

*Original Research*

# Effect of neoadjuvant chemotherapy combined with intraperitoneal chemotherapy after interval tumor cell reduction on the prognosis of advanced epithelial ovarian cancer

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## Abstract

**Objectives:** To investigate the effect of neoadjuvant chemotherapy combined with intraperitoneal chemotherapy after interval tumor cell reduction on the prognosis of advanced epithelial ovarian cancer. **Methods:** A retrospective study was performed among 210 patients with advanced ovarian cancer who were treated with neoadjuvant chemotherapy from May 1, 2007 to December 1, 2015. 121 patients with NACT-IDS (Neoadjuvant chemotherapy followed by interval debulking surgery) were enrolled. The patients were divided into observation group (NACT-IDS + IP group,  $n = 28$ ) and control group (NACT-IDS + IV group,  $n = 93$ ) depending on whether intraperitoneal chemotherapy was used after interval debulking surgery. The effects of intraperitoneal chemotherapy after NACT-IDS on PFS (progression-free survival) and OS (overall survival) were analyzed and the influencing factors were explored through multivariate analysis. The competitive model was used to analyze the effect of intraperitoneal chemotherapy after NACT-IDS on tumor recurrence. Toxicities associated with adjuvant chemotherapy were also analyzed between two groups. The effect of neoadjuvant chemotherapy cycles on prognosis and the correlation between postoperative CA125 decline and recurrence were evaluated. **Results:** Intraperitoneal chemotherapy and R0 (no gross residual) were independent factors for PFS, with HRs of 0.560 (95% CI, 0.342–0.918,  $p = 0.022$ ) and 0.578 (95% CI, 0.377–0.887,  $p = 0.012$ ). There was no independent factor associated with OS. Significant difference in PFS was detected among the R0 + IP group, R0 + IV group, non-R0 + IP group and non-R0 + IV group. In patients with R0 tumor reduction, IP patients showed significantly better PFS, bonferroni adjusted  $p = 0.036$ . In patients without R0 tumor reduction, no significant difference was detected between IP and IV group, bonferroni adjusted  $p = 0.28$ . There were no significant differences of grade 3–4 toxicities, abdominal pain, treatment delays, dose reductions, and treatment modifications in NACT-IDS + IP group and NACT-IDS + IV group. Neoadjuvant chemotherapy cycles ( $\leq 3$  and  $> 3$ ) were not the influencing factors of PFS or OS and did not affect platinum-sensitive relapse or platinum-resistant relapse. The decrease in postoperative CA125 was not related to platinum-sensitive recurrence or platinum-resistant recurrence. **Conclusions:** Neoadjuvant chemotherapy combined with intraperitoneal chemotherapy after interval debulking surgery could improve the PFS of patients with advanced epithelial ovarian cancer compared to intravenous chemotherapy without significant differences in toxicity.

**Keywords:** Interval debulking surgery; Neoadjuvant chemotherapy; Intraperitoneal chemotherapy; Ovarian neoplasms

## 1. Introduction

Epithelial ovarian cancer (EOC) is the most lethal malignancy in female reproductive tract tumors because 75% of patients are diagnosed late with extensive peritoneal implantation metastases and shows acquired drug resistance during treatment [1–3]. Neoadjuvant chemotherapy followed by interval debulking surgery (NACT-IDS) has been widely used in clinical practice because it can reduce the difficulty of surgery and shorten the postoperative recovery time of patients to a certain degree so as to gain time for follow-up supplementary chemotherapy as soon as possible [4–6]. There are many scoring systems for the selection of patients for neoadjuvant chemotherapy, such as, Fagotti,

MD Anderson, and Suidan. The Suidan scoring system is based on three clinical parameters and six imaging features to screen the ovarian cancer patients who could not undergo primary satisfactory tumor cell reduction. Patients with a score of 3 or more should be recommended NACT [7].

Compared with intravenous chemotherapy (IV), intraperitoneal chemotherapy (IP) provides higher concentrations of cytotoxic drugs to the peritoneal cavity [8–10]. Intraperitoneal administration can increase the concentrations of cisplatin and paclitaxel drugs by 20 to 1000 times [11, 12]. Currently, GOG 172 and GOG 252, two large-scale phase III clinical studies on intraperitoneal chemotherapy, have drawn different conclusions [13,14]. Therefore, there



is still a great controversy regarding the use of intraperitoneal chemotherapy after tumor cell reduction for advanced ovarian cancer in clinical practice and it has not been widely accepted as routine first-line treatment [15,16]. In addition, although patients enrolled in GOG 172 and GOG 252 received primary debulking surgery (PDS), the efficacy of intraperitoneal chemotherapy after NACT-IDS has not been clinically evaluated. In view of this clinical problem, this study retrospectively analyzed the patients with advanced ovarian cancer who were initially treated in Peking University Cancer Hospital from May 1, 2007 to December 1, 2015 and explored the effects of neoadjuvant chemotherapy combined with intraperitoneal chemotherapy after intermediate tumor cell reduction on the prognosis of advanced epithelial ovarian cancer.

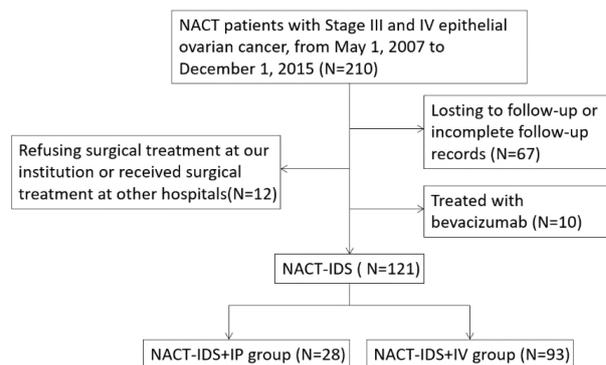
## 2. Materials and methods

### 2.1 Patients

We obtained approval from the institutional review board to conduct a retrospective analysis at Peking University Cancer Hospital & Institute. All consecutive patients with a diagnosis of epithelial ovarian, fallopian tube, or primary peritoneal cancer treated at our institution from May 1, 2007 to December 1, 2015 were reviewed for eligibility. We included all NACT patients of 210 with Stage III or IV disease, which was designated based on the International Federation of Gynecology and Obstetrics (FIGO) staging criteria. Among them, 67 patients were lost to follow-up; 12 patients refused surgical treatment at our institution or received surgical treatment at other hospitals. To distinguish GOG252 from interference with bevacizumab, 10 patients treated with bevacizumab were also excluded. 121 patients with NACT-IDS were actually enrolled at our institution (Fig. 1). In order to evaluate the impact of intraperitoneal chemotherapy on the prognosis, patients with NACT-IDS were adopted intraperitoneal chemotherapy after May 1, 2013 in our center institution. All enrolled patients were diagnosed by needle biopsy or laparoscopic biopsy. Since Poly ADP-ribose Polymerase inhibitor (PARPi) had not been approved in China at that time, none of the patients in this study had received PARPi before the initial recurrence.

### 2.2 Study design

Interval cytoreductive surgical goal of all patients was to perform satisfactory tumor cell reduction, and the standard of satisfactory tumor reduction was defined as the size of residual lesions  $\leq 1$  cm. No gross residual lesion was the ultimate target to pursue. All enrolled patients had a score of 3 or greater according to the Suidan scoring system by the Multidisciplinary Team (MDT) [17], so neoadjuvant chemotherapy was given. The neoadjuvant chemotherapy regimen was provided as: paclitaxel 175 mg/m<sup>2</sup> IV + carboplatin (AUC) 5 IV every 3 weeks or paclitaxel 80 mg/m<sup>2</sup> IV every week + carboplatin (AUC) 5 IV every 3 weeks. After 2 to 3 cycles of chemotherapy, the imaging evalua-



**Fig. 1. Number of screened and enrolled patients.** NACT-IDS, neoadjuvant chemotherapy followed by interval debulking surgery; PDS, primary debulking surgery; IP, intraperitoneal chemotherapy; IV, intravenous chemotherapy.

tion was carried out. If satisfactory tumor cell reduction was considered by Multidisciplinary Team, intermediate tumor cell reduction was adopted. If satisfactory tumor reduction could not be performed, extra chemotherapy should be carried out for 3 to 4 cycles, followed by intermediate tumor cell reduction. Therefore, neoadjuvant chemotherapy cycles ranged from 2 to 6 cycles. All patients were divided into observation group and control group according to different postoperative chemotherapy regimens. Observation group (NACT-IDS + IP group) was defined as the postoperative chemotherapy regimen composed of 3 cycles of intraperitoneal chemotherapy (paclitaxel 175 mg/m<sup>2</sup> IV + cisplatin 75 mg/m<sup>2</sup> IP every 3 weeks) and subsequent intravenous chemotherapy. Control group (NACT-IDS + IV group) was defined as the postoperative chemotherapy regimen composed of intravenous chemotherapy with paclitaxel 175 mg/m<sup>2</sup> IV + carboplatin (AUC) 5 IV every 3 weeks. We believed that no matter the number of neoadjuvant chemotherapy cycles before surgery, 3 cycles of chemotherapy should be guaranteed after surgery. Therefore, patients who had received 6 cycles of neoadjuvant chemotherapy before surgery, the total number of chemotherapy cycles would reach 9. So both observation group and control group had 6 to 9 chemotherapy cycles including neoadjuvant chemotherapy and postoperative chemotherapy. In this study, the upper limit of carboplatin was 600 mg. This study was more interested in the efficacy of intraperitoneal chemotherapy after residual lesions or not, so the subgroup R0 and non-R0 was analyzed. This study was a retrospective study, so there was no trial registration ID.

### 2.3 Disease assessment

Clinical data collected includes age, FIGO stage, histologic type, histologic grade, residual lesion size, chemotherapy cycle (neoadjuvant chemotherapy cycle and postoperative chemotherapy cycle), CA125 levels at diag-

**Table 1. Baseline characteristics of the study population.**

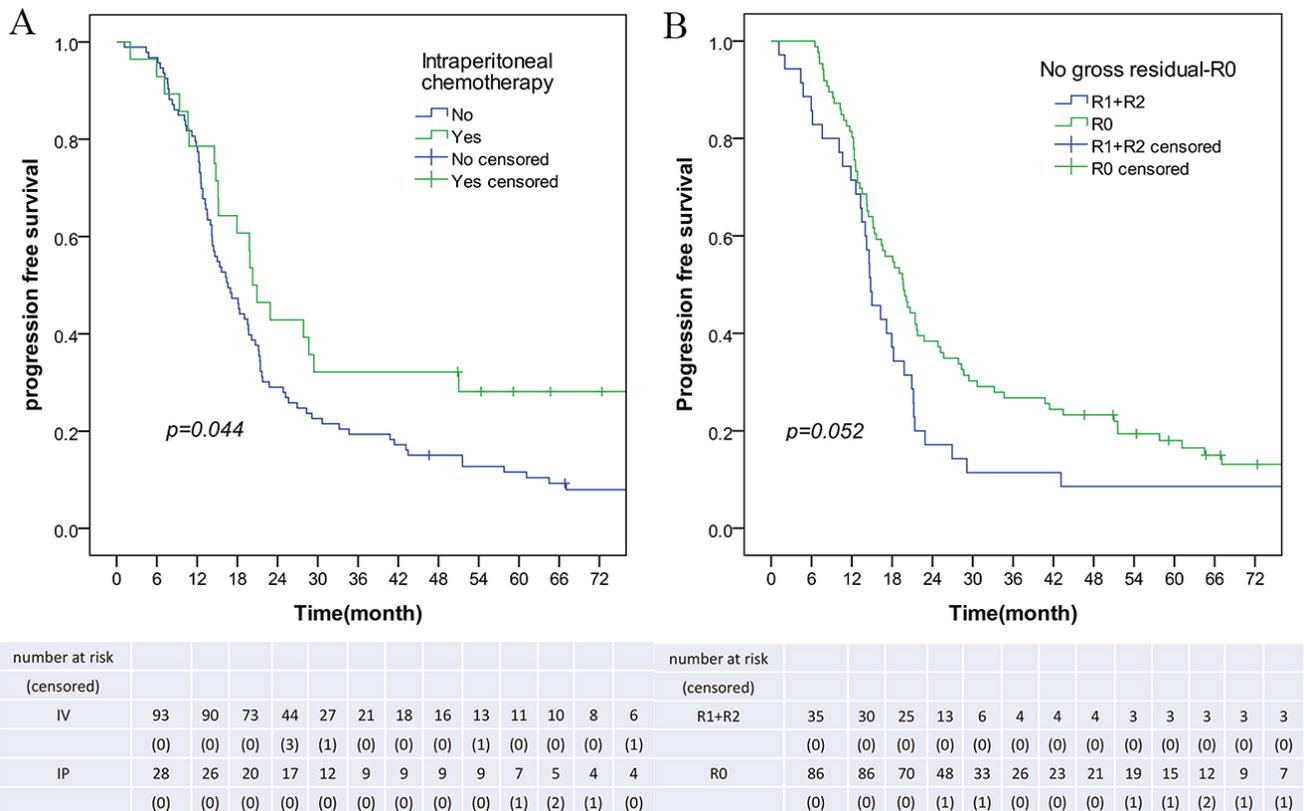
	NACT-IDS + IP Group	NACT-IDS + IV Group	<i>p</i> -value
	( <i>n</i> = 28)	( <i>n</i> = 93)	
Age, years	55.1 ± 11.4	57.7 ± 10.0	0.252
BMI, kg/m <sup>2</sup>	23.9 ± 2.5	24.5 ± 2.9	0.337
ECOG			>0.999
PS = 0	23 (82.1%)	77 (82.8%)	
PS = 1	5 (17.9%)	16 (17.2%)	
FIGO stage			0.084
III	16 (57.1%)	69 (74.2%)	
IV	12 (42.9%)	24 (25.8%)	
Histological subtype			>0.999
Serous	28 (100%)	92 (98.9%)	
Mucinous	0 (0)	0 (0)	
Clear	0 (0)	1 (1.1%)	
Endometrioid	0 (0)	0 (0)	
Others	0 (0)	0 (0)	
Histological grade			0.162
G1	1 (3.6%)	0 (0)	
G2	2 (7.1%)	3 (3.2%)	
G3	26 (89.3%)	90 (96.8%)	
No gross residual			0.168
Yes	17 (60.7%)	69 (74.2%)	
No	11 (39.3%)	24 (25.8%)	
Combined surgery			0.259
No	25 (89.3%)	79 (84.9%)	
Bowel resection	3 (10.7%)	9 (9.7%)	
Extensive upper abdominal debulking	0 (0)	5 (5.4%)	
Pre-treatment CA125 level			>0.999
Normal (<35 U/mL)	0 (0)	1 (1.1%)	
Elevated (≥35 U/mL)	28 (100%)	92 (98.9%)	
CA125 decreased after surgery			0.086
<93%	13 (46.4%)	27 (29.0%)	
≥93%	15 (53.6%)	66 (71.0%)	
NACT cycles			0.186
≤3	20 (71.4%)	77 (82.8%)	
>3	8 (28.6%)	16 (17.2%)	
Total chemotherapy cycles			0.186
≤6	8 (28.6%)	16 (17.2%)	
>6	20 (71.4%)	77 (82.8%)	

PS, performance status; NACT, neoadjuvant chemotherapy; NACT-IDS, neoadjuvant chemotherapy followed by interval debulking surgery; IP, intraperitoneal chemotherapy; IV, intravenous chemotherapy.

nosis, CA125 level within 1 month after surgery, CA125 level at the end of treatment, postoperative intraperitoneal chemotherapy, date of the first recurrence, platinum-sensitive relapse or not, platinum-resistant relapse or not, progression-free survival (PFS) and overall survival (OS). The decrease rate of CA125 after tumor reduction was calculated with the following formula: [(preoperative value of CA125 – postoperative value of CA125)/preoperative value of CA125] × 100%. The results calculated by this formula was converted into a dichotomous variable according to the median. After every 3 chemotherapy cycles, the efficacy

was evaluated according to RECIST 1.1 version of the efficacy evaluation standard for solid tumors.

The date of the first recurrence was defined as the time of imaging discovery of the lesion after completing the last chemotherapy. PFS was defined as the time from the end of the last chemotherapy to the first recurrence. OS was defined as the time from diagnosis to death or the last follow-up date. Platinum-sensitive relapse was defined as the first recurrence 6 months or more after the last chemotherapy and platinum-resistant relapse was defined as the first recurrence within 6 months after the last chemotherapy. No gross



**Fig. 2. Intraperitoneal chemotherapy and R0 tumor reduction are the influencing factors of progression-free survival.** (A) Univariate analysis results of the effects of intraperitoneal chemotherapy after interval debulking surgery on progression-free survival. (B) Univariate analysis results of the effects of R0 tumor reduction after interval debulking surgery on progression-free survival. R0: no gross residual after interval debulking surgery; R1: the size of residual lesions  $\leq 1$  cm after interval debulking surgery; R2: the size of residual lesions  $> 1$  cm after interval debulking surgery.

residual lesion after interval debulking surgery was defined as R0 tumor reduction (R0). The postoperative residual lesions with a diameter  $> 1$  cm were defined as unsatisfactory tumor reduction. The postoperative residual lesions with a diameter  $\leq 1$  cm but no gross residual lesion were defined as satisfactory tumor reduction. Both of them were defined as non-R0 tumor reduction (non-R0).

#### 2.4 Data analysis

Continuous variables were presented as mean  $\pm$  standard deviation and categorical variables were described as numbers with percentages. Differences in features among treatment groups were analyzed with independent *t* test or chi-square test. Univariate and multivariable cox regression was conducted for OS and PFS. Competing risk model was conducted for platinum-sensitive relapse and platinum-resistant relapse. Hazard ratios were calculated with a 95% confidence interval. Kaplan-Meier method was used to compare survival curves among groups. All analyses were conducted with SPSS 22.0 (IBM Corporation, Armonk, NY, USA) and STATA 12.0 (Stata Corporation, College Station, TX, USA) and a two-sided  $p < 0.05$  indicated the statistical significance.

### 3. Results

#### 3.1 Descriptions of the patients

There were 28 patients in the NACT-IDS + IP group and 93 patients in the NACT-IDS + IV group, with mean age of  $55.1 \pm 11.4$  years and  $57.7 \pm 10.0$  years, respectively. All factors were comparable between NACT-IDS + IP group and NACT-IDS + IV group (all  $p > 0.05$ ) (Table 1).

#### 3.2 Survival analysis according to PFS and OS

77 (63.6%) patients suffered death and 105 (86.8%) patients suffered progression. The univariate and multivariate analysis results of NACT-IDS patients according to PFS and OS were in Table 2. The NACT-IDS + IP group showed significantly better PFS compared with NACT-IDS + IV group (median PFS, 20 month vs 17 month,  $p = 0.044$ , respectively) (Fig. 2). Patients with no gross residual showed nearly significantly better PFS compared with those with gross residual (median PFS, 20 month vs 15 month,  $p = 0.052$ , respectively) (Fig. 2). Multivariate Cox analysis showed that intraperitoneal chemotherapy and no gross residual were independent factors for PFS, with HRs of 0.560 (95% CI, 0.342–0.918,  $p = 0.022$ ) and 0.578 (95%

**Table 2. Univariate and multivariate cox analysis results according to PFS and OS.**

	Univariate cox analysis						Multivariate cox analysis			
	PFS			OS			PFS		OS	
	Median (month)	HR (95% CI)	<i>p</i>	Median (month)	HR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>
NACT cycles										
≤3	14	Ref	0.816	42	Ref	0.969				
>3	19	0.942 (0.572–1.552)		52	0.989 (0.553–1.766)					
No gross residual										
No	15	Ref	0.052	44	Ref	0.314	Ref	0.024	Ref	0.314
Yes	20	0.66 (0.434–1.004)		57	0.782 (0.484–1.262)		0.615 (0.43–0.939)		0.782 (0.484–1.262)	
Intraperitoneal chemotherapy										
No	17	Ref	0.044	51	Ref	0.443	Ref	0.024		
Yes	20	0.605 (0.371–0.987)		57	0.801 (0.455–1.411)		0.567 (0.346–0.928)			
CA125 decrease after surgery										
<93%	17	Ref	0.243	46	Ref	0.352				
≥93%	20	0.786 (0.525–1.177)		57	0.801 (0.501–1.281)					

NACT, neoadjuvant chemotherapy; PFS, progression-free survival; OS, overall survival.

CI, 0.377–0.887,  $p = 0.012$ ). There was no independent factor associated with OS (Table 2).

Patients were divided into four groups using intraperitoneal chemotherapy and R0 tumor reduction: R0 + IP, R0 + IV, Non-R0 + IP and Non-R0 + IV group. Significant difference in PFS was detected among the four groups. In patients with R0 tumor reduction, IP patients showed significantly better PFS, bonferroni adjusted  $p = 0.036$ ; however, in patients without R0 tumor reduction, no significant difference was detected between IP and IV group, bonferroni adjusted  $p = 0.28$  (Fig. 3).

### 3.3 Survival analysis according to platinum-sensitive recurrence and platinum-resistance recurrence

80 (66.1%) patients suffered platinum-sensitive recurrence and 25 (20.7%) patients suffered platinum resistance recurrence. The rates of platinum-sensitive recurrence, platinum-resistance recurrence and non-recurrence in NACT-IDS + IP group were 53.6% (15/28), 17.9% (5/28) and 28.5% (8/28), respectively. The rates of platinum-sensitive recurrence, platinum resistance recurrence and non-recurrence in the NACT-IDS + IV group were 69.9% (65/93), 21.5% (20/93) and 8.6% (8/93), respectively. There was a statistical difference in recurrence rate between the two groups ( $\chi^2 = 6.501$ ,  $p = 0.039$ ). The univariate and multivariate analysis results according to platinum-sensitive recurrence and platinum resistance recurrence were in Table 3. Intraperitoneal chemotherapy was nearly significant for platinum-sensitive recurrence with the HR of 0.680 (95% CI, 0.390–1.186,  $p = 0.175$ ). No gross residual was nearly significant for platinum-resistant recurrence with the HR of 0.468 (95% CI, 0.204–1.072,  $p = 0.073$ ).

### 3.4 Toxicity associated with adjuvant chemotherapy

There were no significant differences of grade 3–4 toxicities, abdominal pain, treatment delays, dose reductions, and treatment modifications in NACT-IDS + IP group and NACT-IDS + IV group (Table 4). The completion rate of 3 cycles of intraperitoneal chemotherapy in the NACT-IDS + IP group was 89.3% (25/28). One patient only completed 1 cycle of intraperitoneal chemotherapy due to chemotherapy tube blockage and two patients only completed 2 cycles of intraperitoneal chemotherapy due to pain intolerance and incomplete ileus.

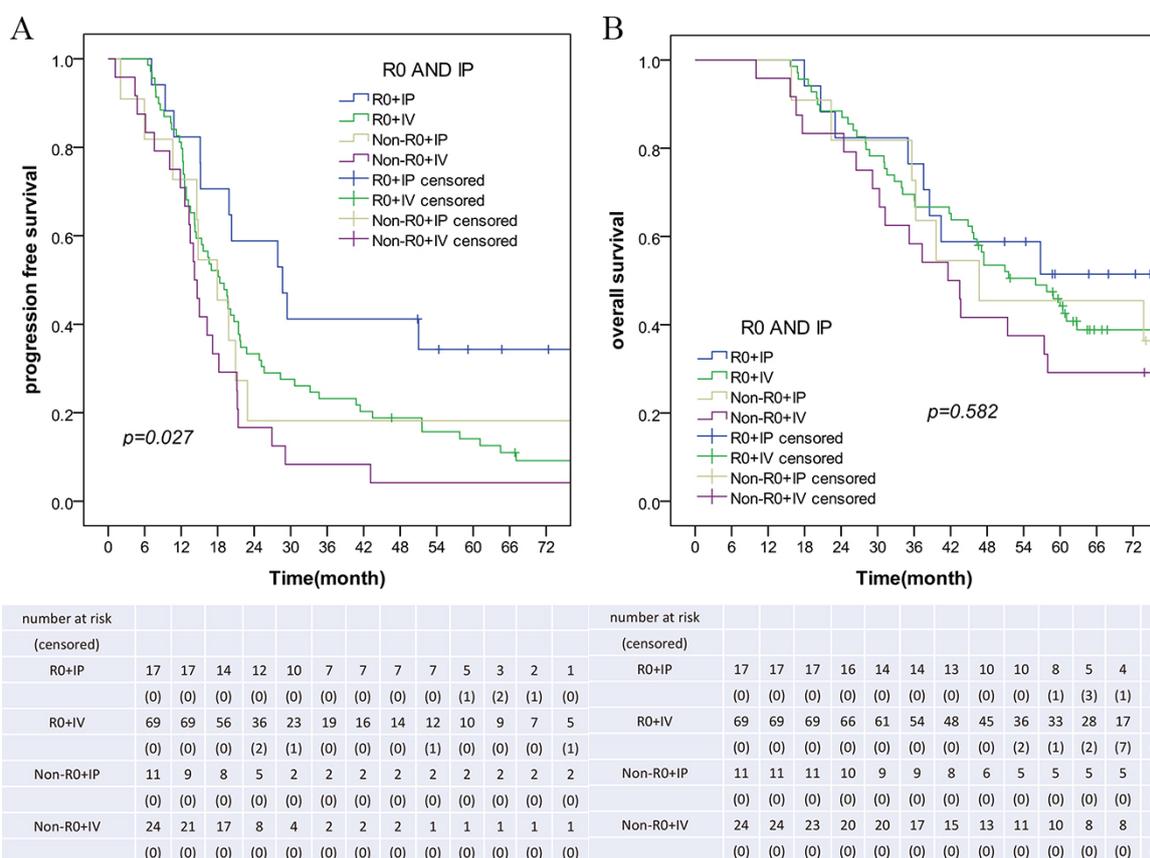
## 4. Discussion

Preclinical and pharmacokinetic data showed that the drug concentration could be increased by several times after intraperitoneal administration, thus reducing systemic absorption. Due to the penetrating depth of chemotherapy drug was limited to the peritoneal surface of tumors with a diameter of several millimeters [18,19], therefore, intraperitoneal chemotherapy is most suitable for satisfactory ovarian cancer tumor cell reduction with small lesions or without residual lesions [20,21]. The NCCN guidelines recommend IP chemotherapy as an alternative after satisfactory tumor cell reduction in FIGO Stages II and III epithelial ovarian cancer [22]. To date, the strongest evidence for the benefits of intraperitoneal chemotherapy comes from GOG 172, in which a total of 429 patients with Stage III epithelial ovarian cancer after PDS (residual lesion <1 cm) were randomly assigned to 6 cycles of IV paclitaxel (135 mg/m<sup>2</sup> D1) + IV cisplatin (75 mg/m<sup>2</sup> D2) or 6 cycles of IV paclitaxel (135 mg/m<sup>2</sup> D1) + IP cisplatin (100 mg/m<sup>2</sup> D2) and IP paclitaxel (60 mg/m<sup>2</sup> D8). The results showed that the PFS of patients receiving intraperitoneal chemotherapy was 23.8 vs 18.3 months of intravenous chemotherapy, with the

**Table 3. Univariate and multivariate competitive risk model results according to platinum-sensitive recurrence and platinum-resistant recurrence.**

	Univariate				Multivariate			
	platinum-sensitive recurrence		platinum-resistant recurrence		platinum-sensitive recurrence		platinum-resistant recurrence	
	HR (95% CI)	<i>p</i>						
NACT cycles								
≤3	Ref	0.874	Ref	0.252				
>3	1.035 (0.522–2.052)		0.598 (0.203–1.762)					
No gross residual								
No	Ref	0.849	Ref	0.073			Ref	0.073
Yes	1.05 (0.630–1.751)		0.468 (0.204–1.072)				0.468 (0.204–1.072)	
Intraperitoneal chemotherapy								
No	Ref	0.175	Ref	0.532	Ref	0.175		
Yes	0.680 (0.390–1.186)		0.706 (0.237–2.100)		0.680 (0.390–1.186)			
CA125 decrease after surgery								
<93%	Ref	0.899	Ref	0.408				
≥93%	0.999 (0.999–1.000)		1.000 (0.999–1.000)					

NACT, neoadjuvant chemotherapy.



**Fig. 3. Analysis of the progression-free survival and overall survival based on intraperitoneal chemotherapy and R0 tumor reduction.** (A) The effects of R0 tumor reduction and intraperitoneal chemotherapy after interval debulking surgery on progression-free survival. (B) The effects of R0 tumor reduction and intraperitoneal chemotherapy after interval debulking surgery on overall survival. R0: no gross residual after interval debulking surgery; Non-R0: the size of residual lesions ≤1 cm or >1 cm after interval debulking surgery; IP, intraperitoneal chemotherapy; IV, intravenous chemotherapy.

**Table 4. Toxicity associated with chemotherapy after NACT-IDS.**

	NACT-IDS + IP Group	NACT-IDS + IV Group	<i>p</i> -value
	( <i>n</i> = 28)	( <i>n</i> = 93)	
Grade 3–4 toxicity			0.376
Yes	10 (35.7%)	42 (45.2%)	
No	18 (64.3%)	51 (54.8%)	
Abdominal pain			0.680
Yes	1 (3.6%)	7 (7.5%)	
No	27 (96.4%)	86 (92.5%)	
Treatment delay			0.290
Yes	4 (14.3%)	22 (23.7%)	
No	24 (85.7%)	71 (76.3%)	
Dose reduction			>0.999
Yes	2 (7.1%)	6 (6.5%)	
No	26 (92.9%)	87 (93.5%)	
Treatment modification			0.683
Yes	1 (3.6%)	8 (8.6%)	
No	27 (96.4%)	85 (91.4%)	

HR of 0.80 (95% CI 0.64–1.00,  $p = 0.05$ ) and the OS of patients receiving intraperitoneal chemotherapy was 65.6 vs 49.7 months of intravenous chemotherapy, with the HR of 0.75 (95% CI 0.58–0.97,  $p = 0.03$ ). However, only 42% of women received all six cycles of the IP protocol in the initial treatment due to grade-3 and grade-4 adverse events. The main reasons for withdrawal are catheter-related, such as infection and blockage [13]. In addition, questions were raised about the tolerance of the control group after the results were published as only 83% of patients received all six cycles of intravenous chemotherapy and were less than the patients expected to be treated with carboplatin and paclitaxel. To address these questions, combined with maintenance therapy, the GOG 252 study was conducted. A total of 1560 patients enrolled in GOG 252 were randomly divided into one of three regimens after primary tumor reduction: paclitaxel (80 mg/m<sup>2</sup>) IV on D1, D8, and D15 + carboplatin (AUC = 6) IV on D1 every 21 days, paclitaxel (80 mg/m<sup>2</sup>) IV on D1, D8, and D15 + carboplatin (AUC = 6) IP on D1 every 21 days, and paclitaxel (135 mg/m<sup>2</sup> D1) IV + cisplatin (75 mg/m<sup>2</sup> D2) IP + paclitaxel (60 mg/m<sup>2</sup> D8) IP every 21 days. All groups were given bevacizumab (15 mg/kg, every 21 days) from the cycle 2 to cycle 22. In this study, there was no statistically significant difference in PFS among the three groups (24.9 vs 27.4 vs 26.2 months), unlike GOG 172 [13]. However, some scholars suggested that the addition of bevacizumab interfered with the interpretation of negative PFS and OS end points [23,24].

The two large-scaled randomized controlled studies do provide contrary conclusions, indicating that the efficacy of intraperitoneal chemotherapy after tumor reduction in epithelial ovarian cancer remained controversial. Unfortunately, as more effective maintenance treatments and the deeper understanding of BRCA/HRD influence first-line treatment regimens, it is increasingly difficult to define

the role of intraperitoneal chemotherapy in the treatment [25]. In addition, the patients enrolled in the above two studies all underwent primary tumor cell reduction of ovarian cancer, and the efficacy of neoadjuvant chemotherapy combined with intraperitoneal chemotherapy after intermediate tumor cell reduction was seldom clinically evaluated. In view of the above situation, this study reviewed the early NACT-IDS cases in our center and the enrolled patients did not receive any maintenance therapy or targeted therapy from the end of chemotherapy to first recurrence so as to exclude the interference factors of other drugs. Therefore, the study could objectively evaluate the role of intraperitoneal chemotherapy in the patients with NACT-IDS. In addition, in this study, the intraperitoneal chemotherapy regimen (paclitaxel 175 mg/m<sup>2</sup> IV D1 + cisplatin 75 mg/m<sup>2</sup> IP D1 every 21 days) was different from that in GOG 172 and GOG 252 (paclitaxel 135 mg/m<sup>2</sup> IV D1 + cisplatin 75 mg/m<sup>2</sup> IP D2 + paclitaxel 60 mg/m<sup>2</sup> IP D8 every 21 days) and we called it the modified intraperitoneal chemotherapy, in which only 3 cycles were given after intermediate tumor cell reduction. Then subsequent intravenous chemotherapy was supplemented. The completion rate of 3 cycles of intraperitoneal chemotherapy was 89.3% in this study, and the differences of grade 3–4 toxicities, abdominal pain, treatment delays, dose reductions, and treatment modifications were not statistically significant, indicating the clinical feasibility and security.

The results suggested that intraperitoneal chemotherapy was an independent influencing factor of PFS and R0+IP group had the best prognosis for PFS. However, no survival benefit was observed. This part of patients might receive PARPi, bevacizumab or immunotherapy in subsequent recurrence, which weakened the impact of intraperitoneal chemotherapy on OS. In addition, this study also provided corresponding answers to the question whether

more cycles of neoadjuvant chemotherapy would induce drug-resistant relapse. Chemotherapy cycles ( $\leq 3$  and  $> 3$ ) were not the influencing factors of PFS or OS and did not affect platinum-sensitive relapse or platinum-resistant relapse. The number of cycles of neoadjuvant chemotherapy did not determine the prognosis and only R0 tumor reduction and intraperitoneal chemotherapy after surgery could improve the PFS of patients. Cox analysis also showed that more than 3 cycles of neoadjuvant chemotherapy did not correlate with platinum-resistant recurrence.

In addition, we also analyzed the correlation between the decrease in postoperative CA125 and platinum-sensitive/platinum-resistant relapse. In the past, perioperative CA125 levels was mainly used to evaluate the impact on PFS and OS, or to guide the timing of surgery for intermediate tumor cell reduction [26–28]. The correlation between perioperative CA125 decrease and platinum-sensitive or platinum-resistant relapse was rarely described. The decrease in postoperative CA125 was not related to platinum-sensitive recurrence or platinum-resistant recurrence, and could not be used as an indicator to determine the prognosis of recurrence.

In the retrospective study, the subjective bias of the operators existed in determining the timing of surgery and the use of postoperative intraperitoneal chemotherapy was also influenced by the patients' own factors, such as the combination of medical diseases and economic factors. Therefore, it was difficult to strictly achieve the balance among various study groups. In addition, the patient data from a single institution can also lead to the bias in the study results. Therefore, larger-scaled multi-center prospective studies are required for providing more accurate data in the future. In addition, it is hard to illustrate results without statistical difference due to the insufficient power.

## 5. Conclusions

Neoadjuvant chemotherapy combined with intraperitoneal chemotherapy after interval debulking surgery could improve the PFS of patients with advanced epithelial ovarian cancer compared to intravenous chemotherapy without significant differences in toxicity.

## Author contributions

WW and MG are co-lead authors. WW designed the research study, searched the clinical data and wrote the manuscript. MG co-designed and co-wrote the manuscript. XL was responsible for data analysis and writing of statistical methods. YG optimized the experimental approach, provided general guidance and oversight the manuscript. HZ optimized the experimental approach. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

## Ethics approval and consent to participate

This study met the requirements of the Helsinki Declaration on human material and data. The study protocol was reviewed and approved by the institutional research ethics committee of Peking University Cancer Hospital & Institute, approval number 2018YJZ35. Patient consent was waived by the Medical Ethics Committee of Peking University Cancer Hospital & Institute.

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## Conflict of interest

The authors declare no conflict of interest.

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