and for proceeding to IDS. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were reported. All tests were two-sided, with $p < 0.05$ considered statistically significant. Analyses were performed using R version 4.5.2 (R Foundation for Statistical Computing, Vienna, Austria), which was used for all statistical analyses conducted for the present manuscript.

3. Results

3.1. Patients' demographic and clinical characteristics

Seventy-four patients were initially identified in the prehabilitation cohort, of whom, seven were excluded due to missing chemotherapy records, eight withdrew from the prehabilitation trials and one died during NACT, yielding 58 patients available for inclusion. In the control cohort, 164 patients were identified; 45 were excluded due to missing chemotherapy data and one died during NACT. The remaining 118 patients were eligible for matching, from which 58 matched controls were selected for the final analysis (Supplementary Fig. 1). The mean age was 68.4 ± 9.3 years in the prehabilitation group and 67.8 ± 9.8 years in the control group ($p = 0.7$). Median baseline BMI was 28.3 kg/m^2 in the prehabilitation group versus 25.5 kg/m^2 in the control group ($p = 0.07$) (Table 1).

At diagnosis, most patients had good performance status (ECOG 0–1, 94.8%), with similar proportions in the prehabilitation and control

Table 1
Baseline demographic and clinical characteristics of the prehabilitation and control groups.*,***

Variable	Total Cohort n^* = 116	Prehab Group n = 58	Control Group n = 58	SMD	*P* value
Age: mean, (SD)	68.1 (9.5)	68.4 (9.3)	67.8 (9.8)	0.07	0.7[a]
Age Group:				0.14	0.5[e]
< 70-year-old	56 (48.3%)	26 (44.8%)	30 (51.7%)		
≥ 70-year-old	60 (51.7%)	32 (55.2%)	28 (48.3%)		
Race:				0.00	0.3[d]
White	110 (94.8%)	55 (94.8%)	55 (94.8%)		
Other	6 (5.1%)	3 (5.1%)	3 (5.1%)		
Ethnicity:				0.3	0.2[d]
Hispanic or Latina	2 (1.7%)	1 (1.7%)	1 (1.7%)		
NOT Hispanic, Latina	111 (95.7%)	54 (93.1%)	57 (98.3%)		
Choose not to disclose	3 (2.6%)	3 (5.2%)	0		
Marital Status				0.3	0.2[e]
Single	8 (6.9%)	3 (5.2%)	5 (8.6%)		
Married	82 (70.7%)	46 (79.3%)	41 (62.1%)		
Widowed	14 (12.1%)	4 (6.9%)	10 (17.2%)		
Divorced	12 (10.3%)	5 (8.6%)	7 (12.1%)		
BMI (kg/m^2): median, (IQR)	27.1 (17.9–48.4)	28.3 (17.9–48.4)	25.5 (19.1–44.1)	0.3	0.07[b]
Underweight and normal weight (<25)	40 (34.5%)	15 (25.9%)	25 (43.1%)		
Overweight (25–29.9)	40 (34.5%)	21 (36.2%)	19 (32.8%)	0.36	
Obese (≥30)	36 (31%)	22 (37.9%)	14 (24.1%)		
Performance status at enrollment:				0.16	0.7[d]
0–1	110 (94.8%)	56 (96.6%)	54 (93.1%)		
≥2	6 (5.2%)	2 (3.4%)	4 (6.9%)		
Comorbidities					
HTN	43 (37.1%)	23 (39.7%)	20 (34.5%)	0.1	0.6[e]
HLP	37 (31.9%)	24 (41.4%)	13 (22.4%)	0.4	**0.03**[e***]
Anxiety/Depression	23 (19.8%)	16 (27.6%)	7 (12.1%)	0.4	**0.04**[e]
CKD	3 (2.6%)	1 (1.7%)	2 (3.4%)	0.1	1[d]
DVT/PE	9 (7.8%)	5 (8.6%)	4 (6.9%)	0.06	0.7[e]
T2DM	10 (8.6%)	5 (8.6%)	5 (8.6%)	0.00	1[e]
CVD	24 (20.7%)	15 (25.9%)	9 (15.5%)	0.26	0.2[e]
None	28 (24.1%)	10 (17.2%)	18 (31%)	0.3	0.08[e]
FIGO stage:				0.00	1[e]
III	56 (48.3%)	28 (48.3%)	28 (48.3%)		
IV	60 (51.7%)	30 (51.7%)	30 (51.7%)		
Baseline Albumin (g/dL): mean, (SD)	3.7 (0.5)	3.7 (0.5)	3.6 (0.5)	0.08	0.7[a]
Baseline Albumin (g/dL):				0.18	0.3[e]
<3.5	41 (35.3%)	18 (31%)	23 (39.7%)		
≥3.5	75 (64.7%)	40 (69%)	35 (60.3%)		
Baseline Ca125 (U/mL): median, (IQR)	963 (26–28,337)	839 (61–12,152)	1134 (26–28,337)	0.21	0.2[b]
Histology				0.38	0.1[d]
Serous	112 (96.6%)	58 (100%)	54 (93.1%)		
Mixed	3 (2.6%)	–	3 (5.2%)		
Clear Cell	1 (0.9%)	–	1 (1.7%)		
BRCA status				0.19	0.6[d]
BRCA mutated	17 (14.7%)	9 (15.5%)	8 (13.8%)		
Negative	95 (81.9%)	48 (82.8%)	47 (81%)		
Unknown	4 (3.4%)	1 (1.7%)	3 (5.2%)		
Reason for NACT**				0.00	1[e]
Patient-related	28 (24.1%)	14 (24.1%)	14 (24.1%)		
Disease related	52 (44.8%)	26 (44.8%)	26 (44.8%)		
Both	36 (31%)	18 (31%)	18 (31%)		
Number of planned NACT cycles: (median, IQR)	3 (3–9)	3 (3–8)	4 (3–9)	0.18	0.4[b]
Planned NACT regimen				0.4	**0.01**[d]
Does Regular	84 (72.4%)	46 (79.3%)	38 (65.5%)		
Dose Dense	6 (5.2%)	1 (1.7%)	5 (8.6%)		
MITO7	19 (16.4%)	5 (8.6%)	14 (24.1%)		
Other	7 (6%)	6 (10.3%)	1 (1.7%)		
Bevacizumab?				0.33	0.08[e]
Yes	9 (7.8%)	7 (12.1%)	2 (3.4%)		
No	107 (92.2%)	51 (87.9%)	56 (96.6%)		

* BMI: Body Mass Index, CA-125: Cancer Antigen 125, CKD: Chronic Kidney Disease, CVD: Cardiovascular Disease, DVT/PE: Deep Vein Thrombosis / Pulmonary Embolism, HLP: Hyperlipidemia, HTN: Hypertension, NACT: Neoadjuvant Chemotherapy, SMD: Standardized Mean Difference, T2DM: Type 2 Diabetes Mellitus, IQR: Interquartile Range, n: Number of participants in a group, SD: Standard Deviation.

** NACT: Neoadjuvant Chemotherapy; Patient-related factors: include poor performance status, low albumin, frailty, or significant medical comorbidities; Disease-related factors: include high tumor burden, unresectable disease, or Stage IV involvement.

[a] Student's t-test (for mean/SD).

[b] Mann-Whitney U test (for median/IQR).

[d] Fisher's Exact test (for categorical data with small cell counts).

[e] Chi-square test (for larger categorical distributions).

*** Bold values indicate statistical significance ($P < 0.05$).

groups (96.6% vs. 93.1%, $p = 0.7$). Baseline albumin levels were within the normal range in 64.7% of patients, with a mean of 3.7 ± 0.5 g/dL and no difference between groups (p = 0.7). Median baseline CA-125 levels were 839 U/mL in the prehabilitation group versus 1134 U/mL in controls ($p = 0.2$). Comorbidities were common in both groups, present in 82.8% of patients in the prehabilitation group and 69.0% of controls ($p = 0.08$). Differences were observed in the prevalence of hyperlipidemia (41.4% vs. 22.4%, $p = 0.03$), and anxiety/depression (27.6% vs. 12.1%, $p = 0.04$).

Most tumors were of serous histology (100% in the prehabilitation group vs. 93.1% in controls, $p = 0.1$). BRCA mutation status was similar between cohorts, with 15.5% of prehabilitation patients and 13.8% of control patients harboring a germline BRCA mutation ($p = 0.6$). Most patients received conventional (72.4%), followed by weekly (16.4%) and dose dense regimen (5.2%). Six patients (10.3%) in the prehabilitation group received carboplatin–mirvetuximab and one control patient received carboplatin–paclitaxel plus metformin as part of clinical trials. Bevacizumab was administered to 12.1% of prehabilitation patients and 3.4% of controls ($p = 0.08$).

3.2. Study outcomes

Treatment delivery and study outcomes for the matched cohort are summarized in Table 2. The proportion of patients achieving RDI ≥85% was 74.1% for carboplatin and 84.0% for paclitaxel in the prehabilitation group, compared with 65.5% and 75.4% in the control group, respectively ($p = 0.3$ for both). Median RDI was 93% (IQR 58–100) versus 91% (63–100) for carboplatin (p = 0.3) and 99% (51–100) versus 92% (65–100) for paclitaxel ($p = 0.05$) in the prehabilitation and control groups, respectively.

Dose reductions occurred in 37.9% of prehabilitation patients and 50% of controls ($p = 0.2$), dose delays in 27.6% of prehabilitation patients versus 41.4% of controls ($p = 0.1$), and dose cancellations in 8.6% of prehabilitation patients versus 20.7% of controls ($p = 0.06$). NACT regimen changes were uncommon in both groups (8.6% vs 10.3%, $p = 1$). Febrile neutropenia occurred in 3.4% of prehabilitation patients and 1.7% of controls (p = 1), while severe neutropenia (Grade ≥ 3) was observed in 15.5% versus 27.6% (p = 0.1). The receipt of GM-CSF support and health care utilization including hospitalizations, and ED visits during NACT were similar between groups. VTE events were diagnosed in 12.1% of the prehabilitation group and 8.8% of the controls ($p = 0.6$). CA125 normalization at the end of NACT was achieved in 46.6% of prehabilitation patients and 43.1% of controls ($p = 0.7$).

A higher proportion of patients in the control group failed to proceed to IDS following NACT (no surgery rates of 6.9% vs. 22.4% in the prehabilitation and control groups, respectively, $p = 0.03$). Among those who underwent surgery, complete cytoreduction was achieved in 48.3% vs. 53.4%, optimal cytoreduction (<1 cm) in 31% vs. 19%, and suboptimal/aborted cytoreduction (>1 cm) in 13.8% vs. 5.2% in the prehabilitation and control groups, respectively. Among patients who did not proceed to IDS, most cases were attributed to disease-related factors (75% vs. 38.5%) in the prehabilitation cohort, whereas in the control group, the majority were due to poor surgical candidacy (46.2%), including frailty, comorbidities, malnutrition and impaired PS (Table 3). Postoperative complications were comparable between groups ($p = 0.9$). There were also no significant differences in blood transfusion rates, length of hospital stays, unplanned ICU admission, or 30-day readmission.

When considering the relationship between chemotherapy tolerance and ability to get to surgery, IDS rates were higher among patients who tolerated >85% RDI of chemotherapy for both drugs in the overall and control cohorts (92% vs 73.2%, $p = 0.012$ for the whole cohort; Table 4) and (91.7% vs 54.5%, $p = 0.002$ in the control cohort) compared

Table 2
Chemotherapy adherence, toxicity, and surgical outcomes between prehabilitation and control groups.

Outcome	Prehab Group (n = 58) [95% CI]	Control Group (n = 58) [95% CI]	P value
RDI ≥85% - Carboplatin	43 (74.1%) [62.5–85.8]	38 (65.5%) [52.9–78.1]	0.3[e**]
RDI ≥85% - Paclitaxel	42 (84%) [73.5–94.5]	43 (75.4%) [63.9–86.9]	0.3[e]
RDI – Carboplatin (%): median (IQR)	93 (58–100)	91 (63–100)	0.3[b]
RDI – Paclitaxel (%): median (IQR)	99 (51–100)	92 (65–100)	**0.05**[b**]
Dose Reductions	22 (37.9%) [25–51]	29 (50%) [37–63]	0.2[e]
Dose Delays	16 (27.6%) [16–39]	24 (41.4%) [28–54]	0.1[e]
Dose Cancellations	5 (8.6%) [1.2–16.1]	12 (20.7%) [10–31.4]	0.06[e]
NACT regime change	5 (8.6%) [1–16]	6 (10.3%) [2–18]	1[e]
Febrile Neutropenia	2 (3.4%) [−1–8]	1 (1.7%) [−2–5]	1[d]
Severe Neutropenia (Grade ≥ 3)	9 (15.5%) [6–25]	16 (27.6%) [16–39]	0.1[e]
Use of GM-CSF support	19 (32.8%) [20–45]	17 (29.3%) [17–41]	0.7[e]
Hospitalization during NACT	8 (13.8%) [1-	5 (8.6%) [1–16]	0.2[d]
ED visits during NACT	19 (32.8%) [20–45]	20 (34.5%) [22–47]	0.8[e]
VTE during NACT	7 (12.1%) [3–21]	5 (8.8%) [1–16]	0.6[e]
CA125 normalization*	27 (46.6%) [33.3–59.8]	25 (43.1%) [29.9–56.2]	0.7[e]
Surgical Outcomes			**0.03**[d]
No surgery	4 (6.9%) [2.4–15.6]	13 (22.4%) [13.2–34.3]	
Complete Cytoreduction (0 cm)	28 (48.3%) [35.8–61]	31 (53.4%) [40.7–65.9]	
Optimal (<1 cm)	18 (31%) [20.3–43.6]	11 (19%) [10.5–30.4]	
Suboptimal/Aborted (>1 cm)	8 (13.8%) [6.7–24.3]	3 (5.2%) [1.5–13.2]	
Postoperative Complications			0.9[d]
No complication (Calvien Dindo 0)	19 (38.8%) [26.1–52.7]	15 (36.6%) [23.2–51.8]	
Minor Complication (Calvien Dindo I-II)	26 (53.1%) [39.2–66.5]	22 (53.7%) [38.6–68.2]	
Major Complication (Calvien Dindo III-IV)	4 (8.2%) [2.8–18.2]	4 (9.8%) [3.4–21.5]	
Blood transfusion	19 (38.8%) [23–50]	17 (41.5%) [25.7–57.2]	0.8[e]
Length of hospital stay (Median, IQR)	5 (2–15)	5 (1–14)	0.8[b]
Unplanned ICU admission	2 (4.1%) [−1.5–9.3]	4 (9.8%) [0.3–19.2]	0.4[d]
Readmission within 30 days postop	6 (12.2%) [2.6–20.5]	7 (17.1%) [5.1–29.1]	0.6[e]

* CA-125: Cancer Antigen 125, CI: Confidence Interval, ED: Emergency Department, GM-CSF: Granulocyte-Macrophage Colony-Stimulating Factor, NACT: Neoadjuvant Chemotherapy, RDI: Relative Dose Intensity, VTE: Venous Thromboembolism.
[b] Mann-Whitney U test (for median/IQR).
[d] Fisher's Exact test (for categorical data with small cell counts).
[e] Chi-square test (for larger categorical distributions).
** Bold values indicate statistical significance ($P < 0.05$).

Table 3
Reasons for not proceeding to interval debulking surgery.

Reason	Prehabilitation ($n = 4$)	Control ($n = 13$)
Disease-related*	3 (75%)	5 (38.5%)
Poor surgical candidacy**	0 (0%)	6 (46.2%)
Treatment-related toxicity	1 (25%)	1 (7.7%)
Patient preference	0 (0%)	1 (7.7%)

* Progression, inadequate response, unresectable disease.
** Impaired performance status, frailty, malnutrition, comorbidities.

to those who did not. However, in the prehabilitation cohort, IDS rates remained high even among patients who did not achieve >85% RDI (94.7%), comparable to those who did achieve >85% RDI (92.3%, $p = 1$).

3.3. Subgroup analysis by age (≥70 years)

In the subgroup analysis of patients ≥70 years old, chemotherapy delivery metrics differed significantly between the prehabilitation and control cohorts (Table 5). Patients in the prehabilitation group had higher RDI for paclitaxel, both as a continuous measure (median RDI 98% [IQR 79–100] vs 86% [65–100], $p < 0.001$) and as a binary threshold of ≥85% (88.5% vs 59.3%, $p = 0.02$). Carboplatin RDI was also higher in the prehabilitation cohort (median 92.5% vs 87%, $p = 0.04$), with a non-significant trend toward a greater proportion achieving RDI ≥85% (75% vs 53.6%, $p = 0.08$). Additionally, rates of chemotherapy dose reductions (37.5% vs 64.3%, p = 0.04) and dose delays (34.4% vs 60.7%, p = 0.04) were significantly lower in the prehabilitation group.

A higher proportion of patients in the prehabilitation group proceeded to IDS following NACT (no surgery rates of 12.5% vs. 42.9% for prehabilitation and control groups, respectively; $p = 0.007$). Among those who underwent surgery, complete cytoreduction was achieved in 43.8% of prehabilitation patients and 46.4% of controls, while optimal cytoreduction (<1 cm residual disease) occurred in 25% and 10.7%, respectively. Postoperative outcomes were similar between groups.

3.4. Multivariable logistic regression analyses

In multivariable logistic regression analyses, prehabilitation remained independently associated with proceeding to IDS in both the overall cohort (OR 13.0, 95% CI 2.02–83.9; $p = 0.007$) and among patients aged ≥70 years (OR 11.1, 95% CI 1.8–69.2; $p = 0.01$). Prehabilitation was also associated with higher odds of achieving an RDI >85% for both agents among patients aged ≥70 years (OR 5.53, 95% CI 1.41–21.65; p = 0.01), whereas this association did not reach statistical significance in the overall cohort (OR 2.27, 95% CI 0.90–5.76; $p = 0.08$). Detailed results are presented in Supplementary Table 1.

4. Discussion

This study suggests that a structured, multimodal prehabilitation program during NACT is associated with improved chemotherapy delivery and a higher likelihood of proceeding to IDS in patients with advanced OC. While favorable differences were observed across the entire cohort, the strongest associations were observed among patients aged ≥70 years. For these older patients, prehabilitation might help mitigate treatment attrition, while significantly increasing the proportion of patients who successfully transition from NACT to surgery.

Table 4
Interval debulking surgery rates according to chemotherapy RDI* in the overall, prehabilitation and control cohorts.*,**

	Total cohort	Prehab cohort	Control cohort
RDI > 85% for both carboplatin and paclitaxel	69 (92%)	36 (92.3%)	33 (91.7%)
RDI < 85% for either or both	30 (73.2%)	18 (94.7%)	12 (54.5%)
p-value	**0.012** **	1	**0.002**

* RDI: Relative Dose Intensity.
** Bold values indicate statistical significance ($P < 0.05$).

Existing data on the impact of prehabilitation on chemotherapy delivery in OC remain limited. In an exercise-only trial, only 54% of patients achieved an average RDI ≥85% [29], whereas a later trial combining exercise and dietary counseling reported that 74.4% of the intervention group reached this threshold [30]. In our cohort, a higher proportion of patients in the prehabilitation group achieved RDI ≥85% for both carboplatin and paclitaxel compared with controls. Notably, the median paclitaxel RDI was significantly higher in the prehabilitation group, accompanied by a strong trend toward fewer dose cancellations. Furthermore, rates of dose reductions (37.9%) and delays (27.6%) compared favorably not only with our historical controls but also with prior exercise-based trials in OC (58.2% and 51.5%, respectively) [31]. Together, these findings support the feasibility of implementing a multimodal intervention during the acute phase of NACT and suggest that the integration of nutritional optimization and psychological support may provide additive benefits beyond exercise alone in maintaining treatment intensity.

The positive association of prehabilitation was particularly evident in patients aged ≥70 years. While the total cohort showed encouraging trends, the older population derived statistically significant benefits across nearly all chemotherapy delivery metrics, including higher RDI for both paclitaxel and carboplatin, and a significant reduction in dose delays and reductions. Older patients with cancer are uniquely susceptible to both age- and disease-related vulnerabilities [32], including frailty [12], sarcopenia [15], diminished physiologic reserve, and heightened susceptibility to treatment-related toxicities [33]. These vulnerabilities are often exacerbated by chronic inflammation, reduced anabolic responsiveness, and declining cardiorespiratory capacity [34]. By targeting modifiable determinants, prehabilitation may enhance metabolic and functional reserve, which could contribute to improved tolerance to systemic therapy [35]. Our findings are consistent with this hypothesis, suggesting that improving physical fitness and protein intake may help preserve clinical eligibility, thereby helping chronologically older patients to remain biologically capable of completing their intended therapy. Notably, the observed association between prehabilitation and improved chemotherapy delivery remained directionally consistent after adjustment for chemotherapy regimen, bevacizumab use, age, PS, and BMI. While the adjusted association did not reach statistical significance in the overall cohort, a significant independent association persisted among patients aged ≥70 years.

A key proposed mechanism underlying improved chemotherapy delivery in patients undergoing multimodal prehabilitation may be improved physiologic resilience during systemic therapy [20]. The combination of resistance training and optimized protein intake directly targets sarcopenia [36], a well-established predictor of chemotherapy toxicity in the current literature [15,37]. In parallel, exercise has been increasingly recognized as a protective strategy against chemotherapy-induced peripheral neuropathy [38], a major driver of paclitaxel dose modification. However, in the present study, formal assessments of sarcopenia, functional status, and neuropathy were not available. Therefore, these mechanisms cannot be directly evaluated, and the observed associations should be treated purely as hypothesis-generating in this context.

One of the most clinically relevant findings of our study was the higher rate of proceeding to IDS among patients undergoing multimodal prehabilitation compared with controls, particularly in the older subgroup. As the primary goal of NACT in advanced OC is to render patients eligible for optimal cytoreductive surgery, failure to proceed to IDS is clinically meaningful and has been associated with significantly shorter disease-free survival and overall survival [8]. Notably, the association between prehabilitation and proceeding to IDS remained

Table 5
Treatment tolerance and surgical outcomes in the subgroup of patients aged 70 years and older.

Outcome	Prehab Group ($n = 32$) [95% CI]	Control Group ($n = 28$) [95% CI]	P value
RDI ≥85% - Carboplatin	24 (75%) [59–91]	15 (53.6%) [34–73.3]	0.08[e,**]
RDI ≥85% - Paclitaxel	23 (88.5%) [75.3–100]	16 (59.3%) [39.5–79.1]	**0.02**[e,**]
RDI – Carboplatin (%): median (IQR)	92.5 (58–100)	87 (71–100)	**0.04**[b]
RDI – Paclitaxel (%): median (IQR)	98 (79–100)	86 (65–100)	**<0.001**[b]
Dose Reductions	12 (37.5%) [20–55]	18 (64.3%) [45–83]	**0.04**[e]
Dose Delays	11 (34.4%) [17–52]	17 (60.7%) [41–80]	**0.04**[e]
Dose Cancellations	4 (12.5%) [0.34–24.6]	7 (25%) [7.9–42.1]	0.2[e]
NACT regime change	4 (12.5%) [0–25]	2 (7.1%) [−3–17]	0.5[d]
Febrile Neutropenia	–	–	–
Severe Neutropenia (Grade ≥ 3)	7 (21.9%) [7–37]	11 (39.3%) [20–59]	0.1[e]
Use of GM-CSF support	13 (40.6%) [23–59]	8 (28.6%) [11–46]	0.3[e]
Hospitalization during NACT	4 (12.5%) [	3 (10.7%) [−1−23]	0.6[d]
ED visits during NACT	13 (40.6%) [23–59]	12 (42.9%) [23–62]	0.8[e]
VTE during NACT	5 (15.6%) [2–29]	1 (3.6%) [−4–11]	0.2[d]
CA125 normalization[*]	12 (37.5%) [19.8–55.2]	15 (53.6%) [33.9–73.3]	0.2[e]
Surgical Outcomes			**0.007**[d]
No Surgery	4 (12.5%) [4.4–27]	12 (42.9%) [26–61.1]	
Complete Cytoreduction (0 cm)	14 (43.8%) [27.7–60.9]	13 (46.4%) [29.1–64.5]	
Optimal (<1 cm)	8 (25%) [12.6–41.7]	3 (10.7%) [3.1–25.9]	
Suboptimal/Aborted (>1 cm)	6 (18.8%) [8.2–34.6]	0	
Postoperative Complications			0.8[d]
No complication (Calvien Dindo 0)	10 (41.7%) [23.9–59.4]	5 (33.3%) [14–58.4]	
Minor Complication (Calvien Dindo I-II)	12 (50%) [33.6–69.7]	9 (60%) [35.3–81.2]	
Major Complication (Calvien Dindo III-IV)	2 (7.4%) [1.6–21.7]	1 (6.7%) [0.7–27.2]	
Blood transfusion	7 (29.2%) [8–43.6]	7 (46.7%) [18.1–75.3]	0.3[e]
Length of hospital stay (Median, IQR)	5 (2–9)	5 (1–9)	0.8[a]
Unplanned ICU admission	2 (8.3%) [−3–17.9]	0	0.5[d]
Readmission within 30 days postop	4 (16.7%) [0.5–29.1]	3 (20%) [−2.9–42.9]	1[d]

[*] CA-125: Cancer Antigen 125, CI: Confidence Interval, ED: Emergency Department, GM-CSF: Granulocyte-Macrophage Colony-Stimulating Factor, IDS: Interval Debulking Surgery, NACT: Neoadjuvant Chemotherapy, RDI: Relative Dose Intensity, VTE: Venous Thromboembolism.
[a] Independent *t*-test.
[b] Mann-Whitney *U* test (for median/IQR).
[d] Fisher's Exact test (for categorical data with small cell counts).
[e] Chi-square test (for larger categorical distributions).
[**] Bold values indicate statistical significance ($P < 0.05$).

significant after adjustment for confounders; however, these exploratory regression models are limited by small sample size and should be interpreted with caution.

Importantly, while maintenance of RDI during NACT has been associated with improved tumor response and increased surgical eligibility in prior studies [39–41], our prehabilitation group appeared to preserve surgical eligibility even among patients who did not achieve ≥85% RDI for carboplatin and paclitaxel, a pattern not observed in controls, where reduced RDI was more consistently associated with failure to proceed to surgery. However, this did not translate into differences in surgical outcomes, as rates of complete cytoreduction were comparable, while numerically higher proportions of aborted or suboptimal procedures were observed in the prehabilitation cohort. Given that surgical resectability in advanced OC is multifactorial and influenced by disease distribution, tumor biology, response to chemotherapy, and others [42], our findings suggest that prehabilitation may primarily preserve the ability to reach surgical exploration rather than modify tumor resectability itself. Accordingly, prehabilitation may function as a treatment-enabling strategy that sustains continuity along a curative-intent pathway, particularly among older and clinically vulnerable patients. Prospective validation is warranted to confirm these preliminary observations.

Despite the clinically meaningful findings observed, several limitations should be acknowledged. First, the non-randomized design introduces the potential for residual confounding and selection bias. Although propensity score matching and multivariable adjustment were performed, unmeasured factors, including treatment engagement and aspects of baseline disease burden, may not have been fully captured. Because the prehabilitation cohort was derived from a prospective voluntary trial, participants may have had greater motivation, engagement, and adherence than historical controls. Second, exclusion of patients with incomplete chemotherapy records, withdrawal from the prehabilitation, or death during NACT may have introduced attrition and survivorship bias. Third, data on surgical complexity, radiologic disease burden, nutritional status, sarcopenia, and physiologic reserve were unavailable, limiting mechanistic interpretation. The historical control period overlapped with the COVID-19 pandemic, which may have influenced treatment delivery or surgical scheduling. However, only one patient during this interval failed to proceed to surgery. Notably, both cohorts were managed by the same group of gynecologic oncologic surgeons, reducing variability in surgical decision-making. However, lack of blinding may have introduced performance bias. Additionally, adherence to exercise, nutritional, and psychological support components were not evaluated, precluding assessment of the relationship between intervention adherence and outcomes. Finally, the small sample size, particularly for subgroup analyses, and the absence of long-term oncologic outcomes limit definitive conclusions. As a pilot observational study designed to generate hypotheses, larger prospective studies are needed to validate these findings and assess their impact on survival and clinical implementation.

5. Conclusion

Multimodal prehabilitation during NACT was associated with more favorable chemotherapy delivery metrics and a higher likelihood of proceeding to IDS, particularly among older patients. These findings suggest that prehabilitation may extend beyond supportive care and could function as a treatment-enabling strategy that may help maintain eligibility for definitive surgical management. Future prospective trials are warranted to determine whether these improvements translate into durable oncologic benefits and to identify the patient populations and interventions most likely to benefit.

CRediT authorship contribution statement

Riham Suleiman: Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Shilpa Mokshagundam:** Writing – review & editing, Validation. **Matthew S. Block:** Writing – review & editing, Validation. **Andrea E. Wahner Hendrickson:** Writing – review & editing, Validation. **Kelly H. Bruce:** Writing – review & editing, Validation. **William A. Cliby:** Writing – review & editing, Validation. **Carrie L. Langstraat:** Writing – review & editing, Validation. **S. John Weroha:** Writing – review & editing, Validation. **Siddhartha Yadav:** Writing – review & editing, Validation. **Amanika Kumar:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Investigation, Conceptualization.

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Appendix A. Supplementary data

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