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# The Impact of BRCA Mutation on the Efficacy of Neoadjuvant Chemotherapy in Advanced Ovarian Cancer

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## Rezumat

***Rolul mutației BRCA în chimioterapia neoadjuvantă pentru cancerul ovarian avansat***

*Obiectiv:* acest studiu retrospectiv a avut ca scop evaluarea impactului statutului mutațional BRCA asupra rezultatelor pacienților cu cancer ovarian avansat tratați fie prin chirurgie de citoreducție primară (PDS), fie prin chimioterapie neoadjuvantă urmată de chirurgie de citoreducție intermediară (NACT-IDS).
*Material şi Metode:* au fost incluşi un total de 79 de pacienți cu cancer ovarian stadiul III-IV, tratați la Spitalul Universitar de Urgență Elias între ianuarie 2014 şi martie 2024. Pacienții au primit fie PDS urmată de chimioterapie, fie NACT-IDS. Caracteristicile clinice şi patologice, supraviețuirea fără progresie a bolii (PFS) şi supraviețuirea generală (OS) au fost analizate şi stratificate în funcție de statutul mutațional BRCA. Analiza Kaplan-Meier şi modelele de hazard proporțional Cox au fost utilizate pentru a compara rezultatele de supraviețuire între pacienții cu mutații BRCA (BRCAmut) şi cei cu BRCA tip sălbatic (BRCAwt) în diferitele grupuri de tratament.
*Rezultate:* grupul BRCAwt a prezentat o tendință uşoară în favoarea PDS în ceea ce priveşte OS (48 luni vs. 38 luni, p = 0,03) şi PFS (22 luni vs. 19 luni, p = 0,552), deşi diferența în PFS nu a fost semnificativă statistic. În contrast, pacienții BRCAmut tratați cu NACT-IDS au demonstrat o OS semnificativ îmbunătățită comparativ cu cei care au urmat PDS (71 luni vs. 50 luni, p = 0,043), în timp ce PFS a fost similară între grupuri (25 luni vs. 23 luni, p = 0,345). Citoreducția completă (R0) a fost obținută într-o proporție mai mare la pacienții BRCAmut (80,8% vs. 56,6% în BRCAwt).

*Concluzie:* statutul mutațional BRCA este un factor critic care influențează rezultatele de supraviețuire în cancerul ovarian avansat. În timp ce pacienții BRCAwt pot beneficia uşor de PDS, pacienții BRCAmut prezintă o OS semnificativ îmbunătățită cu NACT-IDS. Aceste constatări susțin necesitatea unor strategii de tratament individualizate bazate pe statutul BRCA pentru a optimiza rezultatele în cancerul ovarian.

**Cuvinte cheie:** cancer ovarian seros de grad înalt, mutație BRCA 1/2, chimioterapie neoadjuvantă, rezecție post terapeutică, supraviețuire globală

**Abstract**

*Objective:* this retrospective study aimed to evaluate the impact of BRCA mutational status on the outcomes of patients with advanced ovarian cancer treated with either primary debulking surgery (PDS) or neoadjuvant chemotherapy followed by interval debulking surgery (NACT-IDS).

*Material and Methods:* a total of 79 patients with stage III-IV ovarian cancer treated at Elias Emergency University Hospital between January 2014 and March 2024 were included. Patients received either PDS followed by chemotherapy or NACT-IDS. Clinical and pathological characteristics, progression-free survival (PFS), and overall survival (OS) were analyzed and stratified by BRCA mutational status. Kaplan-Meier analysis and Cox proportional hazard models were used to compare survival outcomes between BRCA-mutated (BRCAmut) and BRCA wild-type (BRCAwt) patients across treatment groups.

*Results:* the BRCAwt group showed a slight trend favoring PDS in terms of OS (48 months vs. 38 months, $p = 0.03$) and PFS (22 months vs. 19 months, $p = 0.552$), though the difference in PFS was not statistically significant. In contrast, BRCAmut patients treated with NACT-IDS demonstrated significantly improved OS compared to those undergoing PDS (71 months vs. 50 months, $p = 0.043$), while PFS was similar between groups (25 months vs. 23 months, $p = 0.345$). Complete cytoreduction (R0) was achieved in a higher proportion of BRCAmut patients (80.8% vs. 56.6% in BRCAwt).

*Conclusion:* BRCA mutational status is a critical factor influencing survival outcomes in advanced ovarian cancer. While BRCAwt patients may slightly benefit from PDS, BRCAmut patients exhibit significantly improved OS with NACT-IDS. These findings support the need for individualized treatment strategies based on BRCA status to optimize outcomes in ovarian cancer.

**Key words:** high-grade serous ovarian cancer, BRCA 1/2 mutation, neoadjuvant chemotherapy, interval debulking surgery, overall survival

## Introduction

Ovarian cancer is the third most common gynecological malignancy, following cervical and endometrial cancers, and is the leading cause of death from gynecological cancers in developed countries (1). While its incidence is notably lower than that of breast cancer with 324.000 new cases reported in 2022, ovarian cancer is more lethal with a mortality of 206.000 deaths in 2022 (2). The mortality rate is predicted to increase by 2040 due to the lack of screening methods (3).

Primary cytoreductive or debulking surgery (PDS) aims to remove all visible tumor tissue and is the standard initial treatment for

patients with advanced ovarian carcinoma, followed by platinum-based chemotherapy. Observational studies have indicated that achieving optimal debulking, defined as having residual disease less than 1 cm, is linked to improved overall survival (OS) (4). Currently the role of neoadjuvant chemotherapy followed by interval debulking surgery is to convert a potential resectable ovarian cancer to resectability.

Approximately 15-25% of patients diagnosed with epithelial ovarian cancer (EOC) have germline mutations in the BRCA1 or BRCA2 genes. These mutations are associated with a significantly increased susceptibility of high-grade serous ovarian cancer (HGSOC) to platinum-based chemotherapy, leading to higher response rates and better five-year survival statistics (5).

Studies indicate that individuals with BRCA1/2 mutations show notable sensitivity to platinum-based treatments, particularly neoadjuvant chemotherapy (NACT). For example, research by Gorodnova et al. (6) found that 34% of patients with germline mutations achieved a complete clinical response, compared to just 4% among wild-type individuals. Moreover, a pathological complete response was observed in 46% of those with BRCA1/2 mutations, while only 24% of patients without these mutations experienced similar results. Interestingly, loss of heterozygosity (LOH) of BRCA1 occurred in only 29% of tumor samples from patients who had undergone NACT, contrasting with 82% of BRCA1 tumors in chemonaive patients; however, LOH did not correlate with optimal cytoreduction, progression-free survival (PFS), or overall survival (OS).

Additionally, another investigation highlighted that overexpression of various homo-logous recombination repair (HRR) genes might be linked to more favorable prognoses. This study analyzed RNA expression from 96 fresh frozen HGSOC tumor samples obtained from patients undergoing either primary debulking surgery (PDS) or NACT followed by interval debulking surgery (IDS). The results indicated that RAD51 overexpression was associated with worse outcomes in the NACT-IDS cohort, while in the PDS group, the overexpression of NBN, FANCF, and RAD50 genes correlated with better prognostic outcomes (7). Thus, further investigation into the predictive and prognostic implications of molecular changes in HRR genes is essential.

The main goal of this study is to establish the role of BRCA mutation as a prognostic and predictive factor among patients with advanced ovarian cancer.

## Materials and Methods

### *Study Population*

This retrospective study included patients treated and followed up at the Oncology Department of Elias Emergency University Hospital in Bucharest, Romania, from January 2014 to March 2024. All participants were diagnosed with stage III-IV ovarian cancer and underwent either neoadjuvant chemotherapy consisting of carboplatin (AUC=6) or cisplatin (75 mg/m$^2$) and paclitaxel (175 mg/m$^2$) every three weeks for 3 to 6 cycles followed by interval debulking surgery (IDS) or primary debulking surgery followed by adjuvant chemotherapy which included carboplatin/cisplatin and paclitaxel at the same dosages.

Patients were staged using the AJCC TNM Staging Classification for Ovarian, Fallopian Tube, and Primary Peritoneal Cancer (8$^{th}$ edition, 2017). Clinical staging involved comprehensive imaging, including CT or MRI scans of the chest, abdomen, and pelvis, with brain MRIs for symptomatic patients. Lesions suspected of being metastatic that could not be confirmed through conventional imaging underwent biopsy or an 18F-FDG PET/CT scan. A flowchart of the study is provided in *Fig. 1.*

### *Inclusion and Exclusion Criteria*

Patients included in this retrospective study were diagnosed with stage III–IV ovarian

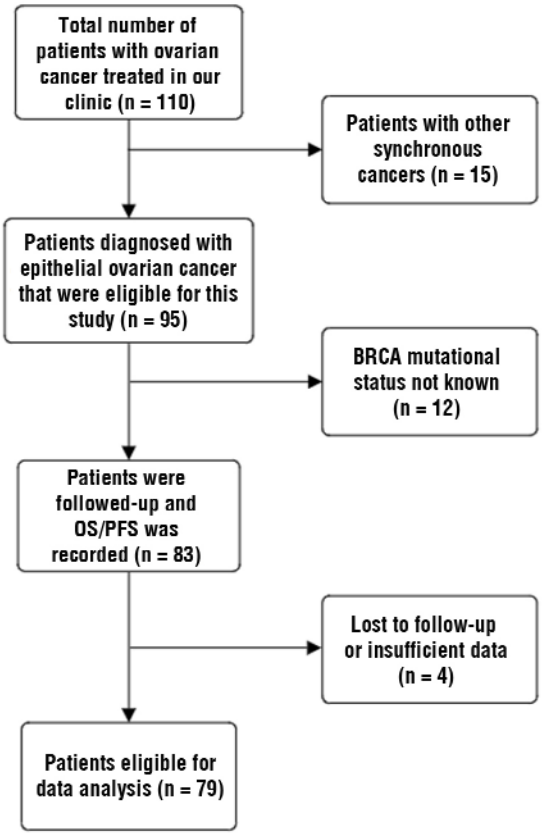


**Figure 1.** Study flowchart

cancer based on the AJCC TNM Staging Classification (8th edition). Eligible participants had histologically confirmed high-grade serous ovarian carcinoma (HGSOC) and underwent either primary debulking surgery (PDS) or neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS). Only those treated with standard platinum-based chemotherapy (carboplatin or cisplatin) in combination with paclitaxel in the neoadjuvant or adjuvant settings were considered. Additionally, all patients had germline BRCA 1/2 mutation testing results available, enabling stratification based on mutation status. To ensure consistency, patients included in the analysis had adequate clinical and pathological data, including progression-free survival (PFS) and overall survival (OS) outcomes. Eligibility was further restricted to individuals with an ECOG performance status of 0–2, and all participants provided signed informed consent for the use of their clinical data in the study.

Patients were excluded if they had non-serous or low-grade ovarian cancer histology or lacked BRCA 1/2 mutation testing results. Those with incomplete clinical or pathological data or who received alternative chemotherapy regimens not aligned with the study protocol were also excluded. Additionally, patients with secondary malignancies or concurrent cancers requiring active treatment, severe comorbidities that precluded surgery or chemotherapy, or deviations from standard treatment protocols were not eligible. These criteria were established to maintain a homogenous study population, ensuring that the findings reflect the true impact of BRCA mutational status on the efficacy of neoadjuvant chemotherapy and subsequent survival outcomes.

### *Data Collection*

The relevant medical data collected from patients included: age, serum cancer antigen (CA) 125 levels on diagnosis, ki67 value on diagnosis and after neoadjuvant chemotherapy maximum diameter of the primary lesion, NAC regimens and cycles, changes in the maximum diameter of primary lesions and total target lesions according to RECIST criteria post-NAC, hematological toxicity of NAC based on Common Terminology Criteria for Adverse Events (CTCAE) 5.0, residual lesions, pathological types, postoperative chemotherapy regimens and cycles, postoperative hematological toxicity, history of PARP inhibitors, PFS, and OS.

### *Laboratory Methods- Germline BRCA1/2 Testing*

In this study, BRCA1/2 mutation testing was performed using next-generation sequencing (NGS) on DNA extracted from patient samples, such as blood or tumor tissue. The testing covered the entire coding regions of BRCA1 and BRCA2, including adjacent intronic sequences. DNA was fragmented, barcoded,

and amplified before being sequenced on an Illumina platform. Detected variants were analyzed and aligned to a reference genome, and variants were classified using established guidelines. Sanger sequencing was used to confirm key mutations, and multiplex ligation-dependent probe amplification (MLPA) was performed to identify large genomic rearrangements. Variants were categorized based on a 5-class system, and the results were used to guide clinical management.

### *Statistical Analysis*

A Student's t-test was used to assess differences in continuous variables, while the chi-square test was employed to evaluate differences in clinical characteristics. Progression-free survival (PFS) and overall survival (OS) were analyzed using the Kaplan-Meier method. Univariate and multivariate Cox regression models were employed to explore the relationship between several clinico-pathological characteristics and the risk of death or recurrence among patients with epithelial ovarian cancer (EOC) allowing for adjustments for potential confounding variables. Statistical analyses were conducted using SPSS software version 26.0, with significance levels set at $p < 0.05$.

## Results

### *Patient's Characteristics*

A total of 79 patients were included in this analysis after applying the inclusion/exclusion criteria. We stratified the clinical characteristics according to BRCA mutational status. The age of patients differed significantly between the two groups. The BRCAwt group was older, with a mean age of 68.9 years (± 4.17), while the BRCAmut group had a younger mean age of 61.3 years (± 5.43).

Regarding clinical stage, most patients in both groups were diagnosed at advanced stages. Stage IIIC was the most common, affecting 13 patients (50%) in the BRCAmut group and 21 patients (39.6%) in the BRCAwt group. Notably, a higher percentage of BRCAwt patients were diagnosed at Stage IV (n=23, 43.4%) compared to BRCAmut patients (n=4, 15.4%).

In terms of ECOG performance status, BRCAmut patients had a better overall status. A majority (n=16, 61.5%) had an ECOG score of 0, indicating no functional impairment, compared to 20 patients (37.7%) in the BRCAwt group. Conversely, the BRCAwt group had more patients with ECOG scores of 2 or higher (n=11, 20.8%), compared to the BRCAmut group (n=3, 11.6%).

Regarding histology, high-grade serous carcinoma was the predominant subtype in both groups but was more frequent in BRCAmut patients (n=22, 84.6%) compared to BRCAwt patients (n=31, 58.5%). Other histological subtypes, such as low-grade serous, mucinous, clear-cell, endometrioid, and carcinosarcoma, were more commonly found in the BRCAwt group, with carcinosarcoma present in 5 patients (9.4%) in BRCAwt versus 1 patient (3.9%) in the BRCAmut group.

For serum CA-125 levels, a greater proportion of BRCAwt patients had elevated levels (>1000 U/ml), with 28 patients (52.8%) compared to 10 patients (38.5%) in the BRCAmut group. This suggests that BRCAwt patients may present with higher tumor burden.

A stark difference was seen in the use of PARP inhibitors (PARPi). Almost all BRCAmut patients (n=24, 92.3%) received PARPi therapy, while only 12 patients (22.6%) in the BRCAwt group were treated with PARPi. This aligns with the established benefit of PARPi in BRCA-mutant ovarian cancer.

Concerning surgical treatment, more BRCAmut patients underwent primary debulking surgery (PDS) (n=15, 60%) compared to BRCAwt patients (n=19, 48.7%). Conversely, interval debulking surgery (IDS) was more common in BRCAwt patients (n=20, 51.3%) than in BRCAmut patients (n=10, 40%).

The resection status showed a higher rate of complete resection (R0) in BRCAmut patients (n=21, 80.8%) compared to BRCAwt patients (n=30, 56.6%). Additionally, more

BRCAwt patients had unresectable disease (n=14, 26.4%) compared to BRCAmut patients (n=1, 3.8%).

When considering neoadjuvant chemotherapy (NACT) cycles, both groups had the majority of patients receiving 3 cycles when applicable, with 7 patients (70%) in the BRCAmut group and 11 patients (55%) in the BRCAwt group. However, a higher percentage of BRCAwt patients received 6 cycles (n=6, 30%) compared to BRCAmut patients (n=2, 20%). In terms of chemotherapy toxicity, BRCAmut patients experienced higher rates of severe neutropenia (n=11, 50%) compared to BRCAwt patients (n=16, 30.2%). Other toxicities, such as anemia, thrombocytopenia, and peripheral neuropathy, were relatively similar between the two groups, though slightly more common in BRCAwt patients. These data are shown in *Table 1*.

**Table 1.** Baseline characteristics of patients stratified by BRCA mutational status

| Characteristics | BRCAmut (n=26) | BRCAwt (n=53) |
|---|---|---|
| Age, years, mean (SD) | 61.3 (±5.43) | 68.9 (±4.17) |
| Clinical stage, n (%) | | |
| Stage IIIA | 2 (7.7%) | 6 (11.3%) |
| Stage IIIB | 7 (26.9%) | 3 (5.7%) |
| Stage IIIC | 13 (50%) | 21 (39.6%) |
| Stage IV | 4 (15.4%) | 23 (43.4%) |
| ECOG, n (%) | | |
| 0 | 16 (61.5%) | 20 (37.7%) |
| 1 | 7 (26.9%) | 22 (41.5%) |
| ≥ 2 | 3 (11.6%) | 11 (20.8%) |
| Histology subtype, n (%) | | |
| High-grade serous | 22 (84.6%) | 31 (58.5%) |
| Low-grade serous | 1 (3.9%) | 5 (9.4%) |
| Mucinous | 2 (7.7%) | 4 (7.5%) |
| Clear-cell | 1 (3.9%) | 5 (9.4%) |
| Endometrioid | 0 (0%) | 3 (5.7%) |
| Carcinosarcoma | 1 (3.9%) | 5 (9.4%) |
| Serum CA-125 (U/ml), n (%) | | |
| ≤1000 | 16 (61.5%) | 25 (47.2%) |
| >1000 | 10 (38.5%) | 28 (52.8%) |
| PARPi usage, n (%) | | |
| Yes | 24 (92.3%) | 12 (22.6%) |
| No | 2 (7.7%) | 41 (77.4%) |
| Type of surgery*, n (%) | | |
| PDS | 15 (60%) | 19 (48.7%) |
| IDS | 10 (40%) | 20 (51.3%) |
| Resection status, n (%) | | |
| R0 | 21 (80.8%) | 30 (56.6%) |
| R1 | 4 (15.4%) | 9 (17%) |
| Unresectable | 1 (3.8%) | 14 (26.4%) |
| Number of NACT cycles (when applicable) | | |
| 3 cycles | 7 (70%) | 11 (55%) |
| 4 cycles | 1 (10%) | 2 (10%) |
| 5 cycles | 0 (0%) | 1 (5%) |
| 6 cycles | 2 (20%) | 6 (30%) |
| Toxicity to CHT (≥3 CTCAE), n (%) | | |
| Neutropenia | 11 (50%) | 16 (30.2%) |
| Anemia | 3 (11.5%) | 9 (17%) |
| Thrombocytopenia | 4 (15.4%) | 7 (13.2%) |
| Emesis | 2 (7.7%) | 4 (7.5%) |
| Diarrhea | 0 (0%) | 1 (1.9%) |
| Periferic neuropathy | 2 (7.7%) | 5 (9.4%) |

*=when resectable; BRCA = BReast CAncer gene, ECOG = Eastern Cooperative Oncology Group, CA 125 = Cancer antigen 125, NACT =neoadjuvant chemotherapy, PDS =primary debulking surgery, IDS =interval debulking surgery, PARPi = PARP inhibitors, CTCAE= Common Terminology Criteria for Adverse Events.

### *The Role of Neoadjuvant Chemotherapy on PFS and OS*

When comparing overall survival (OS) (*Fig. 2*) in ovarian cancer patients who underwent either primary debulking surgery (PDS) or interval debulking surgery (IDS), the Kaplan-Meier survival curves demonstrate that patients in the PDS group tended to have better survival outcomes compared to those in the IDS group. The median OS for patients who underwent PDS was 50 months (95%CI 46.15-53.85), whereas the median OS for those who underwent IDS was 44 months 95%CI (36.55-51.45 months). However, statistical tests of survival distribution equality between the PDS and IDS groups showed no significant difference. The Log Rank test yielded a p-value of 0.149, indicating no statistically significant difference between the two groups.

Similary, comparing progression-free survival (PFS) (*Fig. 3*) between ovarian cancer patients undergoing primary PDS and IDS, the median PFS for the PDS group was 22 months (95%CI 19.74-24.25), while the IDS group had a median PFS of 19 months (95%CI 16.97-21.02). However, statistical analyses, including the Log Rank test (p = 0.552), indicated no significant difference in PFS between the two groups. These findings suggest that while there is a small trend favoring PDS in terms of PFS, the difference is not statistically significant.

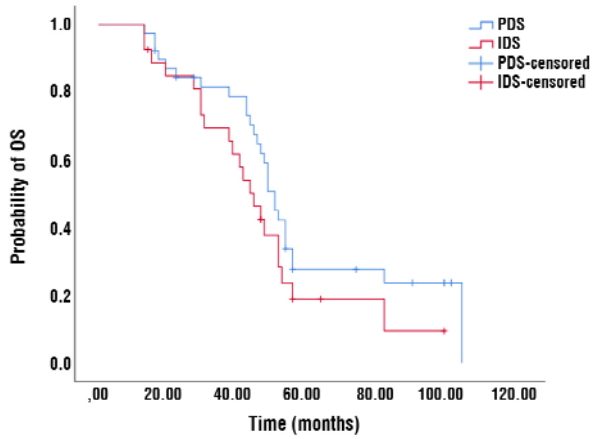


**Figure 2.** Comparative analysis of Kaplan–Meier curves between PDS and IDS patients for overall survival (OS)

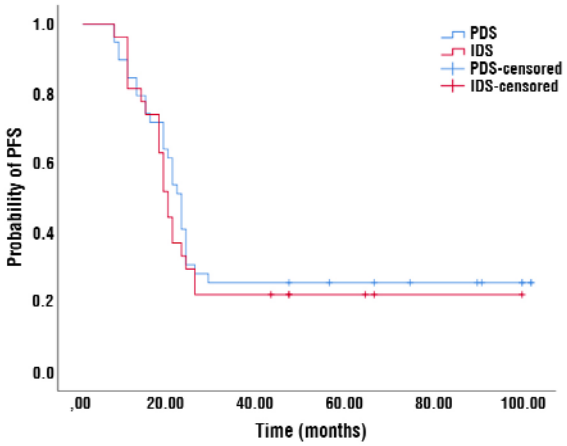


**Figure 3.** Comparative analysis of Kaplan–Meier curves between PDS and IDS patients for progression free survival (PFS)

### *Survival Analysis Based on BRCA Mutational Status*

When comparing overall survival (OS) (*Fig. 4*) among BRCAmt ovarian cancer patients who underwent either PDS or IDS, the Kaplan-Meier survival curves demonstrate that patients in the IDS group tended to have better survival outcomes compared to those in the PDS group. The median OS for patients who underwent PDS was 50 months (95%CI 37.40-62.59), whereas the median OS for those who underwent IDS was 71 months 95%CI (54.97-87.02 months). The log rank test yielded a p-value of 0.043, indicating a statistically significant difference between the two groups.

When comparing overall survival (OS) (*Fig. 5*) among BRCAwt ovarian cancer patients who underwent either PDS or IDS, the Kaplan-Meier survival curves demonstrate that patients in the PDS group tended to have better survival outcomes compared to those in the IDS group. The median OS for

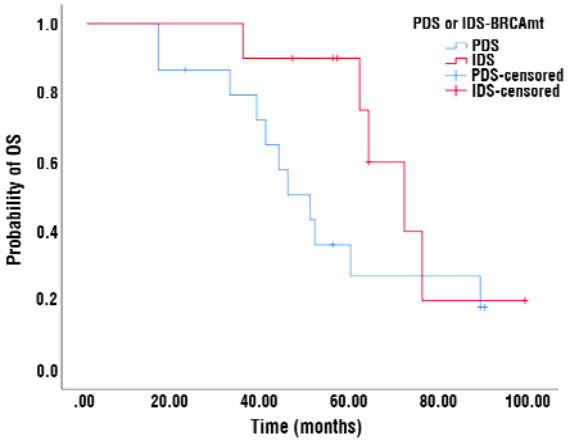


**Figure 4.** Comparative analysis of Kaplan–Meier curves between PDS and IDS patients for overall survival (OS) among BRCAmt patients

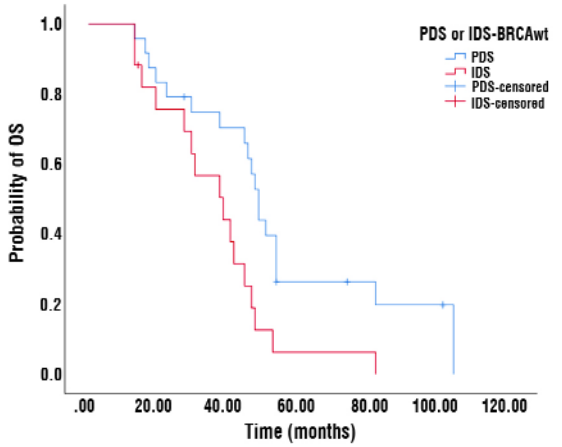


**Figure 5.** Comparative analysis of Kaplan–Meier curves between PDS and IDS patients for overall survival (OS) among BRCAwt patients

patients who underwent PDS was 48 months (95%CI 44.92-51.07), whereas the median OS for those who underwent IDS was 38 months 95%CI (22.54-53.45 months). The log rank test yielded a p-value of 0.03, indicating a statistically significant difference between the two groups.

The Kaplan-Meier survival curves for PFS comparing PDS and IDS among BRCAwt and BRCA-BRCAmt patients demonstrate different trends in these subgroups. In BRCAwt patients, the PFS probability shows a slight advantage for those undergoing PDS compared to IDS (*Fig. 6*). The PDS group maintained a higher progression-free probability beyond 20 months, with censored events indicating some patients achieved prolonged PFS. Despite this, the difference in PFS between PDS and IDS for BRCAwt patients was not statistically significant (Log-Rank p = 0.552). The hazard ratio (HR) comparing IDS to PDS in this subgroup was 1.18 (95% CI: 0.68–2.04), indicating a non-significant increase in risk of progression for IDS patients compared to PDS.

In contrast, BRCAmut patients showed a different pattern. The IDS group displayed a longer PFS than the PDS group, with a higher probability of remaining progression-free throughout the follow-up period. The IDS curve remains relatively stable beyond 40 months, suggesting that IDS may confer a longer-term benefit for BRCAmt patients (*Fig. 7*). The median PFS for the IDS group was 25 months, compared to 23 months for the PDS group, though this difference was also not statistically significant (Log-Rank p = 0.345). The HR for IDS compared to PDS in BRCAmut patients was 0.78 (95% CI: 0.42–1.46), indicating a non-significant reduction in the risk of progression with IDS compared to PDS.

Overall, these findings suggest that while BRCAwt patients may slightly benefit from PDS in terms of PFS, BRCAmut patients could potentially benefit more from IDS, though the differences did not reach statistical significance. The hazard ratios further emphasize the non-significant nature of these differences, underscoring the need for further investigation to better define the impact of debulking surgery timing in relation to BRCA status.

### *Multivariate Analysis to Identify Predictors for Increased Risk of Death and Tumor Progression*

After performing a multivariate analysis (*Table 2*) to identify predictors for increased

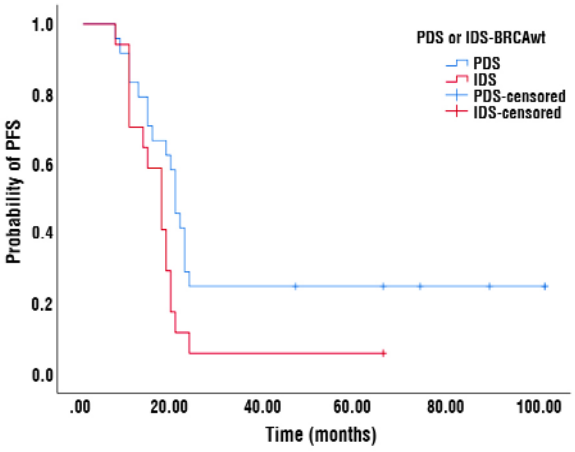


**Figure 6.** Comparative analysis of Kaplan–Meier curves between PDS and IDS patients for progression free survival (PFS) among BRCAwt patients

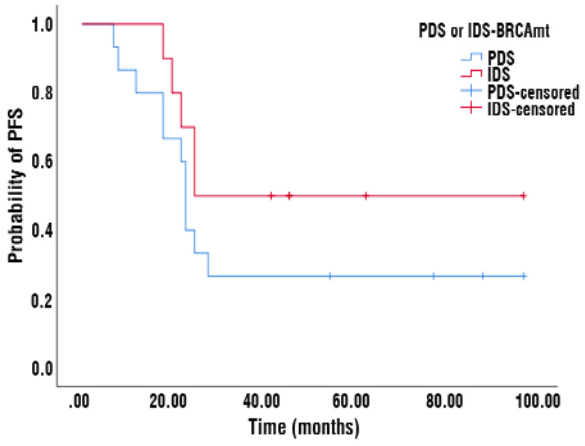


**Figure 7.** Comparative analysis of Kaplan-Meier curves between PDS and IDS patients for progression free survival (PFS) among BRCAmt patients

**Table 2.** Multivariate Cox regression analyses to identify predictors for increased risk of death and tumor progression

| Test Variables | OS HR (95% CI) | p-value | PFS HR (95% CI) | p-value |
|---|---|---|---|---|
| BRCA wild-type/mutant (ref.) | 3.482 (2.157-6.001) | <0.001 | 2.993 (1.982-6.520) | <0.001 |
| ECOG 0-1 (ref.)/2 | 1.985 (1.503-2.419) | 0.085 | 1.451 (1.212-1.798) | 0.157 |
| Stage III (ref.)/ Stage IV | 2.129 (1.789-2.532) | 0.289 | 1.423 (1.150-1.766) | 0.197 |
| R0 resection (ref.)/R1 resection | 2.332 (1.897-2.882) | <0.001 | 1.684 (1.415-2.045) | 0.004 |
| Cancer antigen 125 (CA 125) ≤ 1000 (ref.)/ >1000 | 1.328 (1.107-1.590) | 0.214 | 1.511 (1.235-1.847) | 0.235 |
| Age <65 years (ref.)/>65 years | 1.314 (1.052-1.640) | 0.904 | 1.162 (0.491-1.462) | 0.672 |
| No. of NACT: 3 cycles (ref.)/ 6 cycles | 1.576 (1.301-1.889) | 0.864 | 1.482 (1.237-1.781) | 0.732 |
| PDS (ref.)/ IDS | 2.065 (1.751-2.423) | 0.482 | 1.856 (1.531-2.225) | 0.338 |

BRCA = BReast CAncer gene, ECOG = Eastern Cooperative Oncology Group, CA 125 = Cancer antigen 125, NACT = neoadjuvant chemotherapy, PDS = primary debulking surgery, IDS = interval debulking surgery.

risk of death and tumor progression we report that a significant association was observed between BRCA mutation status and both OS and PFS. Patients with BRCA wild-type, as compared to BRCA-mutant, had a markedly higher risk of death (HR = 3.482, 95% CI: 2.157–6.001, p < 0.001) and disease progression (HR = 2.993, 95% CI: 1.982–6.520, p < 0.001). This emphasizes the well-established prognostic benefit of BRCA mutations, where BRCA-mutant patients tend to have improved survival outcomes, likely due to better responsiveness to targeted therapies such as PARP inhibitors.

The performance status, measured by the ECOG score, showed no statistically significant association with OS (HR = 1.985, p = 0.085) or PFS (HR = 1.451, p = 0.157), though the hazard ratios suggest a trend toward worse outcomes in patients with higher ECOG scores. Similarly, the comparison between Stage III and Stage IV disease did not reveal a statistically significant difference in OS (HR = 2.129, p = 0.289) or PFS (HR = 1.423, p = 0.197), although Stage IV patients appeared to be at higher risk of death and disease progression.

The status of surgical resection, specifically R0 versus R1 resection, was significantly associated with improved survival. Patients who achieved complete cytoreduction (R0) had a significantly lower risk of death (HR = 2.332, 95% CI: 1.897–2.882, p < 0.001) and disease progression (HR = 1.684, 95% CI: 1.415–2.045, p = 0.004) compared to those with residual disease after surgery (R1). This finding underscores the critical importance of achieving complete resection in the surgical management of ovarian cancer to enhance survival outcomes.

In contrast, cancer antigen 125 (CA 125) levels above 1000 were not significantly associated with worse OS (HR = 1.328, p = 0.214) or PFS (HR = 1.511, p = 0.235). While elevated CA 125 levels suggested an increased risk of death and progression, the results were not statistically significant, indicating that CA 125 may not serve as a strong independent prognostic marker in this study population.

Regarding age, being over 65 years did not significantly influence OS (HR = 1.314, p = 0.904) or PFS (HR = 1.162, p = 0.672), suggesting that age alone may not be a critical factor in determining survival, especially when other clinical factors are taken into consideration. Additionally, the number of neoadjuvant chemotherapy (NACT) cycles (3 vs. 6) did not show a significant difference in survival outcomes, with HRs of 1.576 (p = 0.864) for OS and 1.482 (p = 0.732) for PFS, suggesting no clear survival advantage of receiving more cycles of chemotherapy.

Finally, the comparison between primary debulking surgery (PDS) and interval debulking surgery (IDS) revealed no significant differences in OS (HR = 2.065, p = 0.482) or PFS (HR = 1.856, p = 0.338). Although there was a slight trend favoring PDS in terms of survival outcomes, these differences were not statistically significant, indicating that both surgical

approaches may be equally viable depending on individual patient characteristics.

## Discussion

In this retrospective study, we found that when BRCA1/2 mutation status was not considered, both progression-free survival (PFS) and overall survival (OS) after neoadjuvant chemotherapy followed by interval debulking surgery (IDS) were comparable to those observed with primary debulking surgery (PDS) followed by chemotherapy. This finding aligns with the results of previous randomized controlled trials (8,9). However, when accounting for BRCA mutational status, patients with BRCA mutations who underwent NAC-IDS demonstrated an extended OS, although no significant difference in PFS was observed.

The subject of selecting PDS or IDS beyond resecability criteria has been disscused in several other studies such as two retrospective meta-analyses. The first study (10) included 21 trials with a combined total of 835 patients. It demonstrated that the key factors influencing patient survival were the use of platinum-based chemotherapy regimens and achieving optimal debulking surgery. This meta-analysis also found that the weighted average median survival for patients receiving neoadjuvant chemotherapy (NACT) was 24.5 months. Furthermore, it highlighted that performing maximal interval cytoreductive surgery significantly predicted better median survival. However, an increased number of NACT cycles was linked to poorer overall survival (OS).

Another meta-analysis revealed (11) that while NACT increased the rate of optimal cytoreduction, this did not translate into improved OS, particularly when compared to PDS in low-risk patients.

The first major trial of NACT in advanced ovarian cancer, the EORTC 55971 trial (12), randomized 632 patients to either primary cytoreductive surgery followed by platinum-based chemotherapy or NACT followed by interval debulking surgery and further chemotherapy. Median OS was similar in both groups (29 months for PDS vs. 30 months for NACT, HR=0.98, p=0.01), with both groups showing identical progression-free survival (PFS) of 12 months. Independent predictors of improved OS included no residual disease after surgery, lower stage disease, smaller tumor size, endometrioid histology, and younger age. This study confirmed that residual disease, whether after PDS or IDS, is a significant prognostic factor. NACT did not improve OS, postoperative mortality, adverse events, or quality of life. Sub-analyses indicated that patients with stage IIIC disease and smaller tumors benefitted more from PDS, while those with stage IV disease and larger metastatic lesions had better outcomes with NACT and IDS.

Our study results align with findings showing comparable overall survival (OS) between patients undergoing PDS and IDS. Additionally, prognostic factors such as cancer stage and the completeness of resection were confirmed to be significant.

The CHORUS trial (13), a phase III, non-inferiority study, randomized 550 women with advanced ovarian cancer and poor performance status to either primary cytoreductive surgery followed by adjuvant chemotherapy or neoadjuvant chemotherapy followed by interval debulking surgery. The study demonstrated that OS was similar between the two groups, with median OS of 23.7 months in the IDS group and 25.8 months in the primary surgery group (HR=0.89; 95% CI, 0.73-1.08). Progression-free survival was also comparable, with 12 months in the IDS group and 10.7 months in the primary surgery group (HR=0.91; 95% CI, 0.76-1.09). Additionally, the NACT group experienced significantly fewer postoperative complications (Grade 3 and 4), highlighting its potential benefit in reducing surgical morbidity, particularly in patients with poor performance status and extensive disease.

The EORTC 55971 and CHORUS trials, which both explored the timing of surgery in advanced ovarian cancer, emphasized the importance of patient selection when

considering NACT. Both trials indicated that PDS is the standard of care for patients with less extensive disease (FIGO stage ≤ IIIB), while NACT may be more suitable for those with stage IV disease or extensive metastases. Despite these findings, the studies had limitations, including lower rates of complete cytoreduction in the primary surgery arm and variability in surgical expertise across centers. A pooled analysis of these trials reaffirmed that PDS remains optimal for select patients, whereas NACT may improve outcomes in those with more advanced disease, particularly those with large extra-pelvic metastases.

Despite evidence supporting neoadjuvant chemotherapy (NACT) in advanced ovarian cancer, there is no clear consensus on the optimal number of cycles. In practice, patients typically receive 2 to 6 cycles, based on physician preference. Studies by Colombo (14), Xu (15), and Bogani (16) et al. found that more than four cycles may negatively impact outcomes. Although the number of cycles did not significantly affect the likelihood of complete cytoreduction, patients receiving four or more cycles with residual disease after interval debulking surgery (IDS) showed a trend toward worse overall survival (HR=1.76; 95% CI, 0.95-3.22; p=0.06).

Around 15–25% of epithelial ovarian cancer (EOC) patients have germline BRCA1 or BRCA2 mutations, which are linked to increased sensitivity to platinum-based treatments and better five-year survival rates in high-grade serous ovarian cancer (HGSOC). Research indicates that patients with BRCA1/2 mutations respond well to neoadjuvant chemotherapy (NACT). Gorodnova (17) et al. found that 34% of BRCA-mutated patients achieved complete clinical response, compared to 4% of non-mutated patients. Pathological complete response rates were also higher in BRCA-mutated patients (46% vs. 24%). Interestingly, BRCA1 loss of heterozygosity (LOH) was found in 29% of post-NACT tumors, compared to 82% in untreated tumors, though LOH had no impact on outcomes like progression-free survival (PFS) or overall survival (OS).

Our study indicates that BRCA mutational status does not affect progression-free survival (PFS) regardless of whether patients undergo primary debulking surgery (PDS) or neoadjuvant chemotherapy followed by interval debulking surgery (NACT-IDS). However, overall survival (OS) was significantly better in BRCA-mutated patients who underwent NACT-IDS compared to those who had PDS. These results are different to similar studies (18) in which BRCA mutational status was not significant for OS or PFS.

The current literature is conflicting on the impact of BRCA mutational status in relation to NACT response and impact on survival. A retrospective study of 322 ovarian cancer patients (stage IIIB-IV) (19) examined the impact of neoadjuvant chemotherapy followed by interval debulking surgery (IDS) versus primary debulking surgery (PDS) on survival outcomes, stratified by BRCA1/2 mutation status. Among 112 BRCA-mutated and 210 BRCA wild-type patients, NACT was associated with shorter PFS in BRCAmut patients (14.9 vs. 18.5 months; p=0.023) but had no effect on overall survival OS. NACT did not affect PFS or OS in BRCAwt patients. Predictors of improved outcomes included PDS and no residual disease in both groups, with PARP inhibitors significantly prolonging OS in BRCAmut patients. These findings suggest NACT-IDS does not compromise survival regardless of BRCA status.

Another retrospective multicenter study (20) evaluated the impact of BRCA1/2 germline mutations on disease presentation and progression-free survival (PFS) in 273 women with advanced high-grade serous ovarian cancer (stage IIIC-IV). While PFS was similar for BRCA-mutated patients regardless of treatment approach, BRCA wild-type patients showed significantly longer PFS with primary debulking surgery (26 vs. 18 months; p=0.003) compared to neoadjuvant chemotherapy.

A study with results similar to ours assessed the response of ovarian cancer patients to platinum-based neoadjuvant therapy, with a focus on the impact of BRCA muta-

tions. Among 225 OC patients, 35 BRCA mutation carriers were identified. Mutation carriers demonstrated significantly higher complete clinical response rates (34% vs. 4%; p=0.000002) and histopathological response rates (46% vs. 25%; p=0.02) compared to non-carriers (17). Similary, another study (21) analyzed the impact of BRCA mutations on outcomes in 317 breast cancer patients treated with neoadjuvant systemic chemotherapy (NST), finding that BRCA1 carriers had significantly higher pathologic complete response (pCR) rates (46%) compared to BRCA2 carriers and noncarriers (P < .001). While overall survival was similar across groups, BRCA1 carriers achieving pCR demonstrated superior 5-year relapse-free and overall survival, highlighting BRCA1 status as a predictor of treatment response.

The role of PARP inhibitors in frontline treatment of for advanced ovarian cancer has been assessed in several phase 3 trials: SOLO-1, PAOLA-1/ENGOT-OV25, PRIMA/ENGOT-OV26. The SOLO-1 trial (22) evaluated olaparib maintenance therapy in patients with BRCA1/2-mutated advanced ovarian cancer. Olaparib significantly improved progression-free survival (PFS) compared to placebo, with 36% of patients in the olaparib arm and 33% in the placebo arm receiving neoadjuvant chemotherapy (NACT). However, this trial excluded patients with non-BRCA-mutated tumors and did not incorporate bevacizumab.

The PAOLA-1/ENGOT-OV25 (23) trial examined olaparib combined with bevacizumab as maintenance therapy versus bevacizumab alone. Patients receiving olaparib/ bevacizumab demonstrated improved PFS, particularly among those with no residual disease after interval debulking surgery (IDS) (HR=0.61) or optimal debulking after upfront surgery (HR=0.47). Limitations comprise the exclusion of patients ineligible for bevacizumab, restricting generalizability.

The PRIMA/ENGOT-OV26 trial (24) evaluated niraparib as maintenance therapy for high-risk patients, including 67% who underwent NACT and IDS. Sub-analyses to assess outcomes in specific subgroups, such as those with no visible residual disease, are awaited. This trial excluded patients achieving no visible residual disease after primary debulking surgery (PDS), limiting its applicability to routine clinical practice.

The administration of chemotherapeutic regimens in either the neoadjuvant or adjuvant setting significantly alters the mutational landscape and gene expression profiles of tumors and circulating cell-free DNA (cfDNA). These changes are pathway-specific and depend on tumor type and treatment regimens. However, the effects of neoadjuvant chemotherapy (NACT) on the genomic profile of ovarian cancer remain poorly understood due to its limited application in this context. Primary chemosensitivity, which determines the response of the tumor to initial chemotherapy, is influenced by various factors, including pathological response scores, biomarkers (25), genomic alterations, DNA scars, imaging, and circulating tumor markers. This chemosensitivity is critical for predicting the feasibility of achieving complete resection (R0) during interval debulking surgery (IDS) following NACT. The degree of chemosensitivity also affects the success of subsequent maintenance therapies, such as PARP inhibitors or bevacizumab, the risk of developing platinum-resistant relapse, and overall survival (OS) and progression-free survival (PFS). Achieving maximal biological response through systemic therapy and complete surgical debulking is pivotal for optimizing OS outcomes.

A study by Arend et al. (26) investigated gene expression changes in both tumor tissue and plasma cfDNA in 14 ovarian cancer patients undergoing NACT. The analysis revealed significant alterations in genes involved in critical molecular pathways, including cell cycle regulation, ATM signaling, and GADD45 signaling. Additionally, the burden of genetic variants detected in plasma cfDNA decreased substantially post-NACT, although most somatic variants within the tumor remained unchanged.

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therapy, is influenced by various factors, including pathological response scores, biomarkers, genomic alterations, DNA scars, imaging, and circulating tumor markers. This chemosensitivity is critical for predicting the feasibility of achieving complete resection (R0) during interval debulking surgery (IDS) following NACT. The degree of chemosensitivity also affects the success of subsequent maintenance therapies, such as PARP inhibitors or bevacizumab, the risk of developing platinum-resistant relapse, and overall survival (OS) and progression-free survival (PFS). Achieving maximal biological response through systemic therapy and complete surgical debulking is pivotal for optimizing OS outcomes (27,28).

One of the primary limitations of this study is its retrospective design, which may introduce selection bias. The allocation of patients to primary debulking surgery (PDS) or neo-adjuvant chemotherapy followed by interval debulking surgery (NACT-IDS) was based on clinical judgment rather than randomization, which may have influenced the outcomes. Additionally, patient data were collected from a single institution, limiting the generalizability of the findings to broader populations, particularly in centers with different surgical practices or access to advanced therapies.

Another limitation is the small sample size, particularly in the BRCA-mutated group, which limits the statistical power to detect significant differences in progression-free survival (PFS) and overall survival (OS) between treatment groups. The study also included patients with varying disease stages, treatment regimens, and responses to chemotherapy, introducing heterogeneity that may have confounded the results. Furthermore, data on the use of maintenance therapies, such as PARP inhibitors, were not uniformly reported, which may have impacted survival outcomes, especially for BRCA-mutant patients.

Lastly, the study relied on historical data spanning several years, during which treatment protocols and surgical techniques may have evolved. This introduces potential variability in the quality and outcomes of surgical interventions. Future prospective, randomized studies with larger cohorts are needed to validate these findings and better understand the role of BRCA mutational status in determining the optimal treatment approach for advanced ovarian cancer.

## Conclusion

This study demonstrates that BRCA mutational status plays a significant role in determining treatment outcomes for patients with advanced ovarian cancer. Our findings show that while BRCA wild-type (BRCAwt) patients may experience slightly better overall survival (OS) and progression-free survival (PFS) with primary debulking surgery (PDS), the differences in PFS were not statistically significant. On the other hand, BRCA-mutated (BRCAmut) patients benefit more from neo-adjuvant chemotherapy followed by interval debulking surgery (NACT-IDS), with a significant improvement in OS compared to those undergoing PDS. These results underscore the importance of individualized treatment approaches based on BRCA mutational status. BRCA-mutant patients show heightened sensitivity to chemotherapy, particularly in the NACT-IDS setting, likely contributing to their improved outcomes. For BRCAwt patients, PDS remains an important option, especially in those with lower disease burden and better performance status. Future research should explore the nuanced impact of BRCA mutations on the efficacy of neoadjuvant chemotherapy, particularly in relation to molecular and microenvironmental factors that may influence treatment response in advanced ovarian cancer.

### *Authors' Contributions*

Ana M. Popa: conceptualization, methodology, writing – original draft, supervision. Horia-Teodor Cotan: investigation, data curation, formal analysis, writing – review & editing. Cristian I. Iaciu: resources, visualization,

project administration. Cornelia Nitipir: review & editing.

### *Conflicts of Interests*

The authors declare no conflict of interests.

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