

# Primary Debulking Surgery for Stage III Epithelial Ovarian Cancer Has a Better Outcome Than Neoadjuvant Chemotherapy Followed by Interval Debulking Surgery

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## Abstract

**Background:** Ovarian cancer (OC) is the most lethal gynecologic malignancy. About 70% of ovarian cancer patients have advanced disease and often not totally resectable. Previous studies of neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) versus primary debulking surgery (PDS) give inconsistent results. The aim of this retrospective study is to evaluate the outcome of the neoadjuvant chemotherapy followed by IDS versus PDS followed by adjuvant chemotherapy for the International Federation of Gynecology and Obstetrics (FIGO) stage III epithelial ovarian cancer. **Methods:** This study was performed on eligible patients with ovarian cancer admitted in Surgical Oncology and Medical Oncology departments at South Egypt Cancer Institute-Assiut University in the period from January 2010 to December 2015. Patients were divided into two groups, the first group included those who have NACT and underwent IDS plus adjuvant chemotherapy, and the second group included those who underwent PDS followed by adjuvant chemotherapy. **Results:** This study included 380 cases. One hundred and fifty-four patients (40.53%) had IDS. The remaining two hundred and twenty-six patients (59.47%) underwent PDS. In this study, treatment modality was significant for both disease-free survival (DFS) and overall survival (OS). DFS was significantly reduced after IDS when compared to PDS (median DFS: 33.00 months vs. 45.00 months, respectively;  $p < 0.001$ ). Also, OS was significantly reduced after IDS when compared to PDS. (Median OS: 43 months vs. 46 months, respectively;  $p = 0.047$ ). Moreover, this drop of the

survivals mainly occurred in specific subgroups such as the elderly patients, patients with bad performance status, suboptimal cytoreduction, as well as high-grade tumors. **Conclusion:** This study showed that PDS resulted in a better disease-free survival and overall survival than IDS. Moreover, OS and DFS have significantly dropped in specific patients' subgroups. Therefore, patients selection should be considered.

## Keywords

Primary Debulking Surgery, Interval Debulking Surgery, Stage III Ovarian Cancer, Neoadjuvant Chemotherapy

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## 1. Introduction

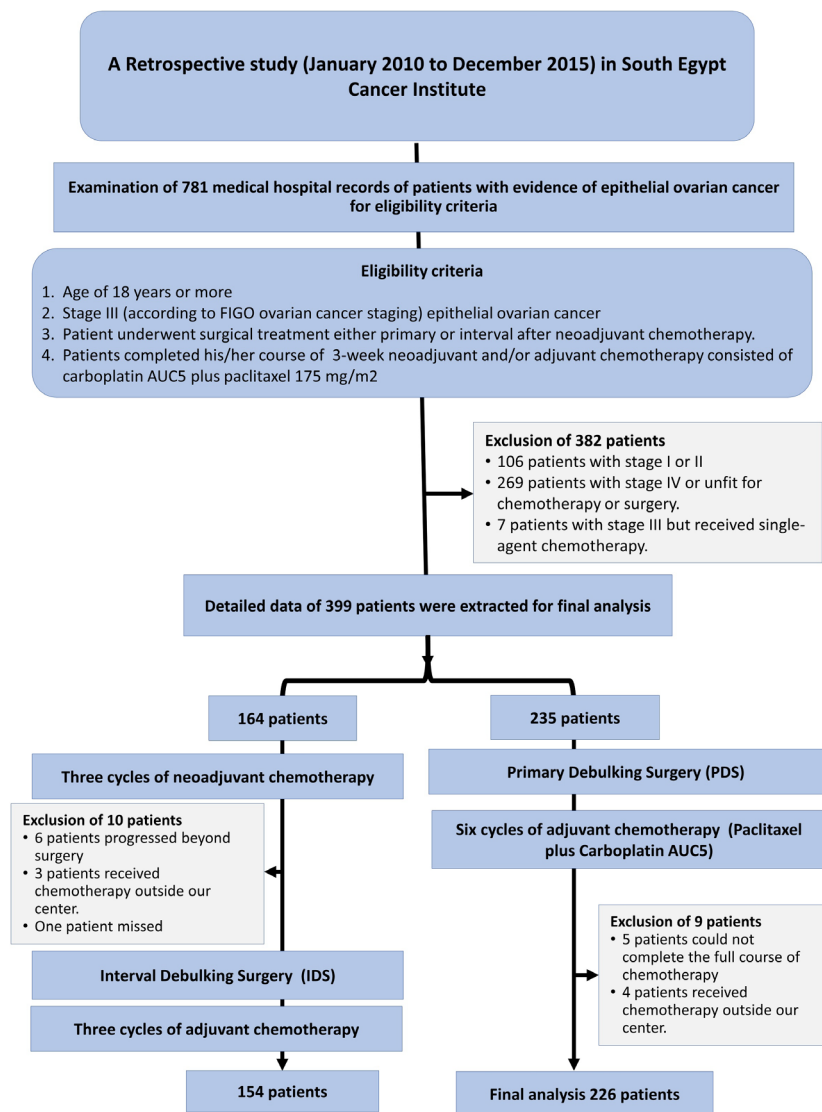
Ovarian cancer (OC) is the fifth most common cause of cancer-related death among women [1]. Of newly diagnosed ovarian cancer patients, about 70% are at the advanced stage because of the lack of symptoms in the early stages of ovarian cancer. The tumors at this stage are mostly not totally resectable. Previously, patients with ovarian cancer had a bad prognosis, with a 5-year survival was about 35%. Recently, survival has been improved due to improvements in diagnosis, surgery, and chemotherapy [2].

Primary surgical treatment of ovarian cancer may have some advantages in the fields of diagnosis and staging, as well as tumor debulking, which is most clear in the International Federation of Gynecology and Obstetrics (FIGO) stage III epithelial ovarian cancer [3] [4] [5]. However, surgery alone will not cure the disease because of its widespread at the time of diagnosis. On the other hand, in advanced disease, neoadjuvant chemotherapy (NACT) may increase the chance of surgical debulking and decrease surgical morbidity and mortality [6]. The results from previous studies comparing the NACT followed by interval debulking surgery (IDS) versus primary debulking surgery (PDS) are inconsistent. Several retrospective studies concluded that there was no difference in disease-free survival (DFS) or overall survival (OS) for patients with advanced ovarian cancer treated with IDS in comparison to PDS [7] [8] [9] [10] [11]. Moreover, Bristow and Chi published a meta-analysis that involved more than 800 patients, showed that NACT compared with PDS was associated with a worse OS, and they suggested that the definitive operative intervention should be performed as early in the treatment program as possible [12]. However, a more recent meta-analysis of multiple central randomized trials concluded that survival was similar in patients treated with NACT followed by interval debulking surgery compared to primary debulking followed by chemotherapy, and they even criticized Bristow and Chi meta-analysis [13] [14]. Therefore, the aim of this retrospective study is to evaluate the outcome of IDS after primary NACT compared to PDS followed by adjuvant chemotherapy for FIGO stage III epithelial ovarian cancer.

## 2. Patient and Methods

### 2.1. Patients

This is a retrospective study performed on all ovarian cancer cases who were admitted to Surgical Oncology and Medical Oncology Departments at South Egypt Cancer Institute, Assiut University in the period from January 2010 to December 2015. The patients' flow chart is shown in **Figure 1** of the CONSORT diagram. In this period, all females aged 18 years or more, diagnosed as stage III (according to FIGO ovarian cancer staging) epithelial ovarian cancer and underwent surgical treatment, either primary or after NACT, had been included in the study. Patients with incomplete data or those who did not complete the NACT were excluded from the study. Patients lost to follow up were considered deaths. The patients were categorized according to their age, performance status, tumor grade, and the extend of cytoreduction or status of optimal debulking.



**Figure 1.** CONSORT diagram.

## 2.2. Treatment and Evaluation

All patients were evaluated properly for accurate staging and underwent all routine laboratory and formal diagnostic radiological investigations. Patients were divided into two groups. The first group included patients who received three cycles of NACT, then IDS, then three additional cycles of adjuvant chemotherapy. The second group included those who have PDS, followed by six cycles of chemotherapy. The chemotherapy was given as a 3-week cycle consisted of carboplatin in a dose of the area under the curve 5 (AUC5) plus paclitaxel 175 mg/m<sup>2</sup>. We collected patients' data, including demographic data, performance status, histopathological tumor grade, chemotherapy, postoperative residue, recurrences, and deaths.

## 2.3. Statistical Analysis

Statistical analysis was performed by SPSS software (Chicago, IL, US) for Windows version 21, applying parametric and non-parametric tests when appropriate. We tested the approximately normal distribution of sample through the Shapiro-Wilk's test and the visual inspection of the histograms. Categorical variables have been expressed as percentages and analyzed through the  $\chi^2$  test or the Fisher's exact test, when appropriate. Statistically significant differences between treatment arms were defined as a p-value less than 0.05.

DFS was defined as the time interval from the date of diagnosis to the date of the documented recurrence of the disease. If there was no documented recurrence, DFS was calculated from the date of diagnosis to the date of the last follow-up or death, whichever occurred first. OS was defined from the diagnosis date to the death date or last follow-up date.

The Kaplan-Meier method was used to estimate survival curves. For each variable, the significance of the difference in the unadjusted survival curves was assessed using the log-rank test.

We calculated hazards ratios (HRs) for survival over the entire follow-up period using a Cox proportional hazards model and 95% confidence intervals (CIs). We entered the prognostic factors in the multivariable model to test their independent significance.

## 3. Results

### 3.1. Demographics and Characteristics of the Patients

During a period of 5 years (January 2010-December 2015), a total of three hundred eighty patients with stage III ovarian cancer met the inclusion criteria of this study, as illustrated in the CONSORT diagram. Of those, two hundred and twenty-six patients (59.47%) underwent PDS followed by six cycles of adjuvant chemotherapy while one hundred and fifty-four (40.53%) patients received three cycles of NACT followed by IDS plus three additional cycles of adjuvant chemotherapy (**Table 1**). Baseline characteristics were balanced between groups. The majority of the patients had a good performance status (92.9% and 88.9% in

**Table 1.** Demographics and baseline characteristics of enrolled patients (N = 380) underwent primary or interval debulking surgery.

Characteristic	Primary Debulking Surgery (n = 226)		Interval Debulking Surgery (n = 154)	
	No	%	No	%
Age, Years				
<b>Median (Range)</b>	55 (40 - 82)		55 (40 - 85)	
<60	140	61.9	105	68.2
≥60	86	38.1	49	31.8
<b>ECOG PS</b>				
0/1	210	92.9	137	88.9
2	16	7.1	17	11.1
<b>Tumor Grade</b>				
Grade I or II	105	46.5	77	50
Grade III	121	53.5	77	50
<b>Cytoreduction</b>				
Optimal	136	60.2	101	65.6
Suboptimal	90	39.8	53	34.4

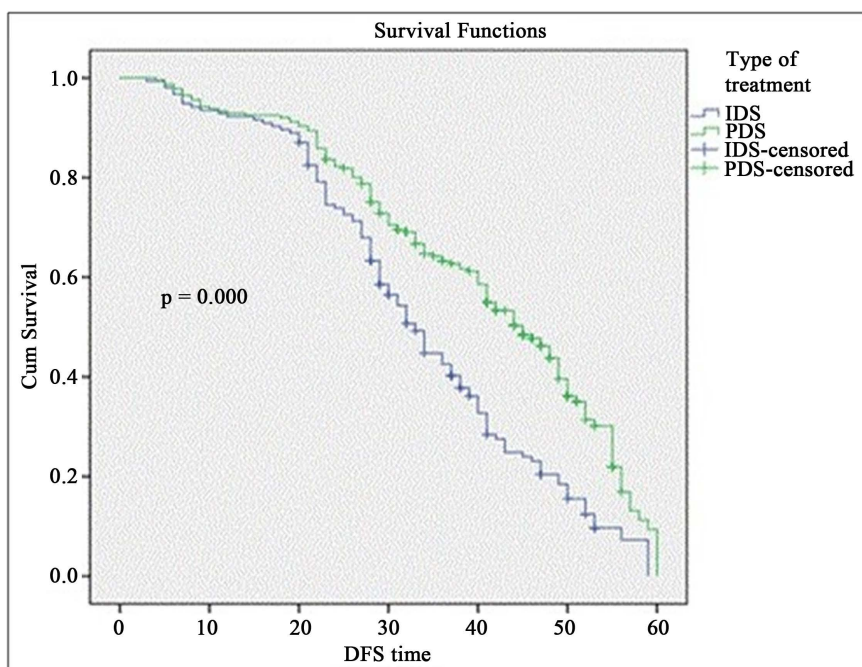
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status.

the PDS and IDS arms, respectively). Also, grade III tumors were present in 50% of the patients in IDS arm, as well as in 53.5% in PDS arm. Optimal debulking was achieved in 136 patients (60.2%) who underwent primary surgery, while this occurred in 101 patients (65.6%) who underwent IDS after neoadjuvant chemotherapy (**Table 1**).

### 3.2. Disease-Free Survival

Univariate analysis revealed that the DFS was significantly reduced after IDS when compared to PDS (median DFS: 33.00 months; 95% CI 30.23 - 35.77 vs. 45.00 months; 95% CI 41.25 - 48.75, respectively;  $p < 0.001$ ) (**Figure 2** and **Table 2**).

Also, there was a statistically significant effect of performance status of the patient on DFS, in favor of PS 0/I (median DFS: 41.00 months; 95% CI 48.69 - 43.31 vs. 8 months; 95% CI 6.39 - 9.61, for patients with PS 0/I vs. those with PS II, respectively;  $p < 0.001$ ) (**Table 2**). Moreover, optimal debulking surgery was associated with higher DFS when compared to suboptimal debulking (median DFS: 45.00 months; 95% CI 41.10 - 48.91 for patients underwent optimal debulking vs. 29.00 months; 95% CI 26.77 - 31.23 for those underwent suboptimal debulking;  $p < 0.001$ ) (**Table 2**). Moreover, there was a significant result regarding the effect of the age of the patient ( $p < 0.001$ ) and the grade of the tumor ( $p = 0.05$ ) on DFS; the details are shown in **Table 2**.



**Figure 2.** Kaplan-Meier analysis of DFS in patients with stage III epithelial ovarian cancer.

**Table 2.** Univariate and multivariate analysis of disease-free survival.

Variable	Median DFS	p Value	HR	p Value	95% CI
	Univariate Analysis of DFS		Multivariate Analysis DFS		
<b>Age</b>					
≤60	50.2	p < 0.001	1.301	0.159	0.902 - 1.877
≥60	41.0				
<b>PS</b>					
0/I	41.0	p < 0.001	0.537	0.003	0.357 - 0.810
II	8.0				
<b>Treatment</b>					
PDS	45.0	0.01	0.537	0.03	0.357 - 0.810
IDS	33.0				
<b>Cytoreduction</b>					
Optimal	45.0	p < 0.001	0.023	0.05	0.007 - 0.073
Suboptimal	29.0				
<b>Grades</b>					
I/II	53.4	0.05	0.116	0.05	0.040 - 0.334
III	41.4				

Abbreviations: CI; confidence interval; DFS, disease-free survival; HR, hazards ratio; IDS, interval debulking surgery; PDS, primary debulking surgery; PS, performance status.

With multivariate analysis, the type of treatment was still significant. This indicated that it was an independent prognostic factor for DFS as primary debulking surgery was associated with about 50% reduction in the risk of disease recurrence with hazards ratio (HR) of 0.53; 95% CI 0.36 - 0.81;  $p = 0.03$  (**Table 2, Table 3**). With subgroup analysis, all patients' subgroups more benefited from PDS for DFS, except patients with PS II who achieved higher DFS with IDS ( $p = 0.007$ ). The details of the subgroup analysis are shown in **Table 4**.

### 3.3. Overall Survival

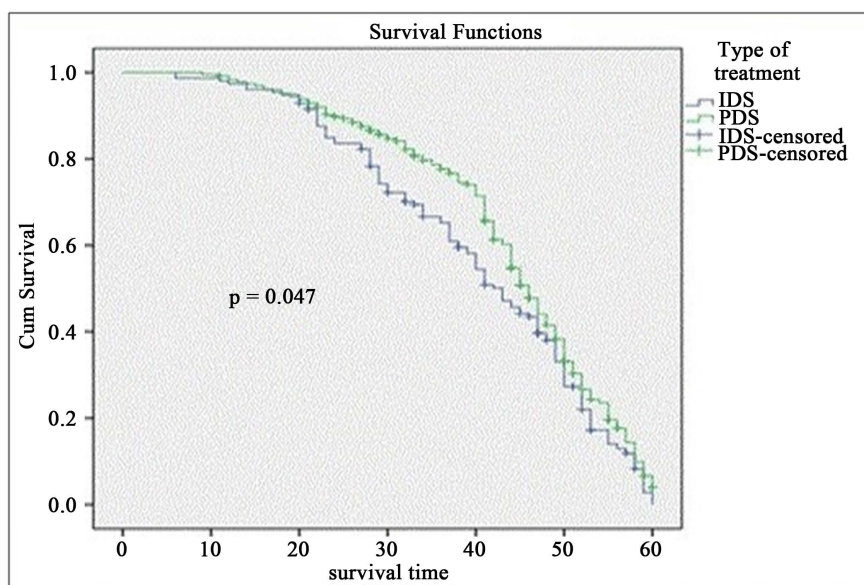
In this study, treatment modality was significant for overall survival (OS), which was significantly reduced after IDS compared to PDS. (median OS: 43 months; 95% CI 39.46 - 46.54 vs. 46 months; 95% CI 44.24 - 47.76, respectively;  $p = 0.047$ ) (**Figure 3 and Table 3**). Also, the PS II, older age, and the high-grade tumor had an adverse effect on OS ( $p < 0.001$ ,  $p = 0.02$ , and  $p < 0.001$ , respectively) (**Table 3**).

With multivariate analysis, the type of treatment appeared as an independent prognostic factor for OS. Hazards ratio for this effect was 1.5; 95% CI 1.10 - 1.70;  $p = 0.017$ , in favoring PDS (**Table 3**). With subgroup analysis, the patients that more benefited from PDS for OS were those with age of less than 60 years old ( $p = 0.04$ ), grade I/II ( $p = 0.000$ ), and PS 0/I ( $p = 0.009$ ) (**Table 4**). The only subgroup that got more benefit in OS from IDS were patients with performance status II (OS of IDS/PDS for patients with PS = II was 33.7/16 months ( $p = 0.000$ )) (**Table 4**).

**Table 3.** Univariate and multivariate analysis of overall survival.

Variable	Median OS (Months)	p Value	HR	p Value	95% CI
	Univariate Analysis		Multivariate Analysis		
<b>Age</b>					
≤60	50.5	0.02	1.301	0.17	0.902 - 1.77
≥60	45.0				
<b>PS</b>					
0/I	41.0	<0.001	4.2	0.001	2.6 - 6.8
II	8.0				
<b>Treatment</b>					
PDS	46.0	0.047	1.5	0.017	1.10 - 1.70
IDS	43.0				
<b>Cytoreduction*</b>					
Optimal	49	0.8	NA	NA	NA
Suboptimal	47				
<b>Grades</b>					
I/II	52.4	<0.001	1.5	0.017	1.1 - 1.7
III	46.4				

\*Cytoreduction was not included in multivariate analysis as it was insignificant in univariate analysis. Abbreviations: CI; confidence interval; HR, hazards ratio; IDS, interval debulking surgery; NA, not applicable; OS, overall survival; PDS, primary debulking surgery; PS, performance status.



**Figure 3.** Kaplan-Meier analysis of OS in patients with stage III epithelial ovarian cancer.

**Table 4.** Subgroup survival analysis according to treatment modality.

Variable	DFS				OS			
	IDS Mean Survival	PDS Mean Survival	Survival Ratio	p Value	IDS Mean Survival	PDS Mean Survival	Survival Ratio	p Value
Age ≤ 60 ys	36	42.8	0.84	<0.001	41.3	45.4	0.9	0.04
Age ≥ 60 ys	30	38.3	0.78	0.006	39.4	41.7	0.95	0.5
PS = 0/I	36.2	43.7	0.82	<0.001	41.5	46	0.9	0.009
PS = II	18.5	7.8	2.3	0.007	33.7	16.2	2	<0.001
Grade = I/II	37.7	42.6	0.88	0.006	36.8	44.3	0.83	<0.001
Grade = III	30.4	39.7	0.84	<0.001	44.3	43.7	1	0.27
Optimal Cytoreduction	40	45.5	0.88	0.001	38.3	45	0.85	<0.001
Suboptimal Cytoreduction	23.7	34.7	0.68	<0.001	44.8	42.3	1.05	0.14

Abbreviations: DFS, disease-free survival; IDS, interval debulking surgery; OS, overall survival; PDS, primary debulking surgery; PS, performance status.

#### 4. Discussion

In this study, primary debulking surgery (PDS) was better in OS and DFS than interval debulking surgery (IDS) for FIGO stage III epithelial ovarian carcinoma. In most of the previous studies, there is no consensus regarding this point which may be due to combining both FIGO stage III and IV as advanced ovarian cancer as well as the differences in the design of the studies [13]-[18]. Therefore, in our study, we evaluated FIGO stage III epithelial ovarian carcinoma separately that may explain more details about the outcome of this category of these patients.



In univariate and multivariate analysis to show the risk factors that may affect OS and DFS, we found that treatment modality was a significant and independent prognostic factor for disease-free survival (DFS) and overall survival (OS) which are significantly better after PDS compared to IDS. We even found that DFS was significantly dropped in patients with bad performance status and suboptimal cytoreduction. Also, OS was significantly reduced in patients with bad performance status, older age, and high-grade tumors.

Regarding subgroup analysis, only the subgroup with performance status II got significant benefit from IDS in terms of DFS (DFS of IDS/PDS was 18.5/7.8 months,  $p = 0.007$ ). Again, the only subgroup that got benefit in OS from IDS was patients with performance status II (OS of IDS/PDS was 33.7/16 months,  $p = 0.000$ ). In this subgroup, OS survival nearly doubled in comparison to PDS. This may be explained that neoadjuvant chemotherapy can resolve pleural effusions and ascites and improve the patient's performance status prior to surgery [19] [20]. These effects may reflect the better outcome of IDS in this subgroup. There have been reports of subjective improvements in the sense of well being and quality of life [21] [22]. It can decrease tumor volume and increase resectability. Thus, patients may have less intraoperative blood loss, shorter operative times, less intensive care unit admissions, and shorter length of hospital stay [23] [24] [25]. These issues are particularly important for patients with medical co-morbidities and a low probability of cure. Therefore, NACT may benefit a selected group of patients with low-performance status.

Optimal cytoreduction is a critical prognostic factor for prolonged survival, whether it is performed before or after chemotherapy. In this study, the overall DFS was significantly reduced from 45 months after optimal cytoreduction to 29 months after suboptimal cytoreduction ( $p = 0.000$ ). However, OS was not significantly different between the two groups (Table 2). Gao et al. demonstrated that patients debulked to no residual disease (RD) after PDS had the longest DFS and OS. For patients debulked to  $RD < 1$  cm or to  $RD \geq 1$  cm after PDS, their prognosis had no significant differences. Moreover, after NACT, patients who were debulked to no RD after IDS had a significantly lower DFS and OS compared to patients with no RD after PDS [26]. These results agree with our results regarding the optimal debulking.

In the 2018 SGO (Society of Gynecologic Oncology) annual meeting on women's cancer, Dr. Beryl suggested a new prospective. If R0 was not attained, low volume disease confined to single anatomic locations ( $\leq 1$  cm-SL) may be an alternative [27]. The study showed that patients with  $RD \leq 1$  cm involving multiple anatomic locations ( $\leq 1$  cm-ML) had similar outcomes to suboptimal debulked ( $RD > 1$  cm) patients. Moving beyond complete cytoreduction, low volume RD may be another option for consideration.

With the improvement of surgical techniques, several previous "unresectable" tumors could now be removed meticulously. In our series, we confirmed that the value of diagnostic laparoscopy for resectability assessment; patients of PDS arm who underwent laparoscopy before surgery showed a significantly higher rate of

complete debulking compared to patients who did not undergo laparoscopy (data not shown). In our opinion, laparoscopic assessment before PDS or IDS should become one of the fundamental diagnostic steps to drive treatment decision.

One of the limitations of the present study is its retrospective nature.

## 5. Conclusion

This study showed that PDS resulted in a better disease-free survival and overall survival than IDS. Moreover, OS and DFS have significantly dropped in elderly patients, patients with bad performance status, suboptimal cytoreduction as well as high grade and undifferentiated tumors. Therefore, patients selection should be considered.

## Conflicts of Interest

Authors have no conflict of interests to declare.

## Ethical Considerations

Approval for this study was obtained from our Ethical Committee.

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## Abbreviation

AUC5: Area under the Curve 5.

CIs: Confidence Intervals.

CONSORT: Consolidated Standards of Reporting Trials.

DFS: Disease-Free Survival.

FIGO: International Federation of Gynecology and Obstetrics.

HRs: Hazards Ratios.

IDS: Interval Debulking Surgery.

NA: Not Applicable.

NACT: Neoadjuvant Chemotherapy.

OC: Ovarian Cancer.

OS: Overall Survival.

PDS: Primary Debulking Surgery.

PS: Performance Status.

RD: Residual Disease.

SGO: Society of Gynecologic Oncology.