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ORIGINAL ARTICLE

A Retrospective clinical study of neoadjuvant chemotherapy for advanced epithelial ovarian cancer

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Abstract

Objective To investigate the clinical efficacy of neoadjuvant chemotherapy (NACT) and the prognostic factors for advanced epithelial ovarian cancer (EOC).

Methods We enrolled 241 patients with stage III and IV EOC who were diagnosed at the Yunnan Cancer Hospital between October 2006 and December 2015. The observation (NACT-IDS) group (n = 119) received 1–3 courses of platinum-based NACT, followed by interval debulking surgery (IDS) and 6–8 courses of postoperative chemotherapy. The control group underwent primary debulking surgery (PDS) (*n* = 122) followed by 6–8 courses of postoperative chemotherapy. We analyzed the general conditions of the operations and the survival of both groups.

Results Operating time, intraoperative blood loss and postoperative hospitalization were significantly lower in the NACT-IDS group ($P < 0.05$). The rate of optimal cytoreductive surgery was significantly higher in the NACT-IDS group ($P < 0.05$). A visible residual lesion was observed in 49 (41.18%) and 48 (40%) cases in the NACT-IDS and PDS groups, respectively, which were not significantly different ($P > 0.05$). The percentage of International Federation of Gynecology and Obstetrics (FIGO) stage IV tumors and the recurrence rates were significantly higher in the NACT-IDS group ($P < 0.05$). The mortality rates were 45.19% (47/104) and 35.19% (38/108) in the NACT-IDS and PDS groups, respectively ($P > 0.05$). Progression-free survival was 23.75 ± 9.98 and 23.57 ± 12.25 months in the NACT-IDS and PDS groups, respectively ($P > 0.05$). Overall survival (OS) was 31.11 ± 15.66 and 29.63 ± 18.00 months in the NACT-IDS and PDS groups, respectively ($P > 0.05$). Optimal cytoreductive surgery with or without residual lesion was an independent influencing factor for advanced OEC in multivariate analysis. OS of patients treated with ≥8 courses of chemotherapy was significantly longer than those treated with < 8 courses.

Conclusion NACT could improve the intra- and postoperative conditions in advanced EOC patients. Although the percentage of FIGO stage IV cancer was significantly higher in the NACT-IDS group, the prognosis was similar in both the NACT-IDS and PDS groups, suggesting that NACT improves the clinical outcome of advanced EOC. Optimal cytoreductive surgery with no residual lesion is a long-term protective factor in advanced EOC. At least 8 courses of chemotherapy overall or ≥ 6 courses postoperatively improves the OS.

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Key words neoadjuvant chemotherapy (NACT); advanced epithelial ovarian cancer (EOC); cytoreduction surgery; prognostic factors

Ovarian cancer is one of the three most common gynecological malignancies and has a high mortality rate. Recently, the incidence of ovarian cancer has increased annually [1]. In 2014, Siegel *et al* [2] reported that 70% of ovarian cancer patients were diagnosed at an advanced stage, with a 5-year overall survival (OS) rate of 44% for all patients and 27% for patients with advanced disease (stage IIIC and IV) with 27%. The treatment of ovarian cancer comprises of primary debulking surgery (PDS), combined with chemotherapy and other comprehensive treatments. The size of the residual lesion is the main factor affecting prognosis [3-4]. Optimal cytoreductive surgery should, therefore, be performed to improve the quality of life and survival of patients. Patients with advanced epithelial ovarian cancer (EOC) usually have extensive intraperitoneal or distant metastases. Some patients have

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large pelvic masses that adhere tightly to other organs and tissues, and only 30–40% of these patients can be treated with optimal cytoreductive surgery [5]. Neoadjuvant chemotherapy (NACT) is proposed in advanced EOC to reduce tumor burden, which may ensure the feasibility of optimal cytoreductive surgery in these patients. This strategy has attracted a lot of attention from clinicians. However, whether NACT improves the quality of life and prolongs progression-free survival (PFS) and OS in advanced EOS is still controversial.

We analyzed the clinical importance of NACT in 241 patients with advanced EOC who were diagnosed and treated at the Yunnan Cancer Hospital from October 2006 to December 2015. We have also determined the possible prognostic factors and hope that our study can be used as a reference for the diagnosis and treatment of EOC patients.

Materials and methods

Patients

We enrolled 241 patients who were diagnosed with advanced EOC (178 stage III and 63 stage IV) between October 2006 and December 2015 at the Yunnan Cancer Hospital. Patients were divided into two groups according to treatment modality: 119 underwent NACT-interval debulking surgery (IDS), and 122 underwent PDS. The observation (NACT-IDS) group (n = 119) received 1–3 courses of platinum-based NACT, followed by IDS and 6–8 courses of postoperative chemotherapy. The control (PDS) group underwent PDS (n = 122) followed by 6–8 courses of postoperative chemotherap.y. All patients received platinum-based chemotherapy: TC (paclitaxel: 175 mg/m^2, intravenous injection; carboplatin: AUC 5–6, intravenous injection, once every 3 weeks); or TP (paclitaxel: 175 mg/m^2 intravenous injection; cisplatin: 75 mg/m^2 intravenous injection, once every 3 weeks). We analyzed age, body mass index (BMI), clinical manifestations, surgical pathological stage, histopathological type, days of hospitalization, days in intensive care, operating time, intraoperative blood loss and transfusion, presence of residual lesions, percentage of patients undergoing cytoreductive surgery, postoperative complications, and effect of NACT on operation, PFS, and OS.

Data analysis

Statistical analysis was performed using the Stata version 12.0 software. Data were analyzed using t test or χ^2 test, and $P < 0.05$ was defined as statistically significant. Survival analysis was performed using the log-rank test and Kaplan-Meier test. Multivariate analysis was performed using the Cox model.

Results

General situation

The general conditions of patients including age, BMI, clinical manifestations, histopathological type and pathological differentiation, were comparable among patients in the NACT-IDS and PDS groups ($P > 0.05$; Table 1). However, surgical pathological stages differed significantly between the two groups ($P < 0.05$).

Surgical condition

The average operating time, intraoperative blood loss, and days of hospitalization were significantly lower in the NACT-IDS group compared to the PDS group ($P < 0.05$; Table 2). There were no significant differences in the intraoperative blood transfusion rates, postoperative days in intensive care and postoperative complications between the groups ($P > 0.05$). A higher percentage of patients in the NACT-IDS group underwent optimal cytoreductive surgery compared to the PDS group (69.75% vs 59.30%, $P < 0.05$). The percentage of patients with a visible residual lesion was comparable in both groups (NACT-IDS: 41.18%; PDS: 40.0%).

Survival analysis

The duration of follow-up ranged from 15 to 125 months. The recurrence rate was 58.04% (65/112) in the NACT-IDS group and 36.28% (41/113) in the PDS group ($P < 0.05$). The morbidity was 45.19% (47/104) in the NACT-IDS group and 35.19% (38/108) in the PDS group ($P < 0.05$). The median PFS and OS for the NACT-IDS group were 23.75 ± 9.98 and 31.11 ± 15.66 months, respectively, compared with 23.57 ± 12.25 and 29.63 ± 18.0 months, respectively, for the PDS group. However, these differences were not significant ($P > 0.05$; Fig. 1 and 2).

Prognostic factors

Univariate analysis showed that age, BMI, comorbidity, pathological grade, residual lesion size, and ascites were not significantly associated with PFS ($P > 0.05$). On the other hand, histopathological type, visible residual lesion, total number of cycles of chemotherapy, and number of cycles of postoperative chemotherapy were significantly associated with PFS ($P < 0.05$). Patients with no visible residual lesion, ≥ 8 cycles of chemotherapy or ≥ 6 cycles of postoperative chemotherapy had improved PFS.

Table 1 Comparison of the two groups in general

Characteristic	NACT-IDS group (n = 119)	PDS group (n = 122)	t/χ^2	P
age (years)	52.36 ± 8.58	52.00 ± 8.69	-0.3174	0.7512
BMI	22.27 ± 3.46	22.13 ± 2.77	2.9297	0.270
Clinical manifestations			8.4555	0.076
Abdominal distension and abdominal pain	97	94		
Physical examination	6	10		
Irregular vaginal bleeding	1	8		
Consciously abdominal mass	11	9		
Other (chest tightness, fatigue, weight loss, frequent urination, urgency, etc.)	4	1		
Surgical pathology			21.7144	0.000
III	72 (0.50%)	106 (86.88%)		
IV	47 (39.49%)	16 (13.11%)		
Histopathological type			21.8478	0.000
Serous carcinoma	64	81		
Mucinous carcinoma	0	10		
Endometriosis	54	34		
Transparent cell carcinoma	0	5		
Hybrid	0	2		
Histopathological grade			0.3187	0.853
Well differentiated	2	3		
Differentiation	15	16		
Poorly differentiated	76	72		
Unknown	26	31		

Table 2 Comparison of the two groups of patients

Characteristic	NACT-IDS group	PDS group	t/χ^2	P
Number of days of hospitalization (days)	19.59 ± 5.46	22.16 ± 7.11	3.1373	0.0019
Intensive care time (days)	0.09 ± 0.52	0.26 ± 0.95	1.7128	0.088
Surgery time (min)	201.75 ± 61.41	235.26 ± 81.72	3.5458	0.0005
Intraoperative blood loss (mL)	496.66 ± 414.50	637.43 ± 648.03	1.9889	0.0479
Intraoperative blood transfusion			-1.6588	0.0985
Yes	25 (21.19%)	37 (30.58%)		
No	93 (78.81%)	84 (69.42%)		
Visible lesion			0.0343	0.853
No visible remnants of the naked eye	49 (41.18%)	48 (40%)		
See the remnants of the naked eye	70 (58.82%)	72 (60%)		
Ideal tumor cell subtraction (example)			4.6158	0.032
Ideal tumor cell subtraction	83 (69.75%)	67 (56.30%)		
Not ideal for tumor cell ablation	36 (30.25%)	52 (43.70%)		
Postoperative complications (example)			2.1566	0.142
No	107 (51.46%)	101 (83.47%)		
Yes	12 (37.5%)	20 (16.53%)		

Table 3 Comparison of survival results between the two groups

Characteristic	NACT-IDS group	PDS group	t/χ^2	*P*
Relapse			10.6818	0.001
Yes	65 (58.04%)	41 (36.28%)		
No	47 (41.06%)	72 (63.72%)		
Death			2.2090	0.137
Yes	47 (45.19%)	38 (35.19%)		
No	57 (54.81%)	70 (64.81%)		
PFS (mouth)	23.75 ± 9.98	23.57 ± 12.25	-0.1232	0.902
OS (mouth)	31.11 ± 15.66	29.63 ± 18.00	-0.6335	0.5271
Median surviva (mouth)	45	50	0.7400	0.3904

Table 4 Single factor analysis of PFS

Fator	group	*n*	OR	95% CI		t/χ^2	*P*
Age (years)						2.16	0.5392
BMI						0.65	0.4198
Complications						3.93	0.2687
Pathology type						24.93	0.0001
	Serous carcinoma	135					
	Mucinous carcinoma	10	3.9999	1.7813	8.9818		
	Endometriosis	88	1.1020	0.6820	1.7806		
	Transparent cell carcinoma	5	16.1711	6.0525	43.2060		
	Hybrid	2	2.0395	0.2792	14.8944		
Pathology differentiation						2.87	0.0902
Visually visible lesions						5.00	0.0253
	yes	142					
	no	97	0.5977	0.3765	0.9488		
Residual lesion size						3.75	0.0529
	< 1	150	0.6432	0.4139	0.9995		
	≥ 1	88					
Postoperative chemotherapy (Total chemotherapy cycle number ≥ 8 months)						16.70	0.0000
	carry out	104	0.3864	0.2394	0.6236		
	undone	129					
						4.10	0.0302
	≥ 6	150	0.6173	0.4007	0.9510		
	< 6	91					
Ascites cytology						0.41	0.5191
	Positive	106					
	negative	93					

Histopathological type demonstrated a hazard ratio (HR) of 3.999 [95% confidence interval (CI) 1.7813–8.9818] for mucinous carcinoma, 1.1020 (95% CI 0.6820–1.7806) for endometrial carcinoma, and 16.1711 (95% CI 6.0525–43.2060) for clear cell carcinoma when compared with serous carcinoma, which suggested worse prognosis (Table 4; $P<0.05$).

Patients with no visible residual lesion or postoperative residual lesions <1 cm, ≥ 8 cycles of chemotherapy and ≥ 6 cycles of postoperative chemotherapy had improved OS ($P< 0.05$). Histopathological type showed an HR of 3.2483 (95% CI 1.4287–7.3854) for mucinous carcinoma, 1.1540 (95% CI 0.7113–1.8721) for endometrial carcinoma, and 18.1405 (95% CI 6.5994–49.8648 for clear cell carcinoma

Table 5 Univariate analysis of OS

Fator	group	example	OR	95% CI		t/χ^2	*P*
Age (years)						0.74	0.3885
BMI						1.21	0.2722
Complications						2.75	0.0973
Pathology type						24.05	0.0001
	Complications	135					
	Pathology type	10	3.2483	1.4287	7.3821		
	Complications	88	1.1540	0.7113	1.8721		
	Pathology type	5	18.1405	6.5994	49.8648		
	Complications	2	3.3455	0.4533	24.6892		
						0.14	0.7057
Visually visible lesions						8.09	0.0044
	Yes	142					
	No	97	0.5057	0.3109	0.8225		
Residual lesion size						5.48	0.0192
	< 1	150	0.5805	0.3707	0.9090		
	≥ 1	88					
Postoperative chemotherapy (Total chemotherapy cycle number ≥ 18 months)						22.58	0.0000
	Carry out	104	0.3864	0.2394	0.6236		
	Undone	129					
Postoperative chemotherapy cycles						9.90	0.0017
	≥ 6	150	0.6173	0.4007	0.9510		
	< 6	91					
Ascites cytology						1.43	0.2312
	Positive	106					
	Negative	93					

Table 6 Multi-factor analysis of OS

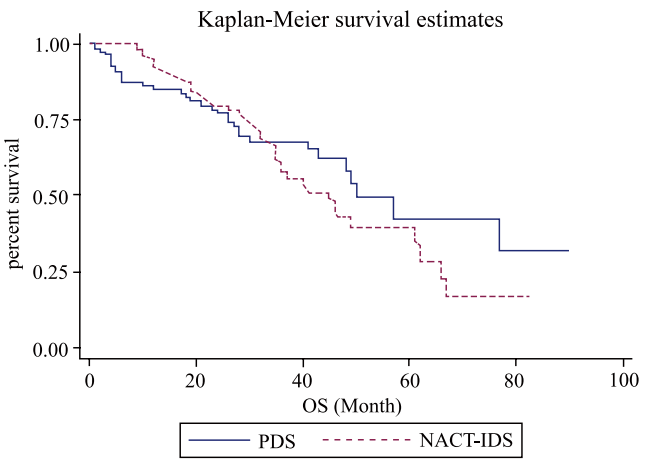
Fator	OR	SE	95% CI		*P*
Age	0.9638	0.1700	0.6821	1.3618	0.834
BMI	1.4413	0.3197	0.9332	2.2262	0.099
Pathology type	1.0154	0.1567	0.7505	1.3740	0.921
Pathology grade	0.7660	0.3196	0.3381	1.7354	0.523
Visually visible lesions	0.3457	0.1564	0.1424	0.8391	0.019
Residual lesion size	0.5572	0.2132	0.2633	1.1795	0.126
Complete postoperative chemotherapy (Total chemotherapy cycle number ≥ 8 months)	0.2551	0.1004	0.1180	0.5519	0.001
Postoperative chemotherapy cycles	0.8929	0.3322	0.4307	1.8514	0.761
Surgical pathology	0.7819	0.2957	0.3726	1.6406	0.515

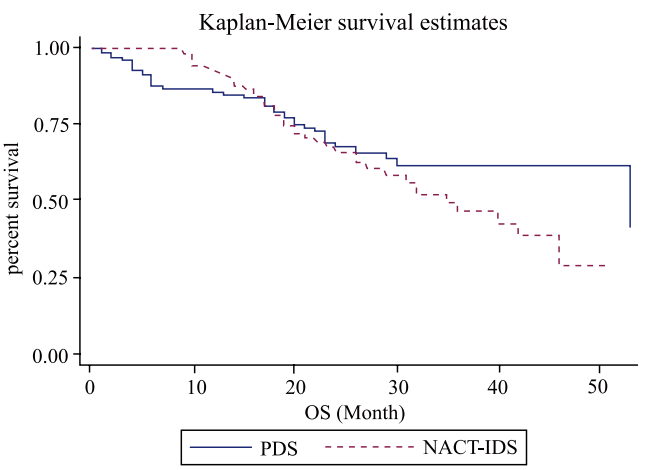
when compared with serous carcinoma, which suggested worse prognosis (Table 5, Fig. 3–6).

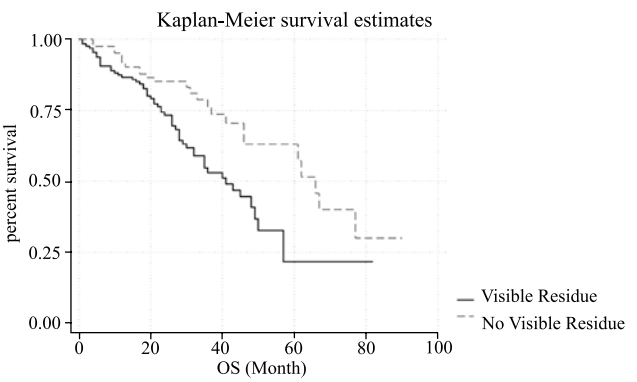
Significant factors from the univariate analyses were selected for multivariate analysis. Presence of visible residual lesion and the number of postoperative cycles of chemotherapy were independent factors for OS in patients with advanced EOC ($P < 0.05$; Table 6). The number of cycles of postoperative chemotherapy was

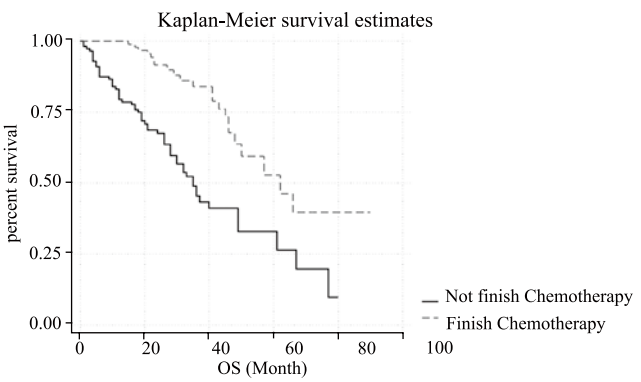
Table 7 Multivariate analysis of OS

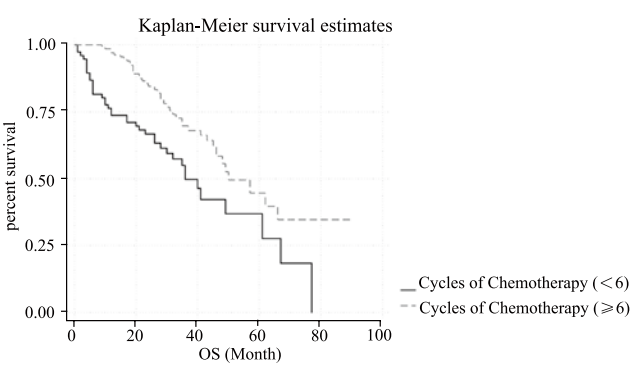
Fator	OR	SE	95% CI		*P*
Age	0.9849	0.1722	0.6991	1.3875	0.931
BMI	1.3227	0.2845	0.8677	2.0164	0.194
Pathology type	0.9361	0.1411	0.6966	1.2580	0.661
Pathology grade	0.5812	0.2386	0.2600	1.2994	0.186
Visually visible lesions	0.6837	0.2765	0.3094	1.5105	0.347
Residual lesion size	0.6301	0.2371	0.3014	1.3174	0.220
Complete postoperative chemotherapy (Total chemotherapy cycle number ≥ 8 months)	0.3478	0.1257	0.1712	0.7064	0.003
Postoperative chemotherapy cycles	1.0877	0.3774	0.5510	2.1473	0.809
Surgical pathology	0.8214	0.2932	0.4080	1.6536	0.582







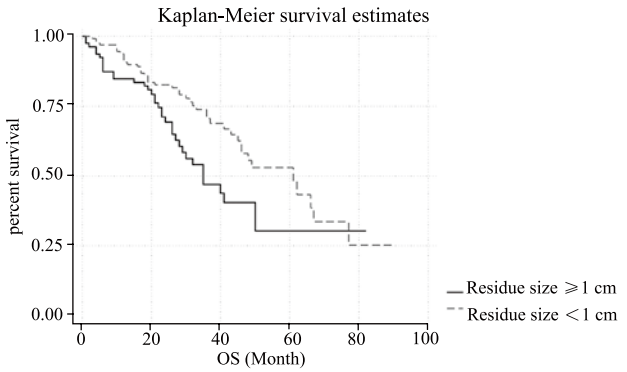




the only independent factor for PFS in patients with advanced EOC ($P < 0.05$) (Table 7).

Discussion

Ovarian cancer is one of the three most common gynecological malignancies and its incidence has been



increasing in the recent years. Epithelial carcinoma is the most common pathological type of ovarian cancer [6], and about 70% of patients are diagnosed with stage III or IV cancer. At present, the principal treatment for ovarian cancer is still cytoreductive surgery, combined with chemotherapy and other comprehensive treatments [7]. Although treatment strategies for EOC have improved, only 45% of the patients can undergo optimal cytoreductive surgery [8]. NACT is recognized by an increasing number of clinicians, but the 5-year survival rate for advanced ovarian cancer patients following NACT is only 30%–55% [9]. A clinical study has shown that compared to PDS, NACT-IDS ensures more patients can be treated using optimal cytoreductive surgery, with an improved quality of life. Whether NACT-IDS can improve prognosis needs further investigation [10].

National Comprehensive Cancer Network (NCCN) guidelines recommend the removal of all visible lesions, and an EORTC–NCIC study showed that an absence of visible lesions is the most important factor for better prognosis of advanced EOC [11]. NACT is an alternative option for patients with advanced EOC, especially those who cannot be treated with optimal cytoreductive surgery [12]. The results of this study show that the ideal tumor reduction rate in the NACT-IDS group was 69.75%, which was higher than that in the PDS group (56.30%), and NACT significantly improved the surgical outcomes in advanced ovarian epithelial carcinoma. In our study, 41.18% and 40.0% of patients in the NACT-IDS and PDS groups, respectively had no visible residual lesions, which was not a significant difference. It has been shown that NACT effectively reduces the tumor burden and induces tumor shrinkage [13–16], which leads to better conditions for optimal cytoreduction surgery [17]. In recent years, an increasing number of researchers have defined optimal cytoreductive surgery as the absence of visible residual lesions. A study by Cochrane confirmed that the HR was lower in patients with no visible residual lesions, thereby suggesting that removal of all visible lesions may prolong patient survival [18–22]. Moreover, in our study, NACT shortened hospitalization and operating times and reduced the intraoperative blood loss. Several studies have confirmed the feasibility and efficacy of NACT-IDS regimens in advanced EOC patients, which have been recognized by most experts [23].

As NACT can improve surgery, we speculated whether it could also improve the prognosis of advanced EOC. EORTC55971 [24] is an international, multicenter, randomized controlled phase III clinical trial involving 59 countries with a total of 670 patients. The results showed that postoperative complications (such as infection, bleeding, and venous thromboembolism) in the NACT-IDS group were significantly fewer than in the PDS group, yet there was no significant difference in OS and PFS. Even when the size of the residual lesion and patient's age were considered, the results remained unchanged. In the follow-up study by Fago-Olsen [25], there was no difference in the median survival time between these two groups. The median survival time of patients with no visible lesions in the PDS group was longer, and the 2-year mortality HR increased in the NACT-IDS group when compared with the PDS group.

Kehoe *et al* performed a non-inferiority, multicenter, phase III randomized controlled trial of NACT in patients with advanced EOC. Although NACT increased the chances of a successful optimal cytoreductive surgery and reduced surgical complications and mortality, it did not improve prognosis. Although several clinical trials have demonstrated that NACT has no significant beneficial effect on OS and PFS when compared with PDS [26–31], some studies have reported a different effect. A study conducted in Yale University School of Medicine showed that patients with extraperitoneal metastases who received NACT had an OS and PFS of 31 and 15 months, respectively, which were significantly higher than those in patients treated with traditional strategies [32].

A meta-analysis of 21 retrospective clinical studies showed that NACT did not prolong the median survival time when compared with PDS, although the optimal cytoreductive surgery rate increased [33]. The results seemed to be contradictory to some extent because there may have been some bias in the retrospective studies. Patients treated with NACT had severe late International Federation of Gynecology and Obstetrics (FIGO) stage cancer, large tumor volume and extensive disease. Consistent with previous studies, we also found that PFS did not differ significantly between the NACT-IDS and PDS groups. However, the percentage of patients with FIGO stage IV cancer in the NACT-IDS group was significantly higher than that in the PDS group (39.49% vs. 13.11%), which could account for the similar PFS and OS. This finding suggests that the NACT-IDS regimen may improve the prognosis of advanced EOC.

In our study, the recurrence rates were 58.04% and 36.28% in the NACT-IDS and PDS groups, respectively. Four factors may have contributed to these results: (1)

retrospective clinical studies can be selectively biased; (2) postoperative residual lesion size measurement can be biased; (3) chemotherapy-resistant patients benefit little from NACT and may have a poor prognosis because they are unable to undergo optimal cytoreductive surgery; (4) presence of cell fibrosis after NACT. It has been reported that tumor stem cells, leading to tumor recurrence, may still be present in fibrotic tissue after NACT [34–36]. More studies are urgently needed to explore the underlying mechanisms.

The effect of age on the prognosis of advanced EOC differs among studies. While some studies demonstrated no association between age and prognosis [37–38], a Danish study of ovarian cancer suggested that age is an important factor for OS [39]. In our study, the onset age of patients was not significantly associated with PFS and OS. Compared with the 51–61-years group (high incidence group in our study), the prognosis in patients aged 29–39 and 62–73 years was poor. As an increasing number of younger women have EOC, comprehensive treatment strategies with individualized considerations will be beneficial.

Most researchers believe that EOC with different pathological characteristics may lead to different prognosis. Bamias *et al*[40] found that serous carcinoma (367 cases, 47.7 months), mucinous carcinoma (24 cases, 15.4 months), and clear cell carcinoma (29 cases, 36.6 months) were significantly different. Two other similar studies found that a serous type pathology was a detrimental prognostic factor [41–42]. The results of our study show that mucinous carcinoma and clear cell carcinoma predict worse prognosis in univariate analysis. Although there was no significant difference in OS, mucinous carcinoma and clear cell carcinoma showed a higher malignant potential. A large number of studies have shown that the prognosis of early mucinous carcinoma is better than that of the serous type. However, our results differed because of the biological characteristics of the advanced mucinous carcinoma–extensive lesions were found in the bowel and peritoneum–which suggest difficulty in surgical removal of the entire tumor, and a high risk of distant metastasis.

In our study, the histopathological grade was not a prognostic factor for PFS and OS. It is believed that a poorly differentiated tumor has a stronger invasive ability that may lead to a poorer prognosis. We did not confirm this in our study, but this may have been because of the sample size. NCCN guidelines advocate optimal cytoreductive surgery to remove all visible lesions or reduce the residual lesions to <1 cm. It has been shown that the postoperative residual lesion size is an independent prognostic factor that adversely affects the prognosis of EOC patients [43–44] and our findings conform with these reports. Several studies have shown that patients who undergo suboptimal cytoreductive surgery have a shorter survival time. On the other hand, even patients diagnosed with FIGO stage IV cancer can benefit from optimal cytoreductive surgery [45–47].

The principal treatment for EOC is optimal cytoreductive surgery with adequate, standardized chemotherapy. The current NCCN guidelines recommend six courses of chemotherapy after surgery. Our findings are consistent with several other studies that have shown that delayed or interrupted postoperative chemotherapy and < 6 cycles of chemotherapy lead to recurrence and poor prognosis [48–50]. Timeous and adequate postoperative chemotherapy were favorable prognostic factors for PFS and OS in advanced EOC patients in both univariate and multivariate analysis. Patients treated with ≥ 6 cycles of chemotherapy each before and after surgery had a better prognosis.

In conclusion, in patients with EOC, NACT can help in preparing them for cytoreductive surgery, as well as improve their surgical outcomes. Even though the number of patients with FIGO stage IV cancer was significantly higher in the NACT-IDS group compared to that in the PDS group, the two groups showed comparable PFS, OS, and mortality, suggesting that NACT can improve the prognosis of advanced EOC. Optimal cytoreductive surgery with no visible residual lesions should be advocated in clinical practice. Treatment with ≥ 6 cycles of postoperative chemotherapy or with ≥ 8 cycles of chemotherapy in total results in a better prognosis. Advanced EOC patients should be evaluated based on their general situation, histopathological types of tumor, and considered for surgery by a gynecological oncologist before treatment. Appropriate, adequate, individualized chemotherapy regimens could improve the quality of life and survival of these patients.

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Conflicts of interest

The authors indicated no potential conflicts of interest.

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