EJGO European Journal of Gynaecological Oncology

# The clinical response of advanced epithelial ovarian cancer patients to neoadjuvant chemotherapy in China

**K. Yao*, C. Bian*, L. Li, Y. Wu, X. Zhao**

[1] *Department of Obstetrics and Gynecology, Affiliated West China Women's and Children's Hospital of Sichuan University, Chengdu (China)*

**Summary**

To evaluate the outcomes of neoadjuvant chemotherapy (NACT) for patients with advanced epithelial ovarian cancer (EOC), and to identify predictors of response to NACT by analyzing the characteristics of patients and guiding future therapy choices in China. Three to four courses of NACT followed by interval cytoreductive surgery (ICS) were utilized to treat advanced EOC patients. The median overall survival (OS) in NACT response group was significantly longer than that of the no response group. Patients with International Federation of Gynecology and Obstetrics (FIGO) Stage IIIC/IV were more likely to respond to NACT. Optimal cytoreductive surgery (OCS) was achieved in 80 (70.2%) patients among 114, and complete cytoreductive surgery (CCS) was achieved in 34 (29.8%) patients. The median OS of patients with no residual tumor was significantly longer than those with residual tumors of 0.1−1.0 cm. The median OS of the ten patients who did not receive surgery was notably worse than patients with residual tumor > 1.0 cm. CA125 sensitivity and specificity were 40.8% and 86.7%, respectively. Present studies provided evidences that NACT was a viable remedy for patients with advanced EOC in China.

*Key words:* Epithelial ovarian cancer (EOC); Neoadjuvant chemotherapy (NACT); Interval cytoreductive surgery (ICS).

## Introduction

Approximately 70% to 80% epithelial ovarian cancer (EOC) patients were at FIGO Stage IIIC/IV on initial diagnosis [1]. Treatment of advanced EOC remains an enormous challenge, making it the leading cause of death among gynecologic malignancies. Cytoreductive surgery (CS) was reported to be able to prolong overall survival (OS) of cohorts diagnosed with advanced EOC [2]. Neoadjuvant chemotherapy (NACT), which was an effective chemotherapy remedy for primary solid tumor, was believed to improve the rate of OCS, thus improving the survival of advanced EOC patients [3]. A large quantity of studies demonstrated similar OS between primary cytoreductive surgery (PCS) group and NACT group [4-7]. As well known, although EOC is a chemotherapy sensitive disease, different responses after NACT are still observed [8].

The aim of current study was to evaluate the outcomes of NACT for patients with advanced EOC, and to identify predictors of response to NACT by analyzing the characteristics of patients and guiding future therapy choices in China.

## Materials and Methods

Women with non-EOC, borderline tumors, early-stage disease, incomplete clinicopathological data, or prior history of cancer were excluded. The authors retrospectively reviewed consecutive patients diagnosed with advanced EOC in West China Women's and Children's Hospital between January 2005 and December 2010. Eligible patients in this study were in FIGO Stage IIIC/IV. Patients were followed up for at least 36 months. Clinical information regarding preoperative characteristics consisted of age, FIGO stage, WHO performance status, serum CA125, histological type, and histological grade.

Paclitaxel/cisplatin or paclitaxel/carboplatin combination regimen was administered as NACT. Patients' responses to NACT were evaluated by means of physical examination, serial CA125 measurement, and CT in accordance with Response Evaluation Criteria in Solid Tumors (RECIST) [9, 10]. Patients who completely or partially responded to NACT were categorized as response group, whereas patients displayed stable or exacerbated diseases were categorized as no response group.

Cox proportional hazards analysis was used to evaluate the prognostic factors that affect survival. No patients were lost at present follow-up. OS was calculated from the date of diagnosis to date of death/last follow-up. OS was analyzed via Kaplan-Meier method. The log-rank test was employed to investigate the differences in OS between groups showing different responses to NACT/ICS. Receiver Operating Characteristic (ROC) curve analysis was performed to find a cut-off valve of continuous variables such as age, initial serum CA125 level, size of largest primary tumor, and size of largest metastatic tumor to predict the responsiveness to NACT.

Data were analyzed using SPSS software version 19.0. The results are expressed as mean ± SD. Comparisons of the four diet groups were performed by one-way analysis of variance (ANOVA), and post hoc analyses were used with Tukey's test for multiple comparisons. *P*-values of less than 0.05 for ANOVA were used to assess significant differences.

*Both authors contributed equally to the work.

Revised manuscript accepted for publication May 9, 2016

Eur. J. Gynaecol. Oncol. - ISSN: 0392-2936
XXXVIX, n. 3, 2018
doi: 10.12892/ejgo3733.2018

7847050 Canada Inc.
www.irog.net

## Results

Median age of all patients was 54 years, ranging from 34 to 75 years. The baseline demography and clinical characteristics of patients are shown in Table 1.

To explore the predictors of patient responsiveness to three to four courses of NACT, ten clinic and pathologic factors, namely age, WHO performance status, FIGO Stage, histological type, histological grade, initial serum CA125 level, malignant pleural infusion, omental cake, largest primary tumor size, and largest metastatic tumor size were chosen. Patients in FIGO Stage IIIC/IV were more likely to respond to NACT ($p = 0.004$), while patients with higher initial serum CA125 level were more likely to have no response to NACT ($p < 0.001$). For the remaining eight factors, no significant difference between NACT response group and no response group was observed. The data is summarized in Table 2.

In terms of responsiveness to three to four courses of NACT, there were 75 (60.5%) patients who showed response to NACT, whereas 49 (39.5%) patients showed no response to NACT. The median OS was 31.0 months (95% CI: 26.4−35.6) in response group, which was significantly longer than that of no-response group (18.0 months, 95% CI: 16.3−19.7, $p < 0.001$) (Figure 1).

There were ten (8.1%) patients who did not receive ICS treatment. OCS was achieved in 80 (70.2%) patients, and complete cytoreductive surgery (CCS) was achieved in 34 (29.8%) patients. After ICS, 45 (36.3%) patients had no residual tumor, 35 (28.2%) patients had residual tumors of 0.1−1cm, and 34 (27.4%) patients had residual tumor with maximum diameter > 1 cm. The median OS of patients with no residual tumor was 33.0 months (95% CI: 28.7−37.2), which was significantly longer than those with residual tumors of 0.1−1.0 cm (25.0 months, 95% CI: 19.2−30.8, $p = 0.047$). The median OS of patients with residual tumor >1.0 cm was 18.0 months (95% CI: 14.6−21.4), showing no significant difference compared to those with residual tumors of 0.1 to 1.0 cm ($p = 0.234$). The median OS of the ten patients who did not receive surgery was 16.0 months (95% CI: 9.8−22.2), which was notably worse than patients with residual tumor > 1.0 cm ($p = 0.034$) (Figure 2).

With the ROC curve analysis used to predict the responsiveness of patients to NACT, the cut-off value of initial serum CA125 level was set as 2,539.50 U/ml (area under

| Characteristics | number(%) |
|---|---|
| Age | 54 |
| WHO performance status | |
| 0 | 87(70.2) |
| 1 | 29(23.4) |
| 2 | 8(6.5) |
| FIGO stage | |
| IIIC | 96(77.4) |
| IV | 28(22.6) |
| CA125(U/ml) before treatment, median(range) | 1370.5(7-6754) |
| Histological type | |
| Serous | 113(91.1) |
| Mucous | 5(4.0) |
| Endometrioid | 3(2.4) |
| Clear cell | 3(2.4) |
| Histological grade | |
| Well differentiated | 5(4.0) |
| Moderately differentiated | 8(6.5) |
| Poorly differentiated | 111(89.5) |

Table 1. — *Baseline demography and clinical characteristics (n=124).*

| | Response group(n=75) | No response group(n=49) | P value |
|---|---|---|---|
| Age,median(range) | 54.5(34-75) | 54.0(39-74) | 0.143 |
| WHO performance status, number(%) | | | 0.544 |
| 0 | 50(66.7) | 37(75.5) | |
| 1 | 20(26.7) | 9(18.4) | |
| 2 | 5(6.7) | 3(6.1) | |
| FIGO stage, number(%) | | | 0.004 |
| IIIC | 65(86.7) | 31(63.3) | |
| IV | 10(13.3) | 18(36.7) | |
| Histological type, number(%) | | | 0.087 |
| Serous | 69(92) | 44(89.8) | |
| Mucous | 3(4.0) | 2(4.1) | |
| Endometrioid | 0(0) | 3(6.1) | |
| Clear cell | 3(4) | 0(0) | |
| Histological grade, number(%) | | | 0.631 |
| Well differentiated | 2(2.7) | 3(6.1) | |
| Moderately differentiated | 5(6.7) | 3(6.1) | |
| Poorly differentiated | 68(90.7) | 43(87.8) | |
| CA125(U/ml) before treatment, median(range) | 1314(7-6423) | 1659(38-6754) | <0.001 |
| Malignant pleural infusion, number(%) | | | 0.456 |
| Yes | 15(20.0) | 11(22.5) | |
| No | 60(80.0) | 38(77.6) | |
| Omental cake, number(%) | | | 0.708 |
| Yes | 31(41.3) | 18(36.7) | |
| No | 44(58.7) | 31(63.3) | |
| Largest primary tumor(cm), median(range) | 5.0(1.0-18.0) | 5.0(2.0-13.0) | 0.143 |
| Largest metastatic size(cm), median(range) | 3.0(1.0-15.0) | 3.0(1.0-10.0) | 0.212 |

Table 2. — *Predictors of response to NACT.*

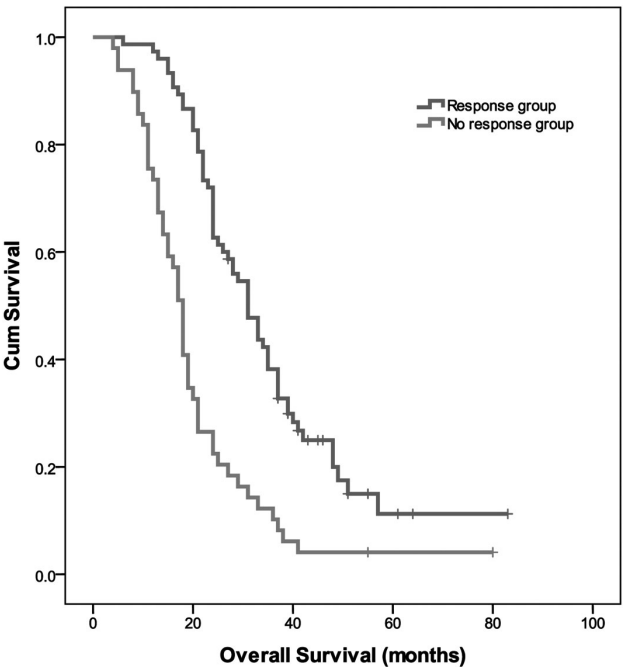


Figure 1. — Kaplan-Meier survival curve showing OS when patients were grouped based on response to NACT.

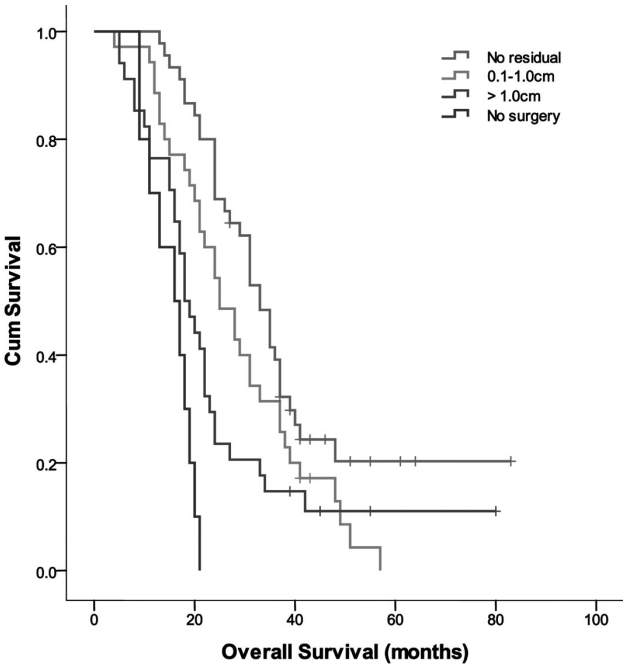


Figure 2. — Kaplan-Meier survival curve showing OS when patients were grouped based on residual tumor.

the curve (AUC) = 0.611). Its sensitivity and specificity were 40.8% and 86.7%, respectively (Figure 3).

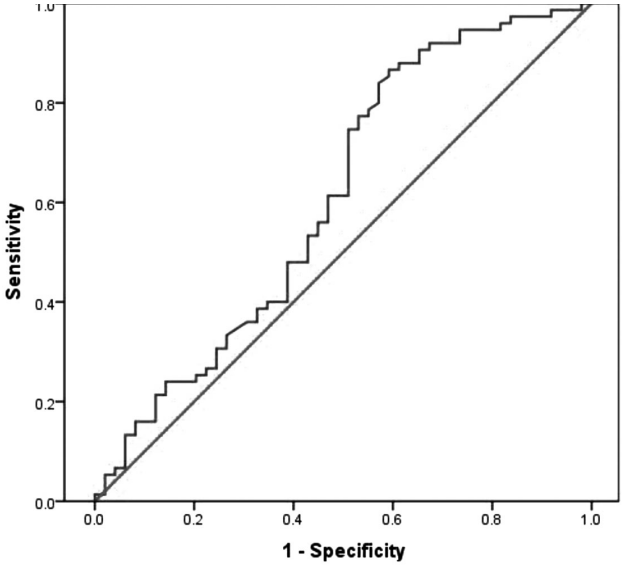


Figure 3. — ROC curve analysis for initial serum CA125 level to predict response to NACT.

## Discussion

Present studies provided evidences that NACT was a viable remedy for patients with advanced EOC. The present study discovered that 75 (60.5%) patients showed positive response to NACT. Following NACT, 114 (91.9%) patients underwent ICS, OCS was achieved in 80 (70.2%) patients, and CCS was achieved in 34 (29.8%) patients. Patients in FIGO Stage IV, whose initial serum CA125 level was higher than 2,539.50 U/ml were more likely to display no response to NACT. OS was significantly longer in patients who responded to NACT compared with those who did not. After ICS, the median OS of patients with no residual tumor was 33.0 months (95% CI: 28.7−37.2), which was significantly longer than those with residual tumors. The present results represent an important goal for gynecologic oncologists and collaborated with them for choosing individual therapeutic strategy for each patient in China.

Since NACT was widely applied on treating advanced EOC 20 years ago, there were still no generally acceptable selection criteria as when to employ NACT and when CS. The selection criteria mainly depended on gynecologic oncologists' estimation rather than an objective criterion.

Several studies demonstrated that NACT could improve patients' WHO performance status prior to surgery and decline surgical invasiveness without compromising the survival of advanced EOC patients [4-6]. Recently, NACT followed by ICS has been considered as a strategy to improve the rate of OCS in advanced EOC. In the present study, NACT followed by ICS, 80 (70.2%) patients received OCS, which was consistent with previous meta-analysis [3, 11] in which the OCS rate was 65.0% and 70.0% respectively. There was no significant difference in the rate of OCS between response group and no response group (74.7% *vs*. 49.0%, $p = 0.146$), however, the rate of

CCS in response group was significantly higher than no response group (48.0% *vs*. 18.4%; $p = 0.035$). This result suggested that it was CCS not OCS which benefitted advanced EOC patients' outcomes.

After NACT, lower OS was observed in the present study compared with the randomized study of EORTC [7] (11 *vs*. 12 months, 25 *vs*. 30 months, respectively), which may result from much more patients with poor differentiation of histological grade (89.5%) in the present study.

The present data revealed that after ICS, OS of patients who were not burdened with residual tumor were comparable to patients who were burdened with residual tumor. The results were consistent with several previous studies [12-14].

Patients in FIGO Stage IV and with higher initial serum CA125 level were more likely to have no response to NACT, which implied more aggressive biological behavior of the EOC and larger EOC burden, resulted in poor NACT outcomes ultimately. Chemotherapeutic agents were reported to exert their maximum effect on preventing tumors from proliferation [15]. Yusuf *et al.* concluded that patients with extensive omental disease were more likely to have less response to NACT [16]. Nevertheless, in the present study, the authors did not find any associations between them. Therefore, patients in FIGO Stage IV and initial serum CA125 level higher than 2,539.50 U/ml were suggested to be treated with PCS instead of NACT followed by ICS.

The selection of subsequent treatment for patients who showed no response to NACT is still under controversy. Mazzeo *et al.* concluded that for patients those maintained stable disease after treatment with NACT, administration of second-line chemotherapy without ICS could achieve outcome similar to NACT [8]. It was reported that, after CS, cell cycle of remaining tumor may transform into active growth phase, thereby rendering these tumor cells more susceptible to chemotherapeutic agents [17]. Thus, patients who have accepted three to four courses of NACT were recommended to receive ICS regardless of the response to NACT, then followed by second-line NACT. Besides extension of OS in advanced EOC, another tremendous goal of clinical treatment was to improve patients' quality of life. Up to now, regardless of NACT or ICS, revealed complications. The present results also displayed similar outcomes. Further therapies should be promoted to improve quality of life by decreasing the complications.

## Acknowledgements

The present study was financially supported by Youth Innovation Sichuan Medical Research topics (Q14038).

## References

[1] Siegel R., Ma J., Zou Z., Jemal A.: "Cancer statistics, 2014". *CA Cancer J. Clin.*, 2014, *64*, 9.

[2] Bristow R.E., Tomacruz R.S., Armstrong D.K., Trimble E.L., Montz F.J.: "Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis". J. Clin. Oncol., 2002, *20*, 1248.

[3] Kang S., Nam B.H.: "Does neoadjuvant chemotherapy increase optimal cytoreduction rate in advanced ovarian cancer? Meta-analysis of 21 studies". Ann. Surg. Oncol., 2009, *16*, 2315.

[4] Hegazy M.A., Hegazi R.A., Elshafei M.A., Setit A.E., Elshamy M.R., Eltatoongy M., *et al.*: "Neoadjuvant chemotherapy versus primary surgery in advanced ovarian carcinoma". *World J. Surg. Oncol.*, 2005, *3*, 57.

[5] Hou J.Y., Kelly M.G., Yu H., McAlpine J.N., Azodi M., Rutherford T.J., *et al.*: "Neoadjuvant chemotherapy lessens surgical morbidity in advanced ovarian cancer and leads to improved survival in stage IV disease". *Gynecol. Oncol.*, 2007, *105*, 211.

[6] Milam M.R., Tao X., Coleman R.L., Harrell R., Bassett R., Dos Reis R., *et al.*: "Neoadjuvant chemotherapy is associated with prolonged primary treatment intervals in patients with advanced epithelial ovarian cancer". *Int. J. Gynecol. Cancer*, 2011, *21*, 66.

[7] Vergote I., van Gorp T., Amant F., Neven P., Berteloot P.: "Neoadjuvant chemotherapy for ovarian cancer". *Oncology*, 2005, *19*, 1615.

[8] Mazzeo F., Berlière M., Kerger J., Squifflet J., Duck L., D'Hondt V., *et al.*: "Neoadjuvant chemotherapy followed by surgery and adjuvant chemotherapy in patients with primarily unresectable, advanced-stage ovarian cancer". *Gynecol. Oncol.*, 2003, *90*, 163.

[9] Eisenhauer E.A., Therasse P., Bogaerts J., Schwartz L.H., Sargent D., Ford R., *et al.*: "New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1)". Eur. J. Cancer, 2009, *45*, 228.

[10] Rustin G.J., Vergote I., Eisenhauer E., Pujade-Lauraine E., Quinn M., Thigpen T., *et al.*: "Definitions for response and progression in ovarian cancer clinical trials incorporating RECIST 1.1 and CA 125 agreed by the Gynecological Cancer Intergroup (GCIG)". *Int. J. Gynecol. Cancer*, 2011, *21*, 419.

[11] Bristow R.E., Chi D.S.: "Platinum-based neoadjuvant chemotherapy and interval surgical cytoreduction for advanced ovarian cancer: a meta-analysis". *Gynecol. Oncol.*, 2006, *103*, 1070.

[12] Polcher M., Mahner S., Ortmann O., Hilfrich J., Diedrich K., Breitbach G.P., *et al.*: "Neoadjuvant chemotherapy with carboplatin and docetaxel in advanced ovarian cancer—a prospective multicenter phase II trial (PRIMOVAR)". *Oncol. Rep.*, 2009, *22*, 605.

[13] Onda T., Yoshikawa H., Yasugi T., Matsumoto K., Taketani Y.: "The optimal debulking after neoadjuvant chemotherapy in ovarian cancer: proposal based on interval look during upfront surgery setting treatment". *Jpn. J. Clin. Oncol.*, 2010, *40*, 36.

[14] Le T., Alshaikh G., Hopkins L., Faught W., Fung M.F.: "Prognostic significance of postoperative morbidities in patients with advanced epithelial ovarian cancer treated with neoadjuvant chemotherapy and delayed primary surgical debulking". *Ann. Surg. Oncol.*, 2006, *13*, 1711.

[15] Norton L., Simon R.: "Tumor size, sensitivity to therapy, and design of treatment schedules". *Cancer Treat. Rep.*, 1997, *61*, 307.

[16] Yildirim Y., Ertas I.E., Dogan A., Gultekin O.E., Gultekin E.: "The predictors of response to neoadjuvant chemotherapy in advanced epithelial ovarian cancer". *J. Surg. Oncol.*, 2012, *105*, 200.

[17] Covens A.L.: "A critique of surgical cytoreduction in advanced ovarian cancer". *Gynecol. Oncol.*, 2000, *78*, 269.

Corresponding Author:
X. ZHAO, M.D.
Department of Obstetrics and Gynecology
Affiliated West China Women's and
Children's Hospital of Sichuan University
No. 20 Renmin Nanlu
Chengdu 610041 (China)
e-mail: zhaoxiasc@sina.com