

# Advanced stage ovarian cancer patients with neoadjuvant chemotherapy suffered worse recurrence free survival

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# Abstract

## Background

Neoadjuvant chemotherapy (NACT) has been applied for the treatment of patients with advanced-stage epithelial ovarian cancer (EOC), fallopian tube cancer, and primary peritoneal cancer, as these patients have a low likelihood of achieving optimal debulking and are thus poor surgical candidates. Herein, we explore the effects of NACT and compare the surgical outcomes and recurrence data in patients who receive interval debulking surgery followed NACT(NACT-IDS) or primary debulking surgery(PDS).

## Methods

A retrospective, single-center, observational study was conducted. Patients with advanced-stage EOC, fallopian tube cancer and primary peritoneal cancer who were treated with NACT or primary debulking surgery were enrolled. The effects of NACT as well as the surgical outcomes and recurrence data were compared between the NACT-IDS and PDS groups.

## Results

The albumin level was elevated ( $42.61 \pm 3.46$  g/L vs.  $37.47 \pm 5.42$  g/L,  $P=0.001$ ) and the levels of CA12-5 and HE4 significantly decreased ( $P=0.002$ ,  $0.003$ ) in patients after neoadjuvant courses. The operation time, amount of blood loss during surgery, rate of bowel resection, time to chemotherapy, and platinum-free interval were comparable between the two groups ( $P \geq 0.05$ ). Recurrence-free survival was worse in the NACT-IDS group than in the PDS group (HR=2.406, 95% CI[1.024, 5.657]).

## Conclusion

NACT improved the condition of advanced-stage patients, but a poor recurrence free survival rate was observed; thus, NACT should not be applied in non-selected patients.

## Background

Epithelial ovarian cancer (EOC) is the fifth most common type of cancer and the leading cause of death due to cancer in women; there were 295,414 newly diagnosed cases and 184,799 deaths in 2018 worldwide<sup>1</sup>, and there were 22,530 cases and 13,980 deaths in 2019 in the United States<sup>2</sup>. The standard management of ovarian cancer is a combination of cytoreductive surgery (primary debulking surgery) followed by platinum-based chemotherapy. The purpose of surgery is ideally to remove the tumor, with less than or equal to 1 cm of residual tumor, which is associated with a survival benefit<sup>3</sup>. However, more than 75% of OC patients diagnosed with advanced-stage disease have accompanying ascites and hypoalbuminemia, which are predictive of severe postoperative complications<sup>4,5</sup>, and complications that occur after surgery delay adjuvant chemotherapy<sup>6</sup>. Therefore, neoadjuvant chemotherapy followed by interval debulking surgery is suggested<sup>7</sup> for patients with advanced-stage disease who have a low

likelihood of achieving optimal debulking and thus are poor surgical candidates. In addition, one study found higher quality of life scores in terms of emotional and cognitive function<sup>5</sup>. Importantly, the survival of patients who receive NACT followed by interval debulking surgery has been found to be no worse than the survival of those treated with PDS<sup>8,9</sup>. Recently, the utilization of NACT has been proven to rapidly decrease 30- and 90-day mortality after surgery<sup>10</sup>.

In this study, we aimed to explore the effects of NACT and to compare the surgical outcomes and long-term recurrence information between an NACT-IDS and a PDS group.

## Methods

### Patient selection

Patients with epithelial ovarian cancer, fallopian tube cancer or primary peritoneal cancer diagnosed by a pathologist and treated with NACT followed by interval debulking surgery (NACT-IDS) from January 1, 2013, to October 31, 2018, were considered potential participants. We also selected patients treated with primary debulking surgery (PDS) followed by platinum-based adjuvant chemotherapy during the same period for inclusion in the control group. The exclusion criteria were as follows: patients diagnosed with other malignant tumors and patients who did not undergo interval debulking surgery after NACT, or loss of follow-up. Informed consent was obtained.

We collected general information, including age, histology type, FIGO stage, and hemoglobin, albumin, alanine aminotransferase, aspartate aminotransferase, CA12-5, and HE4 levels before and after neoadjuvant therapy/surgery. We also collected information on the duration of surgery and the volume of bleeding during surgery as well as information regarding recurrence, platinum-free interval, and recurrence-free survival.

### Follow-up

The follow-up period ended on December 31, 2019, and all included participants underwent regular tests for serum CA12-5 levels and abdominal/pelvic computerized tomography(CT)/ magnetic resonance imaging(MRI). Recurrence was defined as elevated serum CA12-5 levels ( $\geq 35$  U/ml) as assessed by CT/MRI findings. The recurrence free survival was calculated from date of surgery to date of recurrence, and the platinum-free interval was calculated from the last chemotherapy cycle to the time of recurrence.

### Statistical analysis

SPSS 19.0 was applied for the statistical analysis, and  $P \leq 0.05$  was considered statistically significant. We used means  $\pm$  standard deviations (SD) or medians (interquartile ranges) to express quantitative variables, and qualitative variables were expressed as absolute numbers (percentages). Student's unpaired t test for variables with a normal distribution and the Mann-Whitney U test for variables with a

nonnormal distribution were used for the comparison of quantitative variables between the groups, and the Chi-square test was used for qualitative variables. Kaplan-Meier survival analysis was used to analyze recurrence free survival with GraphPad Prism 8.0.

## Results

### Clinical characteristics of the participators

Twenty-five patients received NACT followed by IDS, and 22 patients treated with PDS as the initial treatment were included. The baseline characteristics of the included patients are listed in Table 1. The age, FIGO stage, histology type, adjuvant chemotherapy cycle and rate of bowel resection were comparable between the NACT and PDS groups, while the diameters of the mass were larger in the PDS group than in the NACT group (P = 0.000).

Table 1  
Characteristics of the participated patients

	NACT (n = 25)	PDS (n = 22)	P
Age (y)	58.96 ± 9.87	56.64 ± 10.64	0.442
FIGO stage (n, %)			0.578
Ic	1	3	
IIc	22	16	
IV	2	3	
Histology type (n, %)			0.105
Serous	22	14	
Other	3	8	
Diameter (mm)	44.57 ± 25.74	85.94 ± 37.35	0.000
Neoadjuvant cycle	3 (2,3)	-	-
Adjuvant cycle	5.60 ± 2.33	5.43 ± 1.86	0.787
Bowel resection (n, %)	6, 24%	4, 18.18%	0.627
Length of follow-up, (Mean ± SD)	984.08 ± 543.62	758.41 ± 202.44	0.063

### The effect of NACT

In the NACT group, serum markers were selected to evaluate the effect of NACT before and after the course of chemotherapy. Additionally, we found that the albumin level was elevated after chemotherapy

(P = 0.001), while the CA12-5 and HE4 levels were obviously decreased posttreatment (P = 0.002, 0.003). In addition, the AST and ALT levels were comparable before and after the invention (P = 0.194, 0.074; Table 2).

Table 2  
The serum biomarkers tested pre- and post-NACT

	Pre-NACT	Pos-NACT	P
Albumin, mean, SD (g/L)	37.47 ± 5.42	42.61 ± 3.46	0.001
Hemoglobin, mean, SD (g/L)	120.36 ± 15.91	105.61 ± 13.36	0.000
CA 12 - 5, mean, SD (U/ml)	1610.52 ± 1677.53	215.69 ± 316.39	0.002
HE4, median range (U/ml)	471.70 (77.12, 1527.24)	112.40 (38.81,1272.00)	0.003
ASL, mean, SD (U/L)	26.11 ± 13.78	30.58 ± 11.08	0.194
ALT, mean, SD (U/L)	19.30 ± 16.73	26.51 ± 12.35	0.074

## The surgical outcomes and recurrence data of NACT-IDS and PDS

The preoperative hemoglobin and HE4 levels were lower in the NACT-IDS group than in the PDS group (P = 0.001, P = 0.031), and the AST and ALT levels were higher in the PDS group than in the NACT-IDS group (P = 0.005, P = 0.040); the operation time, blood loss during surgery, rate of bowel resection, and time from surgery to initial chemotherapy were comparable (P > 0.05). After the operation, the levels of hemoglobin and CA12-5 in the NACT-IDS group were lower than those in the PDS group (P = 0.022, P = 0.045). During the follow-up period, there were 14 patients with recurrence in the NACT group and 9 in the PDS group (P = 0.302). Among the patients who had recurrence, the platinum-free interval was 183.86 ± 89.28 days in the NACT-IDS group and 288.75 ± 188.56 days in the PDS group (P = 0.173). Additionally, there were 6/14 (42.86%) patients in the NACT-IDS group whose platinum-free interval was < 6 months and 2/9 (22.22%) patients in the PDS group (P = 0.333) (Table 3). Kaplan-Meier survival analysis for recurrence free survival demonstrated that patients who received NACT followed by IDS had a poor recurrence free survival (P = 0.0441). (Fig. 1)

Table 3  
The surgical outcomes and recurrence data of NACT-IDS and PDS

	NACT (n = 25)	PDS (n = 22)	P
Operation time (min)	216.08 ± 61.23	240.82 ± 60.55	0.176
Blood loss (ml)	300.00(200.00,500.00)	300.00(200.00,600.00)	0.286
Bowel resection (n)	6(24.00%)	4(18.18%)	0.897
Time to chemotherapy (day)	11.00(9.00,18.50)	11.00(10.00,14.75)	0.792
Recurrence, n, %	14(56.00%)	8(36.36%)	0.178
Platinum-free interval (< 6 months), n, %	6(24.00%)	2(9.09%)	0.333
Platinum-free interval, day, mean ± SD	183.86 ± 89.28	288.75 ± 188.56	0.173

## Discussion

Ovarian cancer is the leading cause of death from gynecological malignancy worldwide, as most patients are diagnosed at advanced stages due to a lack of sensitive screening tests and the lack of specific symptoms at early stages. The standard of treatment is surgery followed by platinum-based chemotherapy<sup>11</sup>, and optimal debulking is the goal, as residual tumors decrease progression-free survival and overall survival<sup>12</sup>. To achieve the goal of optimal debulking, multivisceral surgeries such as bowel section and splenectomy are performed<sup>13,14</sup>.

Invasive procedures are associated with high risks of morbidity and mortality; in addition, poor outcomes, such as hypoalbuminemia, are predictive of severe postoperative complications<sup>4</sup>, and complications delay the start of subsequent chemotherapy, which reduces progression-free survival<sup>6</sup>. Therefore, neoadjuvant chemotherapy offers an alternative treatment for patients with advanced ovarian cancer and makes surgery highly feasible<sup>15</sup>. In our study, we found that the level of albumin was elevated after the course of NACT ( $37.47 \pm 5.42$  vs  $42.61 \pm 3.46$ ,  $P=0.05$ ). Cancer patients have low preoperative albumin levels, especially those with advanced-stage disease and patients with ascites<sup>16</sup>; the mechanisms for this low level involve a decrease in amino acid intake and albumin synthesis<sup>17</sup> as well as an increase in albumin leakage to the extravascular space in patients with ascites. There were 21 (80.77%) patients with massive ascites upon diagnosis, and the largest mean diameter of the ascites assessed by ultrasound was  $104.05 \pm 31.75$  mm. After the course of NACT, ascites was not detected in 3 patients, and the largest mean diameter of the remaining cases of ascites was  $65.00 \pm 35.32$  mm ( $t = 3.636$ ,  $P = 0.001$ ). Furthermore, decreases in CA12-5 and HE4 levels were found ( $P=0.05$ ) in the NACT group, and side effects of chemotherapy (lowered hemoglobin levels) also occurred. Previous studies have observed that patients who receive interval debulking surgery after NACT have better surgical outcomes than patients who receive PDS, including less severe surgical complexity, fewer upper abdominal procedures, a shorter

surgical duration, a lower amount of perioperative blood loss, a shorter hospital stay<sup>5,8,18</sup>, and reduced surgical morbidity and mortality<sup>7,8</sup>. In our study, there was no difference in the surgical outcomes between the NACT and PDS groups, as NACT may induce fibrosis, which may influence surgical procedures.

The presence of residual disease after surgery largely impact the prognosis of EOC<sup>19</sup>; one study showed that the 7-year overall survival rate decreased from 73.6% in patients without residual tumors to 21% in patients with any type of residual disease<sup>20</sup>. Therefore, the goal of debulking surgery has been changed from the presence of a residual tumor less than 1 cm in diameter to the presence of no visible tumor<sup>21</sup>; however, advanced-stage disease is associated with a low rate of complete tumor resection<sup>22</sup>. A previous study demonstrated that patients who received IDS after NACT were likely to achieve optimal cytoreduction<sup>20,23</sup> but that they did not have superior survival<sup>24</sup>, and there was a decreasing trend in median survival with an increase in the number of NACT cycles<sup>24,25</sup>. These studies suggest that NACT impacts the evaluation of tumor spread and leads to incomplete tumor resection in potentially resectable areas.

In addition, patients treated with NACT-IDS suffer from recurrence more often than patients treated with PDS<sup>26</sup>. In our study, during the follow-up period, 14 (56.00%) patients experienced recurrence in the NACT group, and 8 (36.36%) had recurrence in the PDS group; the difference was not significant ( $P=0.05$ ). However, recurrence-free survival was poorer in the NACT-IDS group than in the PDS group (HR 2.406, 95% CI[1.024, 5.657]). Rauh-Hain and colleagues found that 88.8% of cases of recurrence in the NACT-IDS group were platinum resistant compared to 55.3% of cases in the PDS group ( $P = 0.001$ )<sup>27</sup>. The same outcome was also found by Gao, who showed that 40.3% of patients in the NACT-IDS group and 23.1% in the PDS group experienced platinum-resistant recurrence and<sup>28</sup>; similarly, NACT induced chemotherapy resistance in cancer stem cell colonies<sup>29</sup>. A limited number of studies have found that the TP53 gene mutation is the most common (70.3%) mutation after courses of NACT compared with before courses of NACT<sup>30</sup>; additionally, in platinum-resistant patients (relapsed within 6 months), the TP53 K351N mutation was significantly more severe in the NACT-IDS group than in the PDS group (57.14% vs 0%,  $P=0.01$ ). Even so, in our study, we found that there was no significant difference in the platinum-free interval ( $164.93 \pm 94.65$  vs.  $288.75 \pm 188.56$ ,  $P = 0.1115$ ) or in the < 6-month PFI (6/25 vs. 2/22,  $P = 0.333$ ).

There were some limitations in this study. First, this was a retrospective analysis in a single institution with a small sample size; thus, much stronger evidence is needed to confirm the results. Additionally, due to limited information, we did not compare overall survival between the two groups.

## Conclusion

NACT improves the performance of patients, but patients suffered more recurrence during the follow-up period. NACT should not be applied in all advanced ovarian cancer patients without selected.

# Abbreviations

NACT: neoadjuvant chemotherapy; IDS: interval debulking surgery; PDS: primary debulking surgery; CT: computerized tomography; MRI: magnetic resonance imaging; SD: standard deviations; CI: confidence interval

# Declarations

## Acknowledgements

None

## Authors' contributions

Cailiang Wu and Xuexin Zhou equally contribution to this manuscript, acquisition of data, analysis, and drafting the article. Yaping Zhu and Wei Bao contributed to the design of the study. Wei Xu, Yinyan He and Zhenyu Sang: interpretation of data. Cailiang Wu, Xuexin Zhou, Yi Miao, Long Zhou and Yiwen Feng: contribution to the concept of the study, coordinated the study. Cailiang Wu, Xuexin Zhou, Xing Li and Xiaoning Ji: contributed to the study execution and analysis.

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## Availability of data and materials

The data and materials used in the present study are available from the corresponding authors.( Also showed in Supplementary File)

## Consent for publication

All of the authors read the final manuscript and consent for publication

## Competing interests

None declared

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## Ethics approval and consent to participate

Our study approved by the Ethics committee of Shanghai General Hospital, and all the informed consent of included patients obtained.

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## Figures

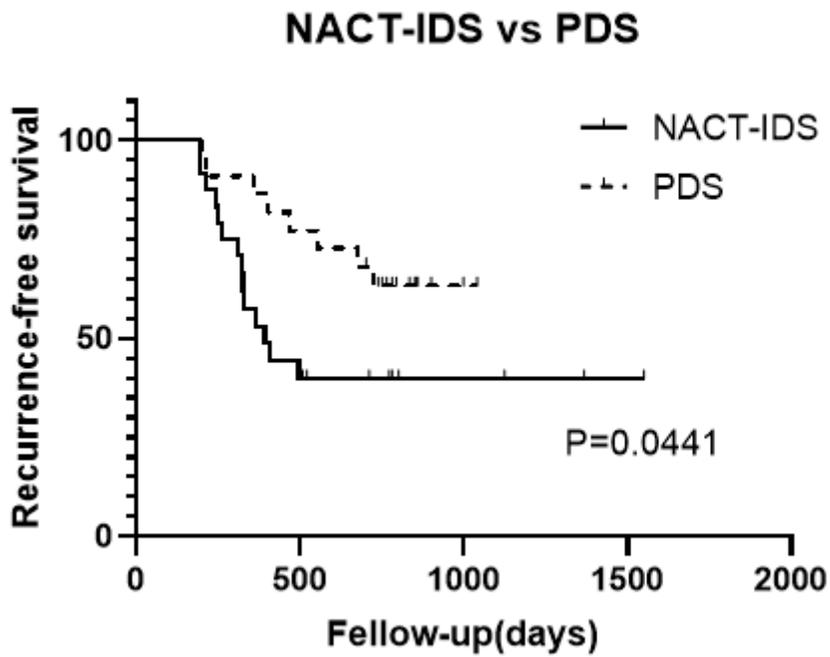


Figure 1

The Kaplan-Meier curve for RFS

## Supplementary Files

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