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Multifactorial impact on the outcome of interval debulking surgery in patients with advanced epithelial ovarian or peritoneal cancers

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ABSTRACT

Objective: To evaluate the impact of multiple clinical features upon the outcome of interval cytoreductive surgery and thus upon the survival in patients with advanced ovarian cancer and primary peritoneal carcinoma.
Methods: A retrospective analysis of patients receiving NACT followed by IDS between 2009 and 2017. Patients were analyzed according to the pre-NACT CA125, pre-IDS CA125, pre-IDS CA125 decline, patients' pre-IDS BMI, multisite bowel involvement and different working years of surgeons, for their influence upon the IDS outcome (e.g. optimal vs suboptimal) and the survival.
Results: After interval debulking surgery following 1–6 cycles of NACT, all patients analyzed were identified as optimal (n = 113) and suboptimal (n = 47) based on patients' record. The PFS/OS were 21/68 months and 9/26 months in optimal and suboptimal groups, respectively (p = .000, p = .000). Although differential levels of pre-IDS CA125, pre-IDS CA125 decline, bowel involvement and surgeons' working years were found to be significantly different between the two groups, surgeons' working years and multisite bowel invasion were the independent factors for IDS outcome, and the latter one was also highly related to survival.
Conclusions: Following NACT, the rate of optimal IDS might be improved for patients without multisite bowel involvement. For those with bowel involvement, management strategy made by well-experienced surgeons might be a key factor for the outcome of IDS.

1. Introduction

The incidence rate of ovarian cancer is rising and has become one of the top ten cancers in Chinese females since 2013 [1]. Most cases are diagnosed at advanced stages due to the asymptotic nature of this malignancy. Statistics on data from 2010 to 2014 showed that the 5-year survival rate of ovarian cancer patients in China was 41.8%, and no significant change was found from previous years [2]. The treatment of ovarian cancer still remains a serious challenge. Platinum-based chemotherapy followed by primary debulking surgery (PDS) is the standard therapy for advanced disease. In recent years, a new procedure to apply the interval debulking surgery (IDS) following neoadjuvent chemotherapy (NACT) is considered an alternative treatment. Several studies have shown that for women with stage III or IV ovarian cancers, treatment with primary chemotherapy or primary surgery resulted in nearly the same survival outcome [3–5]. Compared with PDS, NACT-IDS was associated with lower surgical complexity, shorter operating time, lesser blood loss, shorter hospitalization, and a lower rate of postoperative complications [6]. Studies demonstrated that the optimal or complete IDS led to a better survival outcome over suboptimal surgery [7,8]. An accurate prediction of outcomes of interval debulking surgery can help clinicians to improve the management of ovarian cancers. Identification of the important indicators that are most relevant to patients' survival is a key step toward this goal.

Whether the static serum CA125 levels or its dynamic change would predict the surgical outcome of IDS becomes the hot issue in recent years. Several studies concluded that the pre-IDS CA125 level could be used to predict the IDS surgical outcome [9–12]. and also CA125 level after the 3rd NAC could act as an independent predictor for complete IDS [13]. As for CA125 decline after NACT, studies also indicated it might be a promising marker for prediction of IDS outcome [12,14], even though the proper cut-off is still uncertain.

Obviously, in addition to CA125, other factors such as surgeon's work experience could be correlated to the decision and performance of

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surgical procedures [15]. The cytoreductive procedures for advanced ovarian cancer are more complex than those for other gynecologic malignancies. It requires substantial skills and experience to perform complete or optimal IDS during the operation. Meanwhile, higher body mass index (BMI) and obesity may present a challenge to IDS surgical procedures, which are often related to longer operation time and more blood loss [16,17] as well as surgical outcome of IDS. In addition, abdomen metastasis and bowel involvement could predict a poor prognosis after primary debulking surgery for advanced ovarian cancer [18].

This retrospective study analyzed multiple factors potentially affecting the IDS outcome, to determine whether bowel involvement, surgeon's working years, pre-IDS BMI, pre-treatment CA125, pre-IDS CA125 and CA125 decline after NACT could be associated with IDS surgical outcome and thus, the patient survival. Identification of the significant independent prognostic factor(s) could enable surgeons to apply treatment procedures most beneficial to the patient under consideration.

2. Patients and methods

We reviewed the medical records of 170 patients with advanced epithelial ovarian cancer (EOC), primary peritoneal cancer, or fallopian tube cancer who were treated with NACT-IDS from November 2009 to September 2017 at the Department of Gynecology in the First Affiliated Hospital of Chongqing Medical University (Chongqing, China). The eligibility criteria were as follows: 1) Epithelial ovarian cancer (EOC), primary peritoneal cancer, or fallopian tube cancer; 2) FIGO stage III/IV; 3) Neoadjuvent platinum based chemotherapy (1–6 cycles) followed by IDS; 4) CA125 measurement at the time of diagnosis and prior to IDS; 5) Cytological or histological diagnosis as adenocarcinoma was made before NACT. Ten patients without initial or pre-IDS CA125 value were excluded, leaving 160 patients to be analyzed. Clinical data were extracted from patients' clinical records, which include age, pre-IDS height and weight, diagnosis method (cytological or histological) and date, CA125 values at the time of diagnosis and 3–7 days prior to IDS, cycles and regimens of NACT, IDS surgeons' working years, IDS procedures, the degree of bowel involvement, FIGO stage and grade. Survival data were obtained by follow-up including telephone communication and out-patient or in-patient interview.

Patients received 1 to 6 cycles of NACT, according to gynecological oncologists' decision and patients' will. Patients received intravenous NACT every three weeks, and the dosage was paclitaxel at 175 mg/m^2, cisplatin at 90 mg/m^2 or carboplatin according to Calvert formula at area under the blood concentration-time curve of 5–6. As required, surgeons exercised their best efforts to perform cytoreductive surgery. In this study, no patient received hepatectomy or splenectomy since the preoperative radiological imaging did not indicate that these operations were necessary. An optimal interval debukling surgery was defined as the maximum diameter of residual tumors less than l cm. We reviewed all IDS surgical records and postoperative pathologic reports to assess the degree of bowel involvement. When a single or multisite bulky metastasis growth on the bowel serosa was recorded, bowel involvement was defined. Bowel involvements were recorded in 66 cases and five patients received bowel-removing surgery. Among those 61 patients who did not have bowel resection, 35 patients did not achieve optimal cytoreductive surgery, the surgeon's decision were made based on the evaluation of impossibility of R0 or R1 outcome due to multisite bowel involvements, patient's poor general condition around the time of surgery, or a reluctance to receive enterostomy for those with low portion of rectum metastasis.

Serum was collected 3 to 7 days prior to the first cycle of NACT and IDS, and chemiluminescent immunoassay was performed to determine patients' CA125 levels. Either new lesion appeared through radiological imaging or serum CA-125 levels rose continuously to greater than or equal to 2 times the upper limit of the reference range (35 U/mL) were judged as disease progression. Body mass index (BMI) was calculated with weight in kilograms divided by the square of height in meters. According to the *Chinese Guideline on prevention and control of overweight and obesity*, body mass index(BMI) was divided into 4 groups: low weight (BMI < 18.5), normal (BMI 18.5–23.9), overweight (BMI 24–27.9), obese (BMI ≥ 28) [19].

Patients admitted to the hospital before June 2017 were selected for survival analysis (n = 145), to ensure patients were observed at least 6 months (last follow-up time was December 2017).

2.1. Statistical analysis

The following statistical data were analyzed by using the software IBM SPSS Statistics 22.0. Continuous variables were evaluated with Student's t-test or Mann-Whitney U test. Categorical variables were evaluated with chi-square test. ROC analysis and Youden index was used to determine the appropriate cut-off values of pre-IDS CA-125 and percent reduction of CA125 levels for prediction of the possibility of optimal IDS. The area under ROC curve corresponds to the predictive validity of each threshold. Univariable and Multivariable Logistic Regression analysis were used to detect the independent factors for IDS surgical outcome among pre-IDS BMI, pre-IDS CA125, pre-IDS CA125 decline, bowel involvement and surgeons' working years. The discrimination and calibration of multifactorial model were evaluated by AUC and Hosmer-Lemeshow test. Progression free survival (PFS) and overall survival (OS) was estimated by the Kaplan-Meier estimates and compared by the log-rank test. The Cox proportional hazards model was used to determine the hazard ratio (HR) of variables and independent factors for PFS and OS. The Logistic Regression results were visualized by a monogram using R version 3.3.3. All statistical analyses were performed with two-tailed model and a statistical significance was considered when $p < .05$.

3. Results

A total of 152 patients with advanced epithelial ovarian cancer and 8 patients with primary peritoneal cancer receiving NACT and interval debulking surgery (IDS) during the study period were included. The median follow-up time was 25 months (range 2 to 96 months). The median age was 54 years (range, 28 to 73 years). Most patients had serous or serous-papillary histological type (118 out of 160, 73.8%), stage III disease (123 out of 160, 76.9%), grade 3 carcinoma (103 out of 160, 64.4%). The median surgeons' working time was 22 years (range, 10 to 37 years). The median CA-125 levels at the time of diagnosis, pre-IDS and percent reduction were 1732.9 U/mL (range, 77.6 to 22,491.0 U/mL), 56.85 U/mL (range 1 to 5094.4 U/mL), and 96.24% (range, 0% to 99.96%), respectively. Regarding pre-IDS BMI, 37 patients were defined as overweight (23.1%), 6 as obese (3.8%), 17 as low weight (10.6%), and the other 100 patients as normal range (62.5%). The IDS were performed through laparotomy (131 out of 160, 81.9%) or laparoscopy (29 out of 160, 18.1%). Among all these patients, 66 patients (41.2%) had macroscopic bowel involvement. Median number of NACT cycles was three (range, 1 to 6), and most patients(90%) received no more than three NACT cycles,only one patient received five cycles NACT and two received six cycles.

According to our results, optimal debulking surgery was achieved in 113 patients (70.6%), with the other 47 patients (29.4%) undergone suboptimal cytoreduction. The population characteristics are listed (Table 1). There was no statistical difference in age, histology, FIGO stage, grade, cycles of NACT, CA125 level at diagnosis and pre-IDS BMI between the two groups ($p > 0.05$). Nevertheless, the median CA125 level prior to IDS was lower for optimal IDS group in contrast to suboptimal IDS group (46 U/mL vs 87.9 U/mL, p = .004). More patients were recorded as multisite bowel invasion during the cytoreductive surgery in suboptimal IDS group than optimal group (27.4% vs 74.5%, p = .000).

Table 1
patient characteristics (n = 160).

	Optimal IDS (n = 113)	Suboptimal IDS (n = 47)	p value
Age(years)	53 (30–73)	58 (28–73)	0.383
Histology			0.167
Serous or serous-papillary	85 (75.2%)	33 (70.2%)	
Other types	22 (19.4%)	9 (19.1%)	
Primary peritoneal cancer	3 (2.7%)	5 (10.7%)	
Double cancer	3 (2.7%)	0	
FIGO Stage			0.641
Stage III	88 (77.9%)	35 (74.5%)	
Stage IV	25 (22.1%)	12 (25.5%)	
Grade			0.535
1/2	13 (11.5%)	3 (6.4%)	
3	73 (64.6%)	30 (63.8%)	
Unreported	27 (23.9%)	14 (29.8%)	
Cycles of NACT	3 (1–6)	3 (1–4)	0.580
Pre-IDS BMI (kg/m2)	21.75 (16.03–31.60)	21.77 (17.09–30.85)	0.882
Surgeon's work experience	25 (10–37)	21 (10–37)	0.014
10–25 years	58 (51.3%)	34 (72.3%)	
> 25 years	55 (48.7%)	13 (27.7%)	
CA125 at diagnosis (U/mL)	1785 (118.2–22,491.0)	1532.9 (77.6–13,224.0)	0.316
Pre-IDS CA125 level (U/mL)	46.7 (1–3060)	87.9 (4.7–5094.4)	0.004
< 170	88 (77.9%)	27 (57.4%)	0.009
≥170	25 (22.1%)	20 (42.6%)	
Pre-IDS CA125 decline	96.9% (0–99.9%)	92.1% (0–99.7%)	0.001
< 96%	47 (41.6%)	31 (66.0%)	0.006
≥96%	66 (58.4%)	16 (34.0%)	
Bowel involvement			0.000
Yes	31 (27.4%)	35 (74.5%)	
No	82 (72.6%)	12 (25.5%)	

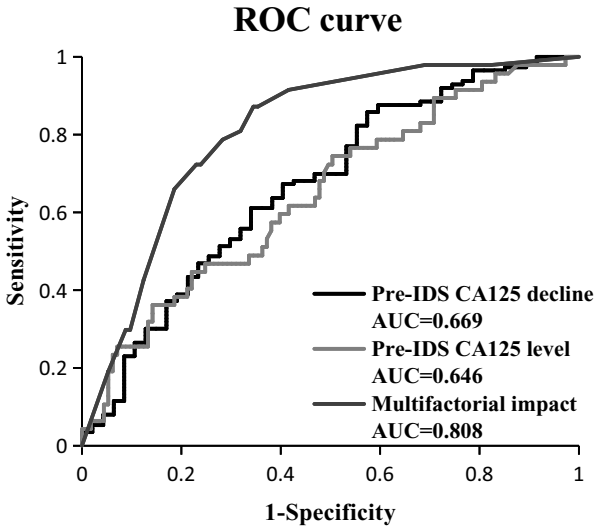

Fig. 1. ROC curve of pre-IDS CA125 decline, pre-IDS CA125 and multifactorial impact.

The ROC curve was plotted (Fig. 1). The AUC (area under curve) value was 0.646 (95% CI 0.553–0.739, p = .004) for pre-IDS CA125 level, and 0.669 (95% CI 0.575–0.764, p = .001) for CA125 decline after NACT. Through regression analysis, combination of pre-IDS CA125, CA125 decline after NACT, surgeons' working years and bowel involvement led to improvement of AUC to 0.808 (95% CI 0.739–0.878, p = .036). The threshold level of 170 U/ml (for pre-IDS CA125 level) and 96% (for pre-IDS CA125 decline) made a significant difference between optimal and suboptimal IDS groups, and displayed the best prognostic prediction as well. As indicated in Fig. 2, better progression free survival was observed in optimal group than suboptimal group in patents with pre-IDS CA125 level < 170 U/ml (17 months vs 13 months, p = .031), and in patients with CA125 decline > 96% as well (18 months vs 14 months, p = .047). However, no significant difference in overall survival was observed between the two groups in the patients with pre-IDS CA125 level < 170 U/ml or in patients with CA125 decline > 96% (p = .56, p = .46, respectively).

Given the effect of learning curve of any surgeons and operation difficulty upon the IDS outcome, surgeons' working years and BMI were considered in the analysis. As shown in Table 2, although longer working years (> 25 years), sharp CA125 reduction (96%) following NACT, lower pre-IDS CA125 level (170 U/mL), and no bowel involvement were significantly correlated with the optimal IDS, multivariate logistic regression analysis revealed that multisite bowel involvement and surgeons' inexperience were two independent risk factors (p < .05) for suboptimal interval debulking surgery. The Hosmer-Lemeshow test yielded a p value of 0.54 for the regression model, indicating that it was well-fitted. A monogram was constructed based on this logistic regression model (Fig. 3).

Patients who were admitted to our hospital before June 2017 were selected for survival analysis (n = 145), and the median progression free survival and overall survival of the 145 patients were 16 months and 47 months, respectively. There was no survival difference between different surgons' working time (PFS p = .786, OS p = .372). As displayed in Fig. 4, those patients achieved optimal IDS had significantly better PFS and OS compared with suboptimal group (p = .000). The median progression free survival was 21 months vs 9 months, with median overall survival of 68 months vs 26 months, respectively. Similarly, those with bowel invasion had poorer PFS and OS than those without (p = .000), with the median PFS and OS of 11 months vs 21 months, and 23 months vs 47 months , respectively.

COX proportional hazards model analyses for progression free survival and overall survival were presented in Table 3. Suboptimal IDS surgery and bowel metastasis were the independent risk factors for poor PFS (HR 2.278 and 1.678, p < .05) as well as poor OS (HR 2.006 and 3.031, p < .05).

4. Discussion

The current study assesses the impact of bowel involvement, surgeon's working years, pre-IDS BMI, pre-NACT CA125, pre-IDS CA125 and CA125 decline after NACT, upon the resectability by IDS and upon the survival of patients with advanced EOC who underwent NACT as primary treatment. Except for pre-IDS BMI and pre-NACT CA125, all the above parameters were found to be associated with the IDS outcome. Surgeons' insufficient experience with < 25 working years and bowel involvement were found to be contributing factors for the thoroughness of debulking surgery. As expected, optimal IDS was confirmed for its improvement of PFS and OS. On the other side, bowel involvement was associated with poorer PFS and OS, which was confirmed with COX proportional hazards model.

Our previous study of a retrospective review for 62 patients concluded that the ratio of serum CA125 decline > 0.95828 might be a predictor for optimal IDS, the median value was set as the cut-off level [20]. In current study with a larger sample size, a similar finding was obtained. Recently pre-IDS CA125 ranging from 20 to 200 U/mL was reported to predict no residual tumor [10–13], H. Mahdi et al. reported that pre-IDS CA125 reduction by 90% was more likely to have complete IDS, and preoperative CA125 < 20 U/mL was a predictor of PFS [14]. Our study supports that pre-IDS CA125 levels < 170 U/ml and CA125 decline > 96% might indicate the possibility of optimal IDS, and thus a longer progression free survival.

The rate of macroscopic bowel involvement in our study was similar to the reported studies [21,22]. Bowel resection rate was low in our study (5 out of 170, 2.94%). This might be largely due to the fact that

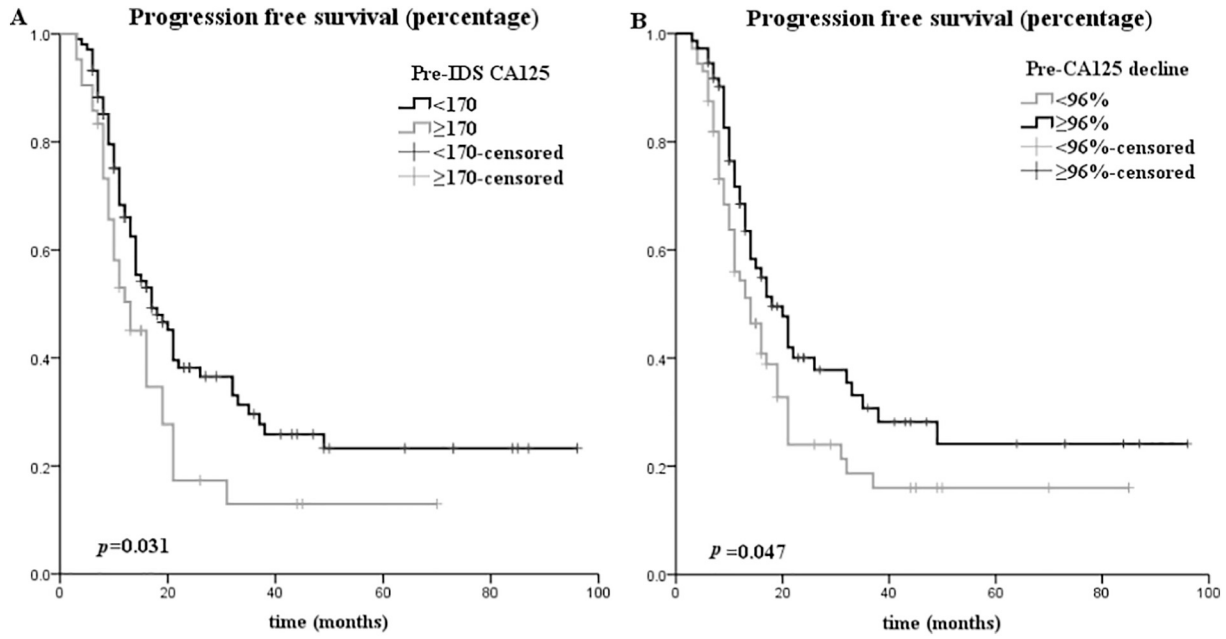

Fig. 2. Progression free survival in group with Pre-IDS CA125 < 170 U/ml vs ≥170 U/ml (A) and Pre-IDS CA125 decline < 96% vs ≥96% (B). (n = 145).

Table 2
Univariable and multivariable analyses for predictors of suboptimal surgery.

Variables	Univariate *p* value	Univariate OR	Multivariate *p* value	Multivariate OR
Pre-IDS BMI (kg/m^2)	0.881	1.008 [0.904–1.126]	–	–
Surgeon's working years (10–25 vs > 25)	0.016	2.480 [1.186–5.187]	0.021	2.737 [1.167–6.422]
Pre-IDS CA125(U/mL) (< 170 vs ≥170)	0.010	0.384 [0.185–0.795]	0.519	0.728 [0.278–1.909]
Pre-IDS CA125 decline (< 96% vs ≥96%)	0.006	2.721 [1.338–5.533]	0.108	2.189 [0.842–5.689]
Multisite bowel involvement (No vs Yes)	0.000	0.130 [0.060–0.281]	0.000	0.163 [0.073–0.363]

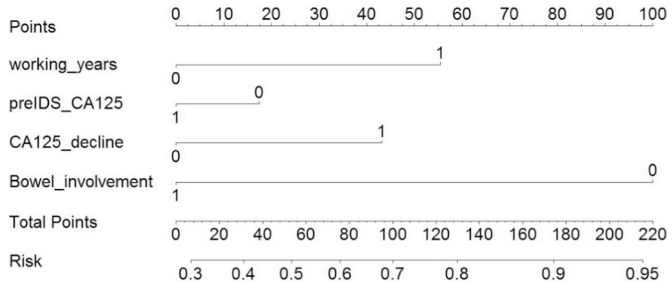

Fig. 3. The visualization of logistic regression results. This monogram incorporates four variables: surgeons' working years (0 = "10–25 years"; 1 = "More than 25 years"), Pre-IDS CA125(0 = " < 170 U/mL"; 1 = "≥170 U/mL"), Pre-IDS CA125 decline (0 = " < 96%"; 1 = "≥96%"), bowel condition (0 = " no multisite bowel involvement "; 1 = "multisite bowel involvement"). Each level of each factor corresponds different points. A straight line was drawn based on the point scale, repeat this for all the parameters, sum the total points, then the matching risk probability for optimal surgery is obtained.

even in this tertiary teaching hospital, it was general gynecologists with 10 years or longer working years other than gynecological oncologists to perform the cytoreductive surgery, and the lack of specialty training in China may affect their decision. Also, patients with bowel involvement, even those with rectum metastasis expressed their antipathy for praeternaturalis anus.

Despite the above advantage of CA125, its diagnostic efficiency is low, and thus a multifactorial analysis was thought necessary. As expected, when bowel condition, surgeons' working years and pre-IDS BMI were considered, the area under ROC curve was improved to 0.808, and the Logistic Regression model was well-fitted (Hosmer-Lemeshow test, p = .54). Although W. Jaeger et al. reported that once bowel is involved, even maximum bowel resections did not prolong survival [18], our data showed that bowel involvement was an independent predictor of suboptimal IDS and thus poorer survival, and bowel resection might contribute to achieve a complete cytoreduction and brought about good results, which was reported elsewhere [22,23]. Further studies with larger sample size are required to determine how the patients with bowel involvement could be best treated with IDS. Besides this, surgeon's working years (> 25 years) was proved to interfere the outcome of IDS, implying that well experienced surgeons might benefit cytoreductive surgery of advanced ovarian cancer, and junior doctors within the learning curve should perform cytoreductive surgery under the guidance of senior ones.

We assumed that patients with high BMI might increase the operating time and complexity of the surgery, especially for those who underwent surgery through laparotomy. Out of our expectation, pre-IDS BMI was not associated with IDS surgical outcome. Given that only 23.1% patients' pre-IDS weight were overweight, 3.8% patients were obese in our study, the role of BMI in interfering the outcome of IDS still needs to be addressed.However, a prospective study including 307 patients with advanced EOC indicated that planned benign gynecological laparoscopy can be performed in obese patients with a high likelihood of completion [24].But for laparotomy, this issue might be addressed further through increasing the case number.

There is no consensus as to the standard cycles of Pre-IDS chemotherapy [25–27], although less than four cycles NACT is now recommended by NCCN guideline. As suggested, we analyzed the association of NACT cycles with IDS outcome and patients' survival, and the results (Supplementary data) did not support the impact of NACT cycles on IDS outcome and overall survival, even though those receiving more

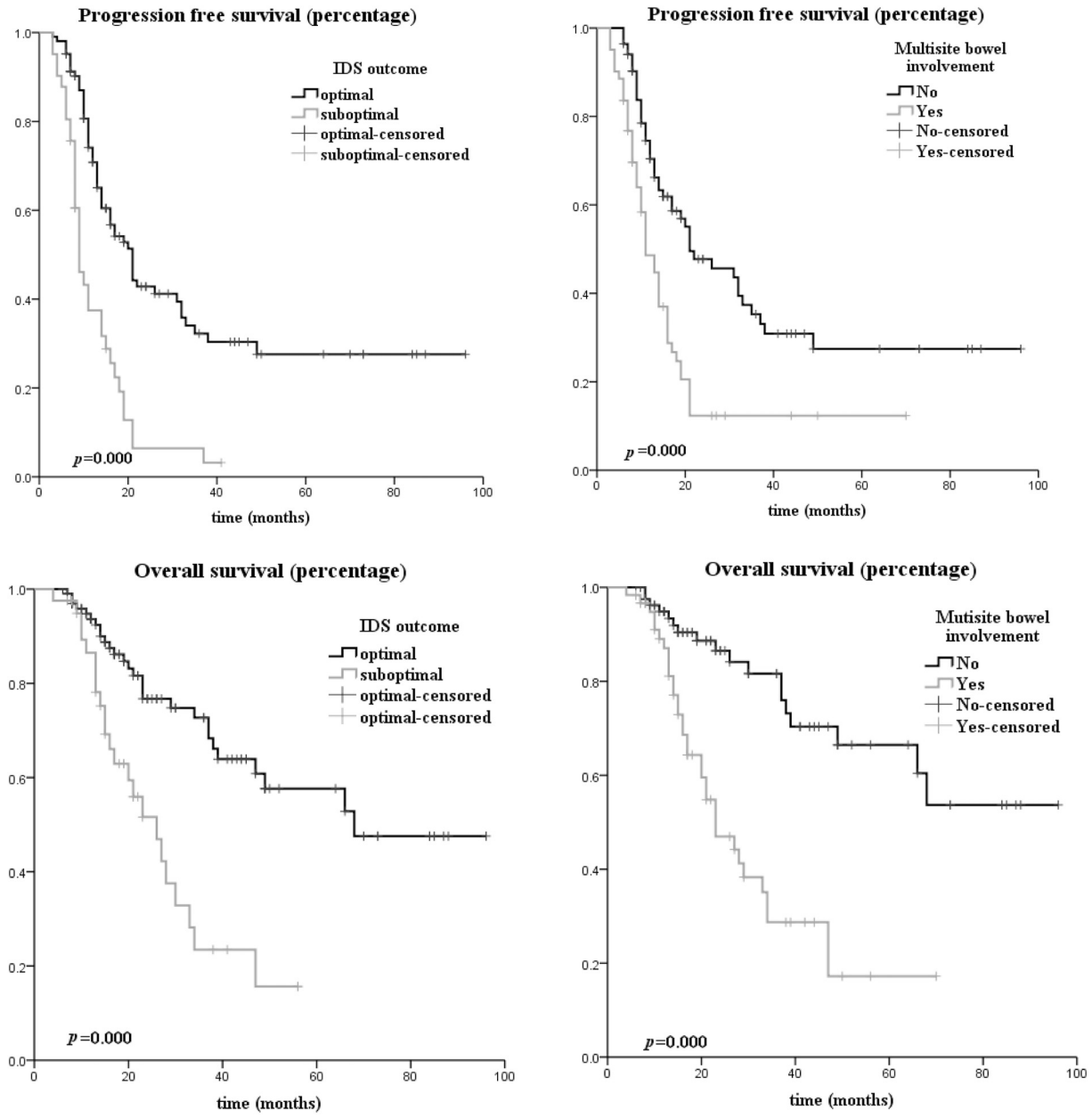

Fig. 4. Survival of patients with IDS outcome and bowel involvement. (n = 145).

than three cycles tended to relapse in a shorter time (11 months vs 17 months, p = .086). Moreover, there was no significant difference between NACT cycles (≤3 vs > 3) and pre-IDS CA125 / pre-IDS CA125 decline(p > .05), which indicated NACT cycles more than three did not benefit to patients' CA125 decline. Further study would be needed to identify this issue.

Limitations should be considered for the interpretation of the results: 1) As a retrospective and a single-center study, it has methodological limitations. 2) The sample size is relatively small, particularly the low bowel resection rate, and follow-up time was relatively short, these may affect the accuracy of the study. 3) The detection of CA125 was limited to before and after NACT. It remains unclear if the CA125 level after IDS could be of a significant value for prognosis. 4) AS an early study in this direction, we did not construct a numerical model/formula for quantitative prediction of patient outcomes based on the factors identified.

Table 3
Multivariable COX proportional hazards model analyses of PFS and OS.

		IDS outcome (optimal vs suboptimal)	Multisite bowel involvement (Yes vs No)	Pre-IDS CA125 level (U/mL) (< 170 vs ≥170)	Pre-IDS CA125 decline (< 96% vs ≥96%)
PFS	*p* value	0.001	0.028	0.539	0.880
	HR	2.278 [1.425–3.642]	1.678 [1.057–2.664]	1.180 [0.695–2.004]	0.962 [0.581–1.594]
OS	*p* value	0.026	0.001	–	–
	HR	2.006 [1.086–3.705]	3.031 [1.603–5.733]	–	–

Altogether, there are multiple factors contribute to the outcome of interval debulking surgery and thus the survival of patients with advanced EOC. Besides a good response to NACT, which would be reflected by a low pre-IDS CA125 level and/or sharp CA125 decline, bowel involvement and surgeons' working years are key factors. For those patients with bowel involvement, especially for those with multisite metastasis, the operation should be performed by practiced surgeons (with > 25 years of working time) or with the help of multidisciplinary assistance, so as to achieve optimal or even complete removing of malignant tissues, and thus a better survival.

Conflict of interest statement

Authors have no conflict of interests to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cca.2019.03.1613.

References

[1] W. Chen, R. Zheng, S. Zhang, et al., Cancer incidence and mortality in China, 2013, Cancer Lett. 401 (2017) 63–71.
[2] C. Allemani, T. Matsuda, V. Di Carlo, et al., Global surveillance of trends in cancer survival 2000–14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries, Lancet (2018).
[3] Ignace Vergote, Claes G. Tropé, Frédéric Amant, et al., Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer, N. Engl. J. Med. 363 (2010) 943–953.
[4] S. Kehoe, J. Hook, M. Nankivell, et al., Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial, Lancet 386 (2015) 249–257.
[5] A.P. Makar, C.G. Trope, P. Tummers, et al., Advanced ovarian cancer: primary or interval debulking? Five categories of patients in view of the results of randomized trials and tumor biology: primary Debulking surgery and interval debulking surgery for advanced ovarian cancer, Oncologist 21 (2016) 745–754.
[6] A. Markauskas, O. Mogensen, R. dePont Christensen, et al., Primary surgery or interval debulking for advanced epithelial ovarian cancer: does it matter? Int. J. Gynecol. Cancer 24 (2014) 1420–1428.
[7] S.J. Chang, M. Hodeib, J. Chang, et al., Survival impact of complete cytoreduction to no gross residual disease for advanced-stage ovarian cancer: a meta-analysis, Gynecol. Oncol. 130 (2013) 493–498.
[8] Giovanni D. Aletti, Sean C. Dowdy, Bobbie S. Gostout, Monica B. Jones, C. Robert Stanhope, Timothy O. Wilson, Karl C. Podratz, William A. Cliby, Aggressive surgical effort and improved survival in advanced-stage ovarian cancer, Obstet. Gynecol. 107 (2006) 77–85.
[9] A. Morimoto, S. Nagao, A. Kogiku, et al., A preoperative low cancer antigen 125 level (< /=25.8 mg/dl) is a useful criterion to determine the optimal timing of interval debulking surgery following neoadjuvant chemotherapy in epithelial ovarian cancer, Jpn. J. Clin. Oncol. 46 (2016) 517–521.
[10] N. Furukawa, Y. Sasaki, A. Shigemitsu, et al., CA-125 cut-off value as a predictor for complete interval debulking surgery after neoadjuvant chemotherapy in patients with advanced ovarian cancer, J. Gynecol. Oncol. 24 (2013) 141–145.
[11] N. Rodriguez, J.A. Rauh-Hain, M. Shoni, et al., Changes in serum CA-125 can predict optimal cytoreduction to no gross residual disease in patients with advanced stage ovarian cancer treated with neoadjuvant chemotherapy, Gynecol. Oncol. 125 (2012) 362–366.
[12] J. Zeng, J. Yin, X. Song, et al., Reduction of CA125 levels during neoadjuvant chemotherapy can predict cytoreduction to no visible residual disease in patients with advanced epithelial ovarian cancer, *primary carcinoma of fallopian tube and peritoneal carcinoma*, J. Cancer 7 (2016) 2327–2332.
[13] A. Pelissier, C. Bonneau, E. Chéreau, et al., CA125 kinetic parameters predict optimal cytoreduction in patients with advanced epithelial ovarian cancer treated with neoadjuvant chemotherapy, Gynecol. Oncol. 135 (2014) 542–546.
[14] H. Mahdi, K.A. Maurer, B. Nutter, et al., The impact of percent reduction in CA-125 levels on prediction of the extent of interval cytoreduction and outcome in patients with advanced-stage cancer of müllerian origin treated with neoadjuvant chemotherapy, Int. J. Gynecol. Cancer 25 (2015) 823–829.
[15] M. Maruthappu, B.J. Gilbert, M.A. El-Harasis, et al., The influence of volume and experience on individual surgical performance: a systematic review, Ann. Surg. 261 (2015) 642–647.
[16] E. Everett, H. Tamimi, B. Greer, et al., The effect of body mass index on clinical/pathologic features, surgical morbidity, and outcome in patients with endometrial cancer, Gynecol. Oncol. 90 (2003) 150–157.
[17] F. Morgan-Ortiz, J.M. Soto-Pineda, M.A. Lopez-Zepeda, et al., Effect of body mass index on clinical outcomes of patients undergoing total laparoscopic hysterectomy, Int. J. Gynaecol. Obstet. 120 (2013) 61–64.
[18] W. Jaeger, S. Ackermann, H. Kessler, et al., The effect of bowel resection on survival in advanced epithelial ovarian cancer, Gynecol. Oncol. 83 (2001) 286–291.
[19] Chinese Guideline on Prevention and Control of Overweight and Obesity, (2003).
[20] D. Zhang, Y.X. Jiang, S.J. Luo, et al., Serum CA125 levels predict outcome of interval debulking surgery after neoadjuvant chemotherapy in patients with advanced ovarian cancer, Clin. Chim. Acta 484 (2018) 32–35.
[21] C.A. Philip, A. Pelissier, C. Bonneau, et al., Impact of neoadjuvant chemotherapy on the rate of bowel resection in advanced epithelial ovarian cancer, Anticancer Res. 36 (2016) 4865–4871.
[22] R. Bachmann, R. Rothmund, B. Kramer, et al., The prognostic role of optimal cytoreduction in advanced, bowel infiltrating ovarian cancer, J. Investig. Surg. 28 (2015) 160–166.
[23] P. Derlatka, J. Sienko, L. Grabowska-Derlatka, et al., Results of optimal debulking surgery with bowel resection in patients with advanced ovarian cancer, World J. Surg. Oncol. 14 (2016) 58.
[24] K. McIlwaine, J. Manwaring, L. Ellett, et al., The effect of patient body mass index on surgical difficulty in gynaecological laparoscopy, Aust. N. Z. J. Obstet. Gynaecol. 54 (2014) 564–569.
[25] A. Phillips, S. Sundar, K. Singh, et al., Complete cytoreduction after five or more cycles of neo-adjuvant chemotherapy confers a survival benefit in advanced ovarian cancer, Eur. J. Surg. Oncol. 44 (2018) 760–765.
[26] C. Akladios, J.J. Bauldauf, F. Marchal, et al., Does the number of neoadjuvant chemotherapy cycles before interval debulking surgery influence survival in advanced ovarian cancer? Oncology 91 (2016) 331–340.
[27] G. Bogani, L. Matteucci, S. Tamberi, et al., The impact of number of cycles of neoadjuvant chemotherapy on survival of patients undergoing interval debulking surgery for stage IIIC-IV unresectable ovarian cancer: results from a multi-institutional study, Int. J. Gynecol. Cancer 27 (2017) 1856–1862.