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Neoadjuvant chemotherapy followed by interval debulking surgery versus primary debulking surgery in the advanced epithelial ovarian cancer – a retrospective cohort study

Neoadjuvantna hemioterapija praćena intervalnom *debulking* hirurgijom nasuprot primarnoj *debulking* hirurgiji kod uznapredovalog epitelijalnog karcinoma jajnika – retrospektivna kohortna studija

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Abstract

Background/Aim. The gold standard in treating the advanced ovarian cancer (AOC) is primary debulking surgery (PDS) followed by platinum-based adjuvant chemotherapy. In the AOC, the extent of tumor resection (residual tumor volume) is the most important prognostic factor for overall survival (OS) and progression-free survival (PFS). Neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) is an experimental treatment of the AOC, introduced in clinical practice in order to improve cytoreduction rate and prolong survival. The aim of this study was to compare the survival and cytoreduction rate of NACT+IDS and PDS in patients with the AOC. **Methods.** This retrospective cohort study included patients with the AOC, separated into two groups. The first group treated with PDS had 59 patients, while the second group, treated with NACT + IDS, had 33 patients. **Results.** A lower rate of suboptimal cytoreduction (39.39%) was found in the NACT + IDS group than in the PDS group (57.63%). The percentage of complete cytoreduction was higher in patients treated with NACT + IDS (51.52%) than in those treated with PDS (38.98%). Nevertheless, median OS and PFS were not significantly different between the groups ($p < 0.05$). OS was 35 months and 31 months in the PDS and NACT + IDS groups, respectively. PFS was 16 months in the PDS and 19 months in the NACT + IDS group. **Conclusion.** Despite the higher rate of optimal debulking surgery after NACT+ IDS, survival of patients treated with method was not better than those treated with PDS. The decision for either NACT+IDS or PDS should be tailored to the individual patient.

Key words:
cytoreduction surgical procedures; drug therapy; gynecologic surgical procedures; ovarian neoplasms; survival; prognosis.

Apstrakt

Uvod/Cilj. Zlatni standard u lečenju uznapredovalog karcinoma jajnika (AOC) je primarna citoreduktivna hirurgija (PDS) nakon koje sledi adjuvantna hemioterapija na bazi platine. Kod AOC, opseg resekcije tumora (rezidualni volumen tumora) je najvažniji prognostički faktor za ukupno preživljavanje (OS) i preživljavanje bez progresije bolesti (PFS). Neoadjuvantna hemioterapija (NACT) praćena intervalnom citoreduktivnom hirurgijom (IDS) je eksperimentalni tretman AOC, uveden u kliničku praksu kako bi se poboljšala citoredukcija i produžilo preživljavanje. Cilj rada je bio da se uporedi stopa preživljavanja i citoredukcije između NACT + IDS i PDS kod bolesnica sa AOC. **Metode.** Retrospektivnom kohortnom studijom bile su obuhvaćene bolesnice sa AOC, podeljene u dve grupe. U grupi lečenoj PDS bilo je 59 bolesnica, dok su u grupi lečenoj NACT + IDS bile 33 bolesnice. **Rezultati**. Utvrđena je niža stopa suboptimalne citoredukcije (39,39%) u NACT + IDS grupi u poređenju sa PDS grupom (57,63%). Procenat potpune citoredukcije bio je viši kod bolesnica lečenih NACT + IDS (51,52%) nego kod onih lečenih PDS (38,98%). Ipak, OS I PDS nisu se značajno razlikovali između grupa ($p < 0,05$). OS je bilo 35 meseci u PDS grupi i 31 mesec u NACT + IDS grupi; PFS je bilo 16 meseci u PDS i 19 meseci u NACT + IDS grupi bolesnica. **Zaključak**. Uprkos višoj stopi optimalne citoredukcije nakon NACT + IDS, preživljavanje bolesnica lečenih na ovaj način nije bilo bolje od preživljavanja bolesnica lečenih metodom PDS. Odluku za primenu NACT + IDS ili PDS treba prilagoditi svakoj bolesnici.

Ključne reči:
citoredukcija, hirurške procedure; lečenje lekovima; hirurgija, ginekološka, precedure; jajnik, neoplazme; preživljavanje; prognoza.

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Introduction

Ovarian cancer represents the second most common gynecological cancer and a leading cause of mortality among cancers in gynecology [1]. The lifetime risk for women to develop ovarian cancer is estimated to be 1 : 70 [2]. The advanced disease is present in 70% of the patients at the time of diagnosis due to ovarian cancer oncogenesis, lack of specific symptoms, and the fact that reliable prevention methods are still unavailable [3]. Therefore, the prognosis is poor, in general with an overall 5-year survival rate of 45%, and even lower in the advanced stages [2].

The gold standard in treating a newly diagnosed advanced ovarian cancer (AOC) is primary debulking surgery (PDS) followed by platinum-based adjuvant chemotherapy [4]. Patients who are not fit for surgery are candidates for primary chemotherapy or symptomatic treatment.

In the AOC, the extent of tumor debulking (cytoreduction) and a residual tumor volume are the most important prognostic factors for overall survival (OS) and progression-free survival (PFS) [4, 5]. Suboptimal cytoreductive surgery (residual disease > 1 cm) has no positive effect on survival [6]. Therefore, the AOC surgery is always made in order to achieve complete (no macroscopical residual disease) or at least optimal cytoreduction (residual disease < 1 cm) [7].

Neoadjuvant chemotherapy (NACT) in ovarian cancer is defined as 3–4 cycles of platinum-based chemotherapy, followed by interval debulking surgery (IDS) and adjuvant chemotherapy. NACT followed by IDS was introduced as a new treatment modality for the AOC with the hypothesis that the application of chemotherapy before surgery could shrink the tumor, make it more resectable, and thus increase the rate of cytoreduction with opposing the patient to a less extensive surgery at the same time. This would be of special importance in those patients where optimal cytoreduction is estimated to be unattainable by primary surgery. Moreover, the ones who are not fit to stand the extensive surgery at the time of diagnosis due to comorbidities or poor general condition can have the benefit of postponing the surgery with neoadjuvant chemotherapy.

Methods

We included NACT + IDS as an experimental treatment in our clinical protocol after the results of the EORTC55971 randomized trial that showed noninferiority of NACT + IDS to PDS in terms of PFS and OS, with less postoperative morbidity and a higher percent of optimal debulking in the experimental arm [8].

The results of treatment and survival of patients with the AOC operated after NACT were compared with the control group of patients treated with PDS in the same period. The main objective of this study was to compare these two treatments in terms of patients' survival and cytoreduction rate.

This retrospective cohort study included patients with advanced epithelial ovarian cancer. Subjects were separated into two groups based on a different treatment modality. The first group was treated with PDS, while the second one was treated with NACT + IDS.

All the analyzed data were gathered in a retrospective manner from our hospital information system. Medical records of the patients with the diagnosis of ovarian cancer operated in our institution from January 1st, 2013 until December 31st, 2017 were analyzed. We included patients with the newly diagnosed ovarian cancer in stages III and IV, as specified by the International Federation of Gynecology and Obstetrics (FIGO) staging criteria [9]. All included patients had histologically proven epithelial ovarian cancer. The protocol used for NACT consisted of paclitaxel in a dose of 175 mg/m^2 of the body surface area with carboplatin in a dose equal to the area under the curve (AUC) of 6, every three weeks.

Patients were considered to have undergone debulking (cytoreductive) surgery if any open surgery with the intention of performing the debulking procedure had been done. A surgical procedure after which no macroscopic disease was visible was defined as a complete debulking surgery. Patients were considered optimally debulked when residual lesions were present after the surgery and were less than 1cm in greatest diameter, while suboptimally debulked were those patients with residual disease bigger than 1 cm.

Estimation of the tumor resectability and the decision for NACT was made by the multidisciplinary Oncology Board for the gynecological tumors from our institution. The decision was based on a clinical examination, performance status, comorbidities, imaging results, CA125 levels, and previous diagnostic laparoscopy in individual cases. In all the cases where optimal cytoreduction seemed to be unachievable with primary surgery, NACT was advised.

Follow-up data were collected from patients' records and individual communication. The first day of follow-up corresponds to the date of the first cycle of chemotherapy in the NACT + IDS group, or the date of the operation in the PDS group. PFS was measured to the date of the first radiological progression of the disease. In cases where no progression was documented before, PFS was calculated to the date of the last contact and the date of death. OS was calculated to the time of death. Surviving patients were censored at the time of the last contact. Patients who were lost to follow-up were censored within the date of the last contact. CA125 values were expressed in U/mL.

This study was approved by the Ethical Committee of our institution and conducted in accordance with the Helsinki Declaration.

Statistical analysis

For the continuous variables, the correlation between investigated variables was represented with Pearson's correlation coefficient. Spearman's rank-order correlation was used for the analysis of ordinal variables. Student's *t*-test and χ^2 test were used for the comparison of variables between groups. Survival was analyzed using a Kaplan Maier method. Differences in survival were estimated by the

use of Log-rank (Mantel-Cox) and Gehan-Breslow-Wilcoxon tests. *P*-values at the level of 0.05 were considered statistically significant. Microsoft Excel 2007 with Statistica 13 software package (StatSoft Inc., Tulsa, OK, USA; University License University of Novi Sad) was used for statistical analysis.

Results

The control group of patients who underwent PDS had 59 patients (group 1), while the study group treated with NACT + IDS consisted of 33 patients (group 2).

In the NACT + IDS group, patients received 3.61 cycles of NACT on average. The decision for NACT was based on cytological findings from ascites or pleural effusion in 23/33 patients (69.70%), while 10/30 patients (30.30%) had histologically confirmed epithelial ovarian cancer by tumor biopsy prior to NACT. Resectability was determined mostly by imaging results in 30/33 (90.9%) of patients, and only 3/33 (9.1%) of patients had diagnostic laparoscopy to estimate the possibility of complete debulking. Imaging estimated complete response to NACT was obtained in 2/33 (6.06%) of the patients, partial response was obtained in 29/33 (87.88%), while 2/33 (6.06%) had stable disease after NACT. All the patients in this group had serous ovarian cancer confirmed after the operation, except two where the tumor tissue was not found in the surgical specimen (these were the same two patients with a complete response to NACT).

In the analysis of joint data from both cohorts, a moderate positive correlation was found between the level of cytoreduction and PFS ($r = 0.43$, $p < 0.05$), and the level of cytoreduction and OS ($r = 0.38$, $p < 0.05$) (Tables 1 and 2). This correlation was confirmed using a Kaplan Maier method, where a significant difference in OS was observed between each of the three groups of patients with separate levels of cytoreduction ($p < 0.05$). The group with complete cytoreduction had better OS than both groups with optimal and suboptimal cytoreduction, while the group with optimal cytoreduction had superior OS than the one with suboptimal cytoreduction (Figure 1). A negative correlation was found

Table 1
Pearson's correlation analysis of the examined parameters

Parameters	Pearson's correlation coefficient			
	Age	PFS	OS	CA125
Age		-0.1308	-0.0954	0.0552
PFS	-0.1308		0.8010*	-0.1558
OS	-0.0954	0.8010*		-0.1276
CA125	0.0552	-0.1558	-0.1276	

***Marked correlations are significant at $p = 0.05$ level.**
PFS – progression free survival; OS – overall survival.

Table 2
Spearman's rank-order correlation analysis of the examined parameters.

Parameters	Spearman's rank-order correlation coefficient					
	PFS	OS	Cytoreduction	FIGO stage	Age	CA125
PFS			0.435*	-0.221*		
OS			0.383*	-0.163		
Cytoreduction	0.435*	0.383*		-0.066	-0.086	-0.313*
FIGO stage	-0.221*	-0.163	-0.066		-0.080	0.197
Age			-0.086	-0.080		
CA125			-0.313*	0.197		

*** Marked correlations are significant at $p = 0.05$ level.**
PFS – progression free survival; OS – overall survival; FIGO – Federation of Gynecology and Obstetrics.

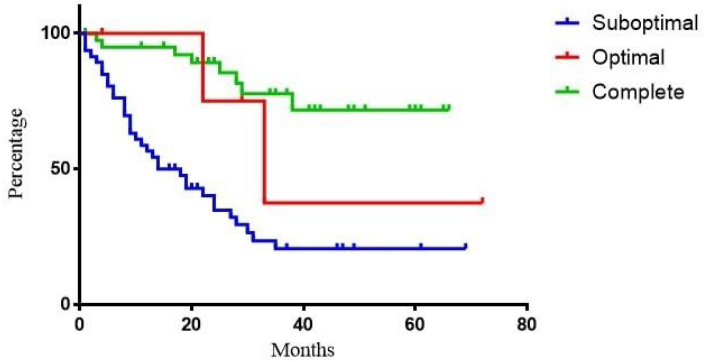

Fig. 1 – Kaplan-Meier curves of the overall survival (OS) for groups of patients with complete, optimal, and suboptimal cytoreduction.

to be significant between FIGO stage and PFS (r = -0.22, $p < 0.05$) and levels of CA125 and cytoreduction rate (r = -0.31, $p < 0.05$). (Tables 1 and 2). Higher levels of CA125 at the time of diagnosis were associated with a lower cytoreduction rate. Except above mentioned, other analyzed parameters were not in a significant correlation (Tables 1 and 2).

The significant difference between groups was found in CA125 levels before treatment (568 U/mL in the PDS vs. 1,129 U/mL in the NACT group; $p < 0.01$; Cohen's d = 0.64-medium effect size) (Figure 2). The median total number of chemotherapy cycles was 4.90 in the PDS group, significantly lower compared with 7.67 in the NACT + IDS group ($p < 0.001$; Cohen's d = 1.17 – large effect size) (Figure 2). Note that in the NACT + IDS group, the total number of cycles represents a sum of neoadjuvant and adjuvant treatment. Groups did not differ significantly in patients' age (Figure 2).

The distribution of FIGO stages in the two examined groups is shown in Figure 3. We observed the lower percentage of stage IIIb and the higher percentage of stage IVa in the NACT + IDS group. The difference between the two groups in the FIGO stage was found to be significant (χ^2 (4) = 2.97, $p = 0.56$).

We detected 39.39% of patients with suboptimal

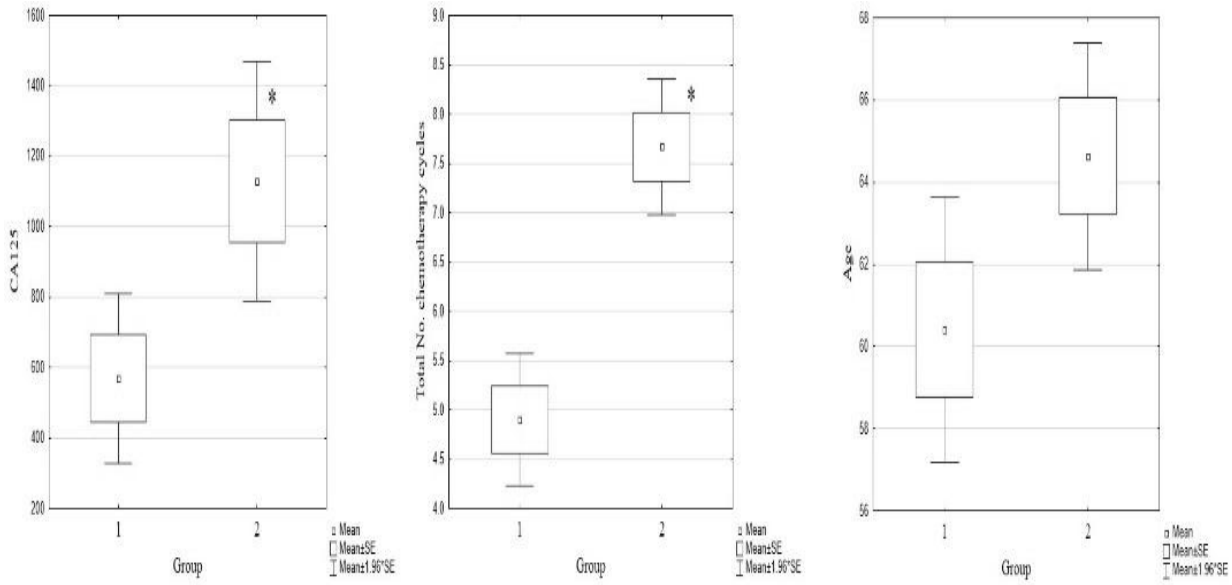

Fig. 2 – Box-plot graphs of the variables compared between the groups (* – statistically significant at $p = 0.05$ level).
Group 1 – patients treated by neoadjuvant chemotherapy + interval debulking surgery;
Group 2 – patient treated by primary debulking surgery.

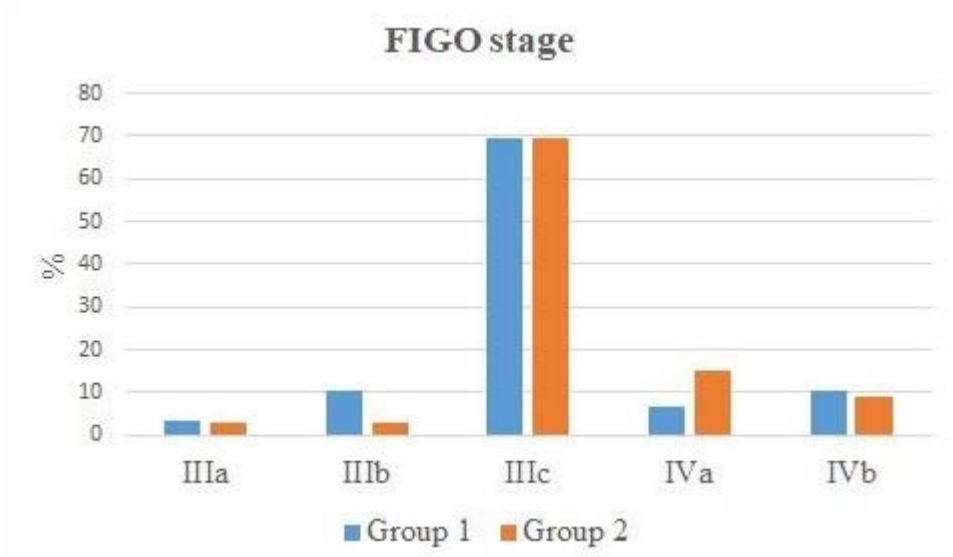

Fig. 3 – Difference in the FIGO – Federation of Gynecology and Obstetrics (FIGO) stage distribution between the examined groups.
For the explanation of the terms Group 1 and Group 2 see under Figure 2.

cytoreduction in the NACT + IDS group, which was lower than 57.63% observed in the PDS group. Furthermore, the rate of complete cytoreduction was higher in patients treated with NACT + IDS (51.52%) than in those treated with PDS (38.98%). This difference among examined groups in cytoreduction was significant (χ^2 (2) = 3.41, p = 0.18) (Figure 4).

Nevertheless, the median OS was not significantly different between the groups. This period was 35 months and 31 months in the PDS and the NACT + IDS group, respectively (p < 0.05) (Figure 5). Likewise, we did not observe a statistical difference in PFS, which was 16 months in the PDS and 19 months in the NACT + IDS group (p < 0.05) (Figure 6). The median follow-up time was 37 months in the PDS and 43 months in the NACT + IDS group.

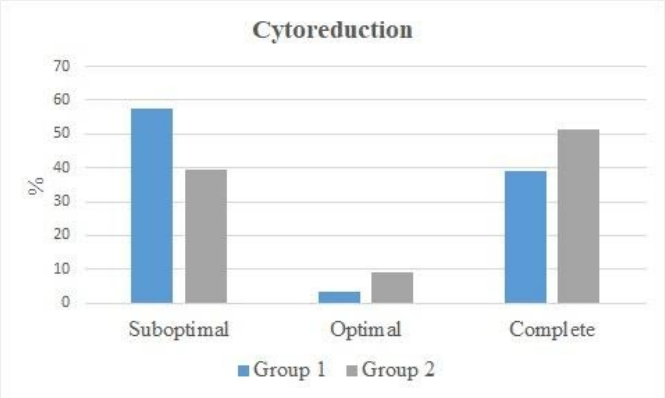

Fig. 4 – Difference in the cytoreduction rate distribution among the examined groups.
For the explanation of the terms Group 1 and Group 2 see under Figure 2.

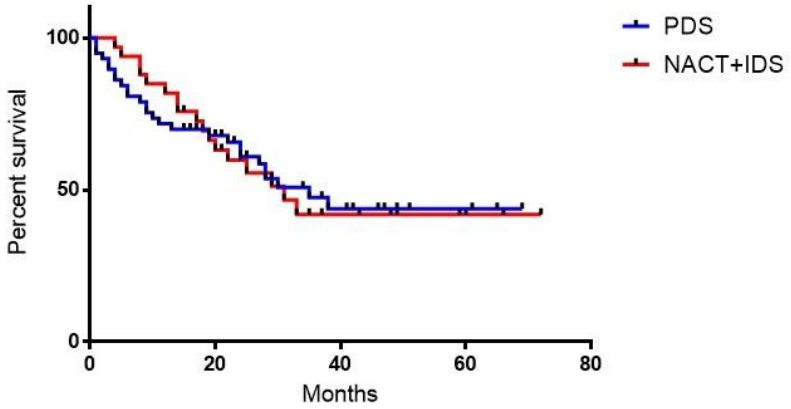

Fig. 5 – Kaplan-Meier curves of the overall survival (OS) for the examined groups of patients.
PDS – primary debulking surgery; NACT – neoadjuvant chemotherapy; IDS – interval debulking surgery.

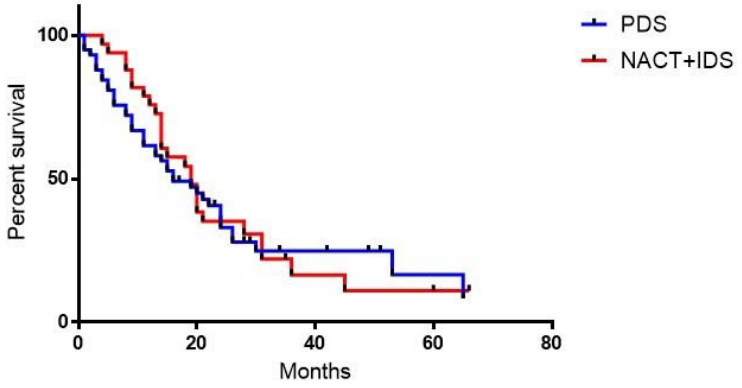

Fig. 6 – Kaplan-Meier curves of the progression-free survival (PFS) for the examined groups of patients.
For the abbreviations see under Figure 5.

Discussion

So far, it has been concluded in several studies that the primary goal of ovarian cancer surgery should be a complete cytoreduction with no residual disease since one improves the survival of patients with the AOC [5–8, 10–12]. Median survival is 1.5 months longer for every 10% increase of patients inside the cohort who are submitted to maximal cytoreductive surgery [5]. Still, patients with the residual disease up to 1 cm have better survival than those with the residual disease bigger than 1 cm [7, 13]. Therefore, optimal cytoreduction is appropriately defined as a residual disease < 1 cm and should continue to be the preferred surgical outcome in all the patients where the complete cytoreduction is unachievable. A positive correlation between the level of cytoreduction and survival of patients with the AOC was confirmed in our study, where better cytoreductive surgery with less residual disease corresponds to the longer OS.

We achieved optimal cytoreductive surgery (residual tumor < 1 cm) in 60.61% of patients in the NACT + IDS group, which was higher compared with 42.37% obtained in the PDS group. These results are similar to the ones from the randomized studies, where the optimal debulking rate was better after NACT + IDS than after the primary surgery [8, 10, 14]. The optimal debulking rate was 80.6% in the NACT + IDS group and 41.6% in the PDS group in EORTC55971 study [8], 73% vs. 41% in favour of NACT + IDS in CHORUS study [10], and 82% and 37%, in NACT + IDS and PDS group, respectively, in recently presented Japanese study [14].

Still, the higher rate of optimal debulking surgery observed in the NACT group did not mean better survival of patients treated with NACT + IDS compared with those treated with primary surgery. OS was 31 months in the NACT + IDS group and 35 months in the PDS group, without statistical difference. Additionally, the difference was not found in PFS, where we observed periods of 19 and 16 months in the NACT + IDS and the PDS group, respectively. Perspective, longer follow-up and a larger study population could alter the results and make the difference in survival between these groups statistically significant. Results of the three randomized trials published so far proved that the treatment with NACT + IDS does not yield longer survival than one with PDS [8, 10, 14]. On the other hand, two of these trials demonstrated noninferiority of NACT + IDS vs. PDS in terms of survival [8, 10].

It is questionable why the obvious difference in the extent of cytoreduction observed in this study and previous trials does not mirror in longer survival of patients treated with NACT + IDS. One of the explanations is that NACT can encourage the development of chemo-resistant clone cells, which reflects in lower survival than expected. A larger tumor mass at the start of NACT, due to its more numerous and heterogeneous cell population, has a higher potential for the selection of drug-resistant cells [15]. In Bristow's meta-analysis, median survival after NACT + IDS was lower than after PDS and was approximateve to that of suboptimally debulked patients after the primary surgery [16]. This can be explained by the selection bias of observational studies included in the meta-analysis where patients selected to NACT + IDS tend to be older, have worse performance status, have more comorbidities, and larger tumor burden. Partly, that was the case in our study, where the NACT + IDS group had higher FIGO stages than the PDS group. Also, significantly higher levels of CA125 at the time of diagnosis observed in the NACT + IDS group can reflect a larger tumor burden in this group. One of the potential confounders in our study could be the total number of chemotherapy cycles that patients received, which was higher in the NACT + IDS group and could give this group advantage over the PDS group in terms of survival. The average number of NACT cycles in our study was 3.61. It was observed that more than 4 cycles of NACT have a negative impact on median survival [16].

Should all patients with AOC have the same treatment, and should it be NACT + IDS or PDS? Subgroup analysis of the EORTC55971 trial demonstrated that the patients diagnosed in FIGO stage IIIc with the metastasis bigger than 5 cm and stage IV do better after NACT + IDS, while those in stage IIIc with the metastasis smaller than 5 cm had better survival if they underwent PDS [8]. The recent multicentric observational study showed the better survival of patients with ovarian cancer in FIGO stage IIIc if they underwent PDS, while there was no difference in survival between the NACT + IDS and PDS groups in stage IV disease [17]. Since the use of NACT + IDS for stage IIIa and IIIb ovarian cancer is unsupported with data from randomized studies, primary cytoreductive surgery remains the treatment of choice for those patients. Hence, some patients with AOC benefit more from NACT + IDS, some others from PDS. ESGO guidelines for ovarian cancer surgery [18] recommend that the primary surgery be the treatment of choice only when complete cytoreduction seems viable in patients fit for radical surgery. NACT is suggested in all other cases, and IDS is done only if the complete debulking appears achievable after a favorable response to NACT. Vergote et al. [19] suggested using certain criteria for the selection of patients for NACT based on the extent of the disease, tumor resectability, and a general condition of the patient.

As can be seen from the above recommendations, it is important to predict residual tumor volume before cytoreductive surgery in order to determine the best treatment for each patient and avoid interventions that are without benefit. Resectability can be predicted with certain accuracy using a CT scan, with sensibility 64–79% to presume suboptimal cytoreduction [20]. Same can be done with the help of several clinical and radiological criteria, all associated within a predictive model which has an accuracy of 73% [21]. Laparoscopy could be useful in prognosis of suboptimal cytoreduction, with a good sensitivity of 69–96% and 100% specificity [22]. In addition to conventional preoperative diagnostics, it can lower the percent of unsuccessful laparotomies from 39% to 10% [23]. Tumor marker CA125 can serve as a complement in decision-making since it lacks the accuracy to be used alone [24]. Higher levels of CA125 at the time of diagnosis lower the possibility

of optimal debulking, as observed in our and previous studies [24].

The data we have so far are inconclusive and motivate further research. Future trials with a different selection of patients and the use of bevacizumab in the neoadjuvant setting may elicit new evidence that can have implications in clinical practice and improve the survival of patients with ovarian cancer.

Conclusion

AOC treatment should be tailored to the individual patient and based on patients' age, performance status, comorbidities, histology, stage of the disease, and tumor resectability. PDS stays the standard of care in treating the AOC, while NACT + IDS should find its place in carefully chosen patients.

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