JBUON 2021; 26(4): 1306-1312
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

ORIGINAL ARTICLE

Neoadjuvant chemotherapy combined with laparoscopic cytoreductive surgery in patients with advanced ovarian cancer

Aiping Wen[1,2]*, Lei Zhao[3]*, Le Luo[4], Chengchao Du[2], Xin Luo[1]

[1]Department of Gynecology and Obstetrics, the 1st Affiliated Hospital of Jinan University, Guangzhou, China [2]Department of Gynecology and Obstetrics, Affiliated Hospital of North Sichuan Medical College, Nanchong, China. [3]Department of Gynecology and Obstetrics, Dujiangyan Medical Center, Chengdu, China. [4]Sichuan Key Laboratory of Medical Imaging, Affiliated Hospital of North Sichuan Medical College, Nanchong, China.

*Aiping Wen and Lei Zhao contributed equally to this work

Summary

Purpose: *We aimed to explore the clinical efficacy and safety of neoadjuvant chemotherapy (NACT) combined with minimally invasive laparoscopic cytoreductive surgery in the treatment of patients with advanced ovarian cancer (AOC).*

Methods: *The clinical data of 116 patients with AOC were divided into NACT group (NACT combined with laparoscopic cytoreductive surgery, n=58) and control group (cytoreductive surgery alone, n=58). The short-term efficacy, surgery-related indexes, incidence of adverse reactions, and changes in levels of serum human epididymis protein 4 (HE4), vascular endothelial growth factor (VEGF) and carbohydrate antigen 125 (CA125) before and after treatment were compared between the two groups. The survival status of patients after treatment was recorded.*

Results: *The operation time, intraoperative blood loss, ascites volume, postoperative ventilation time, and average postoperative length of hospitalization in NACT group were all significantly shorter and less than those in control group. The optimal cytoreduction rate in NACT group was far higher than that in control group. The overall response rate in NACT group was obviously higher than that in control group. After treatment, the levels of serum HE4, VEGF and CA125 greatly declined in the two groups compared with those before treatment, while they were obviously lower in NACT group than those in control group. The follow-up results revealed that the median overall survival (OS) was 31.1 months and 28.9 months, and the 3-year OS rate was 43.1% (25/58) and 31.0% (18/58), respectively, in NACT group and control group.*

Conclusion: *NACT can significantly shorten the duration of cytoreductive surgery of AOC, reduce intraoperative blood loss, accelerate postoperative recovery, raise the optimal cytoreduction rate, and enhance the clinical efficacy, without greatly improving the survival time of patients.*

Key words: *ovarian cancer, neoadjuvant chemotherapy, cytoreductive surgery, curative effect*

Introduction

Due to unobvious early symptoms and signs, 70-80% of patients with ovarian cancer have been already in the late stage when diagnosed, and they need to undergo cytoreductive surgery [1]. However, patients with advanced ovarian cancer (AOC) often have extensive pelvic-abdominal or systemic metastasis, and some patients have poor postoperative quality of life or refuse to undergo invasive surgery, so satisfactory tumor shrinkage can be realized in only 30-60% of patients with AOC [2]. Satisfactory cytoreductive surgery is to excise the primary and metastatic lesions as much as possi-

Corresponding author: Xin Luo, MD. Department of Gynecology and Obstetrics, The 1st Affiliated Hospital of Jinan University, No. 613, West Huangpu Avenue, Tianhe District, Guangzhou, Guangdong 510630, China
Email: tluox@126.com; Tel: 86013392692068
Received: 17/05/2021; Accepted: 25/06/2021

ble, so that there are no visible residual lesions or the maximum diameter of residual lesions <1 cm after operation [3]. Due to the implantation metastasis and adjacent tissue infiltration in patients with AOC, the optimal cytoreduction rate is only 30-40% [4]. Therefore, AOC patients whose tumor tissues cannot be completely resected by surgery can undergo targeted preoperative chemotherapy to raise the optimal cytoreduction rate through reducing tumor burden. Such a new therapeutic strategy is called neoadjuvant chemotherapy (NACT) [5], which can reduce tumor burden and postoperative complications, and improve the optimal cytoreduction rate [6-8]. However, whether NACT has an impact on the survival time and survival rate of AOC patients remains controversial.

In the present study, the efficacy and safety of NACT combined with laparoscopic cytoreductive surgery in the treatment of patients with AOC were explored, so as to provide references for the treatment of such patients.

Methods

General data

A total of 116 patients diagnosed with AOC by surgical histopathology were selected. Inclusion criteria: 1) patients diagnosed with OC by histopathology for the first time, 2) those in Federation International of Gynecology and Obstetrics (FIGO) stage III and IV, and 3) those with an expected survival time >3 months. Exclusion criteria: 1) patients who previously received related treatments that may affect the treatment outcome, such as immunotherapy, anti-tumor therapy or ovary-related surgery, 2) those complicated with severe diseases in heart, liver, kidney, hematopoietic or endocrine system, 3) those with a history of ovarian or uterine surgery, 4) those complicated with other malignant tumors, or 5) those with mental illness. The patients were aged 37-69 years old, with an average of (54.58±9.77) years old, and they were divided into NACT group (NACT combined with laparoscopic cytoreductive surgery, n=58) and control group (cytoreductive surgery alone, n=58) according to different treatment methods. The baseline data had no statistically significant differences between the two groups (Table 1, p>0.05), and they were comparable. This study was approved by our Hospital Ethics Committee, and the patients and their families were informed and signed the informed consent form.

Treatment methods

In NACT group, NACT was conducted for 2 courses (2-3 weeks) first, and then gynecological and imaging examinations were performed, followed by cytoreductive surgery. According to postoperative pathological results, platinum-based routine chemotherapy was further performed. In control group, initial cytoreductive surgery was performed first, and then platinum-based routine chemotherapy was conducted after surgery.

NACT (Paclitaxel + cisplatin or carboplatin) chemotherapy regimen was adopted. Cisplatin (Nanjing Pharmaceutical Factory Co., Ltd., NMPN H20030675) (75-100 mg/m^2) was added into 500 mL of glucose (50 g/L) for intravenous infusion at 1 d. Cisplatin could be replaced with carboplatin (Qilu Pharmaceutical Co., Ltd., NMPN

Table 1. Baseline demographic and clinical characteristics of the studied patients

Characteristics	*NACT group (n=58)* *n (%)*	*Control group (n=58)* *n (%)*	*p value*
Age	53.79±9.58	55.03±9.61	0.488
Histology			0.732
Serous carcinoma	53 (91.4)	51 (87.9)	
Mucinous carcinoma	2 (3.4)	3 (5.2)	
Endometrioid adenocarcinoma	2 (3.4)	3 (5.2)	
Clear cell carcinoma	1 (1.7)	1 (1.7)	
Histological grade			0.652
Well differentiated	3 (5.2)	4 (6.9)	
Moderately differentiated	5 (8.6)	7 (12.1)	
Poorly differentiated	50 (86.2)	47 (81.0)	
FIGO stage			0.221
III	38 (65.5)	44 (75.9)	
IV	20 (34.5)	14 (24.1)	
PS Score			0.395
0	31 (53.4)	26 (44.8)	
1	17 (29.3)	24 (41.4)	
2	10 (17.2)	8 (13.8)	

NACT: neoadjuvant chemotherapy; FIGO: Federation of Гynecology and Obstetrics; PS: пerformance status.

H20020180), and the dose of carboplatin (mg) = blood concentration set - area under the concentration-time curve (AUC) (mg/mL/min) × [creatinine clearance rate (mL/min) + 25] (AUC=5). Paclitaxel (Yangtze River Pharmaceutical Group, NMPN H20058719) (135-175 mg/m^2) was added into 500 mL of normal saline for intravenous infusion within 3 h at 1 d. The treatment lasted for 2 courses, 21 d as 1 course. Before drug administration, dexamethasone was given to prevent allergic reactions. During chemotherapy, the patient's blood routine and biochemical indexes were closely monitored, various complications were promptly handled, and medication and dosage were adjusted in time.

Cytoreductive surgery: The laparoscopic lymph node dissection was performed for the whole uterus, bilateral appendages and greater omentum, as well as pelvic and para-aortic lymph node dissection, and metastatic pelvic tumor was resected as much as possible. Due to fixed or deep location of lesions and extensive tumor metastasis, satisfactory cytoreductive surgery was failed in some patients. Satisfactory cytoreductive surgery means that the diameter of residual tumor lesions after surgery is <1 cm, and it is best to excise all visible lesions.

Platinum-based routine chemotherapy was performed for at least 3 cycles after surgery.

Observation indexes

The operation time, intraoperative blood loss, amount of ascites, size of intraoperative residual lesions (standard for optimal cytoreduction: no residual lesions), and length of hospitalization were recorded. The incidence of postoperative adverse reactions, such as incision infection, intra-abdominal hemorrhage, common iliac vein injury, urinary system infection and lower limb vein thrombosis, was also recorded. Before and after treatment, the levels of serum human epididymis protein 4 (HE4), vascular endothelial growth factor (VEGF) and carbohydrate antigen 125 (CA125) were detected in both groups via enzyme-linked immunosorbent assay.

Efficacy evaluation: The efficacy was evaluated by Response Evaluation Criteria in Solid Tumors of World Health Organization and Ovarian Cancer Therapeutic Effect Criteria of International Society of Gynecologic Cancer. Complete response (CR): The tumor disappeared for more than 4 weeks. Partial response (PR): The product of the two maximum vertical diameters of tumor was reduced by more than 50%, and there was no lesion expansion or new lesions for more than 4 weeks. Stable disease (SD): The product of the two maximum vertical diameters of tumor was reduced by less than 50%, or increased by no more than 25%, and there were no new lesions for more than 4 weeks. Progressive disease (PD): The product of the two maximum vertical diameters of tumor was increased by more than 25%, or there were new lesions. Response rate = CR rate + PR rate.

The survival status of patients was recorded through follow-up until May 2020. The overall survival (OS) refers to the duration from the first day of treatment to death or the last follow-up.

Statistics

SPSS 22.0 software was used for statistical analysis. Measurement data were expressed as mean ± standard deviation (x±s), and t-test was performed for intergroup comparison. Enumeration data were expressed as rate (%), and x^2 test was performed for intergroup comparison. The survival curves were plotted using the Kaplan-Meier method, and log-rank test was performed to detect whether the difference in survival rate is statistically significant between the two groups. $p<0.05$ suggested the statistically significant difference.

Table 2. Comparison of parameters related to surgery

Parameters	*NACT group (n=58)* *n (%)*	*Control group (n=58)* *n (%)*	*p value*
Operation time (min)	242.71±37.47	276.83±46.39	0.001
Blood loss (ml)	554.62±115.49	706.33±129.29	0.001
Ascites volume (ml)	743.82±153.14	1085.18±212.88	0.001
Hospital stay time (d)	10.6±2.1	11.7±2.3	0.008
Postoperative ventilation time (d)	1.8±0.7	2.2±0.8	0.005
Size of postoperative residual lesion, cm			0.033
<1	43 (74.1)	32 (55.2)	
≥1	15 (15.9)	26 (44.8)	
Complications			
Incision infection	1 (1.7)	3 (5.2)	0.309
Intra-abdominal hemorrhage	3 (5.2)	5 (8.6)	0.464
Sigmoid colon injury	0 (0)	0 (0)	1.000
Common iliac vein injury	0 (0)	2 (3.4)	0.154
Urinary system infection	2 (3.4)	5 (8.6)	0.242
Lower limb vein thrombosis	0 (0)	1 (1.7)	0.315

NACT: neoadjuvant chemotherapy.

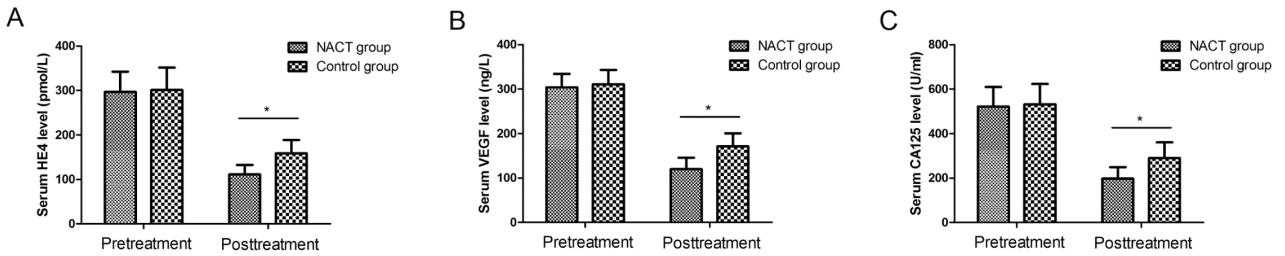

Figure 1. The difference between pretreatment HE-4 **(A)**, VEGF **(B)** and CA125 **(C)** levels of patients in the two groups had no statistical significance (p>0.05). The serum levels of HE-4, VEGF and CA125 were significantly decreased in patients of the two groups (p<0.05). Posttreatment HE-4 **(A)**, VEGF **(B)** and CA125 **(C)** levels of patients in NACT group were significantly lower than those of control group. *p<0.05.

Results

Surgery-related indexes

The operation time, intraoperative blood loss, ascites volume, postoperative ventilation time, and average postoperative length of hospitalization in NACT group were all significantly shorter and less than those in control group [(242.71±37.47) min *vs.* (276.83±46.39) min, (554.62±115.49) mL *vs.* (706.33±129.29) mL, (743.82±153.14) mL *vs.* (1085.18±212.88) mL, (1.8±0.7) d *vs.* (2.2±0.8) d, (10.6±2.1) d *vs.* (11.7±2.3) d] (p<0.05). In NACT group, the maximum diameter of postoperative residual lesions was <1 cm in 43 cases and ≥1 cm in 15 cases, and the optimal cytoreduction rate was 74.1% (43/58). In control group, the maximum diameter of postoperative residual lesions was <1 cm in 32 cases and ≥1 cm in 26 cases, and the optimal cytoreduction rate was 55.2% (32/58). It can be seen that the optimal cytoreduction rate in NACT group was far higher than that in control group (p=0.033).

The main postoperative complications included incision infection, intra-abdominal hemorrhage, common iliac vein injury, urinary system infection and lower limb vein thrombosis. The incidence rate of postoperative incision infection was 1.7% and 5.2%, that of intra-abdominal hemorrhage was 5.2% and 8.6%, that of common iliac vein injury was 0% and 3.4%, that of urinary system infection was 3.4% and 8.6%, and that of lower limb vein thrombosis was 0% and 1.7%, respectively, in NACT group and control group, displaying no statistically significant differences (p>0.05) (Table 2).

Evaluation of clinical response rate

The clinical efficacy was assessed in all patients after treatment. The overall response rate in NACT group was obviously higher than that in control group [72.4% (42/58) *vs.* 51.7% (30/58)], and there was a statistically significant difference (p=0.022) (Table 3).

Table 3. Comparison of clinical efficacy of patients in the two studied groups

Parameters	*NACT group (n=58) n (%)*	*Control group (n=58) n (%)*	*p value*
CR	13 (22.4)	7 (12.1)	
PR	29 (50.0)	23 (39.7)	
SD	11 (19.0)	19 (32.8)	
PD	5 (8.6)	9 (15.5)	
ORR	42 (72.4)	30 (51.7)	0.022

NACT: neoadjuvant chemotherapy; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; ORR: overall response rate.

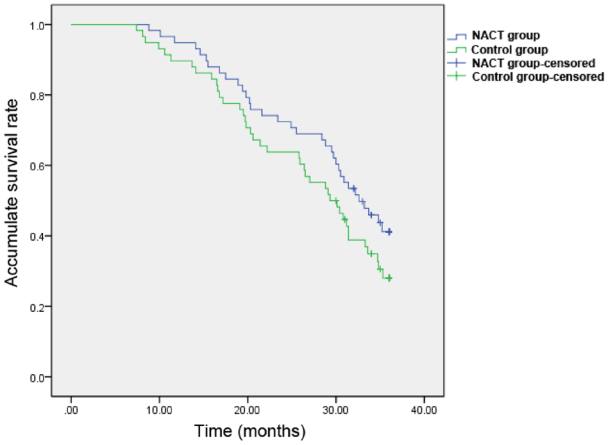

Figure 2. Kaplan-Meier survival curve of patients in the two groups. The difference between overall survival rate of patients in the NACT group and control group had no statistical significance. (p=0.130).

Comparison of serum HE4, VEGF and CA125 levels between the two groups

The levels of serum HE4, VEGF and CA125 declined from (296.64±45.86) pmol/L and (301.14±50.20) pmol/L before treatment to (111.23±21.34) pmol/L and (158.75±29.83) pmol/L after treatment, from (303.74±30.41) ng/L and (310.69±32.39) ng/L before treatment to (119.85±25.66) ng/L and (170.93±29.61)

ng/L after treatment, and from (521.36±88.27) U/mL and (531.58±91.79) U/mL before treatment to (197.48±51.68) U/mL and (289.84±70.57) U/mL after treatment, respectively, in NACT group and control group. It can be seen that after treatment, the levels of serum HE4, VEGF and CA125 greatly declined in the two groups compared with those before treatment ($p<0.05$), while they were obviously lower in NACT group than those in control group ($p<0.001$) (Figure 1).

Follow-up results of survival status

All patients were followed up for 7-36 months. The median OS was 31.1 months and 28.9 months, and the 1-, 2- and 3-year OS rate was 94.8% (55/58) and 89.7% (52/58), 72.4% (42/58) and 63.8% (37/58), 43.1% (25/58) and 31.0% (18/58), respectively, in NACT group and control group. The survival curves of patients were plotted using the Kaplan-Meier method. It was confirmed through log-rank test that there was no statistically significant difference in OS between the two groups ($p=0.130$) (Figure 2).

Discussion

OC is characterized by high morbidity and recurrence rates and poor prognosis. As proposed in the National Comprehensive Cancer Network Standard Guidelines at present, the satisfactory cytoreductive surgery means that the visible lesions are resected, and the diameter of residual lesions after surgery is <1 cm [9]. However, severe surrounding tissue infiltration and metastasis often occur in AOC, which brings great difficulties to surgical resection of tumor tissues and reduces the optimal cytoreduction rate [10]. Therefore, exploring the optimal therapeutic regimen for patients with AOC has always been a research hotspot for gynecological tumor. NACT combined with cytoreductive surgery is a new therapeutic strategy for the treatment of patients with AOC. Studies have confirmed that NACT can reduce tumor burden, improve the quality of surgery, reduce complications, and raise the quality of life of OC patients [11-13]. At present, the impact of NACT on the survival status of patients with AOC remains controversial.

In the present study, 116 patients with AOC were enrolled for a control study. The results showed that cisplatin-based + paclitaxel chemotherapy before surgery could effectively inhibit tumor cell proliferation, shrink tumor tissues, and reduce operation difficulty, so that intraoperative blood loss was reduced, operation time was shortened, and postoperative recovery of patients was promoted. At the same time, it could reduce the amount of ascites and the massive loss of protein *in vivo*. In NACT group, the intraoperative blood loss and amount of ascites were markedly less, and the operation time and length of hospitalization were markedly shorter than those in control group. The above findings confirmed that NACT performed before cytoreductive surgery can improve the operation effect and shorten the treatment time. Both optimal cytoreduction rate and clinical response rate in NACT group were higher than those in control group. Preoperative NACT can weaken the adhesion between OC lesions and surrounding tissues, reduce the tumor burden, and shrink the cancer focus, thereby lowering the operation difficulty and raising the optimal cytoreduction rate and treatment effect.

HE4 is one of the novel tumor markers, mainly expressed in the glandular epithelium of genital tract and distal renal tubule. In OC, HE4 is highly expressed, and its expression level is not affected by the patient's menstrual status [14]. CA125 is a kind of glycoprotein detected from epithelial OC antigens, and mainly derived from the coelomic epithelium during embryonic development. CA125 is not expressed in normal ovarian tissues, but its expression can be seen in the serum of patients with epithelial ovarian tumors (including benign, borderline and malignant ovarian tumors), especially in epithelial OC patients mostly with a high expression of serum CA125. Therefore, CA125 has high sensitivity but poor specificity in the diagnosis of OC [15]. It has been found that the sensitivity of CA125 or HE4 alone in the diagnosis of OC is 43.3% and 72.4%, respectively, while the sensitivity of the combination of the two can be up to 76.4% [16]. In this study, the levels of serum HE4, VEGF and CA125 in NACT group were greatly lower than those in control group after treatment, indicating that tumor cells are effectively killed and tumor burden is significantly reduced after NACT.

Whether NACT can improve the prognosis and prolong the survival time of patients with AOC is still controversial. Lim et al. [17] believed that although NACT can reduce the scope of cytoreductive surgery, tumor stem cells may still survive in the scar tissues formed by tumor necrosis after chemotherapy, resulting in chemotherapy resistance and tumor recurrence. Bristow and Chi argued that the survival time of patients with AOC (n=24) is positively correlated with the proportion of satisfactory tumor shrinkage after cytoreductive surgery, but the survival time of patients is reduced by about 4.1 months with each additional NACT [18]. According to the relevant studies of Taşkın et al. [19] and Rauh-Hain et al. [20], although NACT increases the probability of satisfactory tumor shrinkage in cytoreductive surgery and reduces the incidence of

perioperative complications, neither PFS nor OS of patients is prolonged. In this study, the results also showed that no statistically significant differences were observed in the median OS and survival rate between the two groups (p>0.05). It can be seen that preoperative NACT and cytoreductive surgery may be unable to prolong the survival time of patients. Therefore, the therapeutic regimen with a smaller scope of surgery, a lower incidence rate of complications and better prognosis may be more suitable for patients with AOC.

There were still deficiencies in this study. For example, the number of cases was smaller, the follow-up content was not comprehensive enough, the tumor progression of patients was not studied, and the quality of life of patients was not evaluated. Therefore, further multi-center large-sample randomized controlled clinical studies are still needed to confirm the conclusions made in this study.

Conclusions

NACT can significantly shorten the duration of cytoreductive surgery of AOC, reduce intraoperative blood loss, accelerate postoperative recovery, raise the optimal cytoreduction rate, and enhance the clinical efficacy, without greatly improving the survival time of patients.

Funding acknowledgements

This study was financially supported by the "Government- Universities" Specific Cooperative Scientific Research Project of Nanchong (No.21YFZJ0096,18SXHZ0251, 20SXQT0282).

Conflict of interests

The authors declare no conflict of interests.

References

1. Coleridge SL, Bryant A, Lyons TJ, Goodall RJ, Kehoe S, Morrison J. Chemotherapy versus surgery for initial treatment in advanced ovarian epithelial cancer. Cochrane Database Syst Rev 2019;2019:CD005343.
2. Vergote I, Trope CG, Amant F et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. N Engl J Med 2010;363:943-53.
3. Brand AH, DiSilvestro PA, Sehouli J, Berek JS. Cytoreductive surgery for ovarian cancer: quality assessment. Ann Oncol 2017;28:i25-9.
4. Makar AP, Trope CG, Tummers P, Denys H, Vandecasteele K. 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 2016;21:745-54.
5. Elies A, Riviere S, Pouget N et al. The role of neoadjuvant chemotherapy in ovarian cancer. Expert Rev Anticancer Ther 2018;18:555-66.
6. Li X, Du X. Neoadjuvant chemotherapy combined with interval cytoreductive surgery in ovarian cancer. JBUON 2019;24:2035-40.
7. Fagotti A, Ferrandina G, Vizzielli G et al. Phase III randomised clinical trial comparing primary surgery versus neoadjuvant chemotherapy in advanced epithelial ovarian cancer with high tumour load (SCORPION trial): Final analysis of peri-operative outcome. Eur J Cancer 2016;59:22-33.
8. Vergote I, Trope CG, Amant F et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. N Engl J Med 2010;363:943-53.
9. Cardenas-Goicoechea J, Wang Y, McGorray S et al. Minimally invasive interval cytoreductive surgery in ovarian cancer: systematic review and meta-analysis. J Robot Surg 2019;13:23-33.
10. Lee YY, Lee JW, Lu L et al. Impact of interval from primary cytoreductive surgery to initiation of adjuvant chemotherapy in advanced epithelial ovarian cancer. Int J Gynaecol Obstet 2018;143:325-32.
11. Leary A, Cowan R, Chi D, Kehoe S, Nankivell M. Primary Surgery or Neoadjuvant Chemotherapy in Advanced Ovarian Cancer: The Debate Continues. Am Soc Clin Oncol Educ Book 2016;35:153-62.
12. Vergote I, Coens C, Nankivell M et al. Neoadjuvant chemotherapy versus debulking surgery in advanced tubo-ovarian cancers: pooled analysis of individual patient data from the EORTC 55971 and CHORUS trials. Lancet Oncol 2018;19:1680-7.
13. Nishio S, Ushijima K. Clinical significance of primary debulking surgery and neoadjuvant chemotherapy-interval debulking surgery in advanced ovarian cancer. Jpn J Clin Oncol 2020;50:379-86.
14. Huang J, Chen J, Huang Q. Diagnostic value of HE4 in ovarian cancer: A meta-analysis. Eur J Obstet Gynecol Reprod Biol 2018;231:35-42.
15. Dochez V, Caillon H, Vaucel E, Dimet J, Winer N, Ducarme G. Biomarkers and algorithms for diagnosis of ovarian cancer: CA125, HE4, RMI and ROMA, a review. J Ovarian Res 2019;12:28.
16. Zhang L, Chen Y, Wang K. Comparison of CA125, HE4, and ROMA index for ovarian cancer diagnosis. Curr Probl Cancer 2019;43:135-44.

17. Lim MC, Yoo HJ, Song YJ et al. Survival outcomes after extensive cytoreductive surgery and selective neoadjuvant chemotherapy according to institutional criteria in bulky stage IIIC and IV epithelial ovarian cancer. J Gynecol Oncol 2017;28:e48.
18. Bristow RE, Chi DS. Platinum-based neoadjuvant chemotherapy and interval surgical cytoreduction for advanced ovarian cancer: a meta-analysis. Gynecol Oncol 2006;103:1070-6.
19. Taskin S, Gungor M, Ortac F, Oztuna D. Neoadjuvant chemotherapy equalizes the optimal cytoreduction rate to primary surgery without improving survival in advanced ovarian cancer. Arch Gynecol Obstet 2013;288:1399-403.
20. Rauh-Hain JA, Rodriguez N, Growdon WB et al. Primary debulking surgery versus neoadjuvant chemotherapy in stage IV ovarian cancer. Ann Surg Oncol 2012;19:959-65.