—Original—

Serum CA 125 Level after Neoadjuvant Chemotherapy is Predictive of Prognosis and Debulking Surgery Outcomes in Advanced Epithelial Ovarian Cancer

Tomohiko Matsuhashi[1,2], Toshiyuki Takeshita[3], Akihito Yamamoto[3], Rieko Kawase[3], Takashi Yamada[1], Keisuke Kurose[3], Daisuke Doi[4], Katsuyuki Konnai[2], Ryo Onose[2] and Hisamori Kato[2]

[1]Department of Obstetrics and Gynecology, Nippon Medical School Chiba Hokusoh Hospital, Chiba, Japan
[2]Department of Gynecology, Kanagawa Cancer Center, Kanagawa, Japan
[3]Department of Obstetrics and Gynecology, Nippon Medical School, Tokyo, Japan
[4]Department of Obstetrics and Gynecology, Nippon Medical School Musashi Kosugi Hospital, Kanagawa, Japan

Recently, neoadjuvant chemotherapy followed by interval debulking surgery (NACT-IDS) has been recommended for selected patients with International Federation of Gynecology and Obstetrics (FIGO) stage III or IV disease and bulky tumors. The aim of this study was to evaluate associations between post-NACT serum CA 125 levels, surgical outcomes, and clinical outcomes in patients with advanced epithelial ovarian cancer. We retrospectively analyzed 107 patients with FIGO stage III or IV ovarian cancer who were treated with NACT-IDS at the Gynecology Department of Kanagawa Cancer Center between January 2001 and December 2012. Serum CA 125 levels after NACT were significantly lower in the complete/optimal IDS group compared to the suboptimal IDS group (mean±standard deviation: 48.1±27.6 *vs*. 346.5±295.2 U/mL, $p<0.01$). Patients with low preoperative CA 125 levels (<35 U/mL) had a higher probability of optimal IDS (78.1 ± 41.9% *vs*. 33.3 ± 19.2%, $p<0.01$) and longer progression-free survival (mean ± standard deviation: 30.4 ± 14.3 months *vs*. 21.3 ± 7.3 months, $p<0.05$) than patients with high CA 125 levels (>100 U/mL). Patients with low CA 125 levels (<35 U/mL) had a higher probability of complete/optimal IDS and longer progression-free survival compared to patients with high CA 125 levels (>100 U/mL). (J Nippon Med Sch 2017; 84: 170–176)

Key words: cancer antigen 125, interval debulking surgery, neoadjuvant chemotherapy, ovarian cancer, prognosis

Introduction

Each year, more deaths are caused by ovarian cancer than by any other gynecologic malignancy. Furthermore, ovarian cancer is the sixth most common cancer among women worldwide[1]. Steady advances in treatment strategies, such as surgical techniques and optimal combinations of chemotherapeutic agents, have improved 5-year survival for patients with ovarian cancer. Unfortunately, however, the prognosis generally remains poor[2]. Most ovarian cancers are asymptomatic before the development of secondary peritoneal dissemination and carcinomatous ascites. Consequently, >60% of ovarian cancers are diagnosed as International Federation of Gynecology and Obstetrics (FIGO) Stage III or above, some of which are already inoperable upon diagnosis.

Neoadjuvant chemotherapy (NACT) with a taxane and platinum-based regimen has recently been recommended for patients with advanced epithelial ovarian cancer (EOC) who cannot tolerate primary debulking surgery (PDS) and/or patients with advanced EOC for whom optimal cytoreduction is not feasible. For a select group of patients with advanced EOC, NACT has been recommended instead of exploratory laparotomy followed by adjuvant chemotherapy because NACT followed by interval debulking surgery (IDS) was shown to have fewer complications compared to PDS, without any statistically

Correspondence to Tomohiko Matsuhashi, MD, Department of Obstetrics and Gynecology, Nippon Medical School Chiba Hokusoh Hospital, 1715 Kamagari, Inzai, Chiba 270–1694, Japan
E-mail: t-matsuhashi@nms.ac.jp
Journal Website (http://www2.nms.ac.jp/jnms/)

significant difference, in therapeutic efficacy in randomized trials[3–5].

Cancer antigen 125 (CA 125), the protein encoded by the *MUC16* gene, is the most frequently used tumor marker for ovarian cancer[6]. Because CA 125 is easily measured, simple to evaluate, and reflective of tumor growth, it is considered a particularly efficient method to evaluate treatment efficacy. Reductions in CA 125 levels before and after primary treatment (e.g., NACT or debulking surgery, followed by adjuvant chemotherapy) predicts the prognoses of advanced EOC patients[7–11]. However, the correlation between post-NACT CA 125 levels and successful IDS remains controversial, despite a great deal of clinical interest.

To evaluate the associations between CA 125, surgical outcomes, and clinical outcomes, we retrospectively analyzed 107 patients with FIGO Stage III/IV EOC who were treated with NACT followed by IDS at the Kanagawa Cancer Center (Yokohama, Japan) over the past 12 years: January 2001 to December 2012.

Patients and Methods

Patients

In this study, we retrospectively enrolled 110 patients with presumed FIGO Stage III/IV EOC, based on the results of computed tomography/magnetic resonance imaging, who underwent NACT-IDS at the Department of Gynecology (Kanagawa Cancer Center, Yokohama, Japan) between January 2001 and December 2012. Our surgical practice and procedure for ovarian cancers did not change during those years. A combination of taxane and a platinum-based agent (paclitaxel [175 mg/m^2] and carboplatin, area under the curve [AUC] 6 or docetaxel [70 mg/m^2] and carboplatin, AUC 6) was administered parenterally as NACT in 107 patients. For 3 patients, however, CAP (cyclophosphamide [500 mg/m^2], doxorubicin [50 mg/m^2], and cisplatin [50 mg/m^2]) or intraperitoneal carboplatin was administered; these patients were excluded from our analyses. All patients were provided with verbal and written information regarding the use of their anonymized clinical records for research, and all patients approved such use. This study was granted approval by the appropriate Institutional Review Board of the Kanagawa Cancer Center. Patient records were anonymized and de-identified prior to analysis.

Measurement of Serum CA 125 Levels

Serum CA 125 levels were measured using an automated enzyme immunoassay (Abbot Diagnostics, Chicago, IL, USA). The cut-off value was set at 35 U/mL, as recommended in clinical practice.

Data Collection and Statistical Methods

Information was collected on age, histological type, stage of disease, serum CA 125 levels (before [pre-CA 125] and after NACT [post-CA 125]), frequency of NACT administration, outcomes of IDS, progression-free survival (PFS), and overall survival (OS). All histopathological diagnoses were performed by a pathologist in the Pathology Department of the Kanagawa Cancer Center and were confirmed by a second pathologist. Clinical stage was determined according to the 2014 FIGO staging system.

Estimates of survival were calculated using the Kaplan-Meier method and compared between groups using the log-rank test. Probability (p)-values below 0.05 were considered statistically significant. All analyses were conducted using Statistical Package for the Social Sciences for Windows, software version 12.0 (SPSS Inc., Chicago, IL, USA).

Results

The mean patient age at diagnosis was 60.5 ± 10.1 years (range, 36–77 years). Of the analyzed cases, 78.5% (N= 84/107) were histopathologically classified as high-grade serous carcinomas, 11.2% (N=12/107) were classified as clear cell carcinomas, 2.8% (N=3/107) were each classified as mucinous carcinomas and endometrioid carcinomas, and 4.7% (N=5/107) were classified as undifferentiated carcinomas. Stage IV disease was detected in 44.9% of patients (N=48/107).

Patients were stratified into two groups, according to IDS evaluation (**Table 1**). We compared the clinical findings between these groups, including serum CA 125 levels (before and after NACT), progression-free survival (PFS), and OS. The groups did not differ significantly in terms of age, frequency of NACT administration, stage of disease, or rate of high-grade serous carcinoma, which is the most common histological type of epithelial ovarian cancer. In the complete/optimal IDS group, post-NACT serum CA 125 levels (mean ± standard deviation: 48.1 ± 27.6 *vs*. 346.5 ± 295.2 U/mL, $p<0.01$) were significantly lower, and PFS (28.7 ± 9.5 *vs*. 16.1 ± 8.0 months, $p<0.05$) and OS (31.3 ± 6.6 *vs*. 21.0 ± 8.2 months, $p<0.05$) were significantly longer than in the suboptimal IDS group. To estimate the timing of IDS that would lead to adequate success rates during chemotherapy, we compared chronological decreases in serum CA 125 levels in the complete/optimal IDS and suboptimal IDS groups. Unexpectedly, the frequency of NACT before CA 125 levels

Table 1 Characteristics of patients with suspected International Federation of Gynecology and Obstetrics (FIGO) Stage III/IV ovarian cancer (N=107) according to surgical results after interval debulking surgery (IDS)

Patient characteristics	Complete/optimal IDS group (N=77)	Suboptimal IDS group (N=30)	*p*-value
Age, years (range)	59 (36–77)	61 (38–75)	
FIGO Stage, N (%)			
III	44 (57.1)	15 (50.0)	
IV	33 (42.9)	15 (50.0)	
Histopathological type, N (%)			
HGSC	63 (81.8)	21 (70.0)	
EC	1 (1.3)	2 (6.7)	
MC	3 (3.9)	0 (0.0)	
CCC	6 (7.8)	6 (20.0)	
UC	4 (5.2)	1 (3.3)	
Courses of NACT, N (%)			
6	56 (72.7)	22 (73.3)	
≤5	21 (27.3)	8 (26.7)	
Courses of NACT before CA 125 levels halved*	1.94±0.77	1.75±0.79	$p>0.05$
Courses of NACT before CA 125 levels<35 U/mL*	3.77±1.34	3.57±1.27	$p>0.05$
Pre-NACT CA 125 levels (U/mL)*	2,895.1±647.2	2,345.1±860.2	$p>0.05$
Post-NACT CA 125 levels (U/mL)*	48.1±27.6	346.5±295.2	0.003
Post-NACT CA 125 levels<35 U/mL, N (%)	53 (68.8)	8 (26.7)	0.0016
PFS, months*	28.7±9.5	16.1±8.0	0.025
OS, months*	31.3±6.6	21.0±8.2	0.033

HGSC, high-grade serous carcinoma; EC, endometrioid carcinoma; MC, mucinous carcinoma; CCC, clear cell carcinoma; UC, undifferentiated carcinoma; NACT, neoadjuvant chemotherapy; CA 125, cancer antigen 125; OS, overall survival; PFS, progression-free survival.

*mean±standard deviation (SD) was used for summary statistics

halved (1.94 *vs*. 1.75, $p>0.05$), and pre-NACT CA 125 levels that dropped below 35 U/mL (3.77 *vs*. 3.57, $p>0.05$) were similar in both the complete/optimal IDS and suboptimal IDS groups.

Patients were also stratified into two groups according to post-NACT serum CA 125 levels: low-CA 125 (<35 U/mL) and high-CA 125 (>100 U/mL; **Table 2**). The cut-off values for serum CA 125 levels were selected to provide comparisons of chemotherapy-susceptible and chemotherapy-resistant cases. We compared post-NACT serum CA 125 between the two groups in terms of complete/optimal IDS achievement rates and prognoses. Age, frequency of NACT administration, and pre-NACT serum CA 125 levels were similar in both groups.

When compared with the high-CA 125 group, the low-CA 125 group had superior rates of complete/optimal IDS (78.1 ± 41.9% *vs*. 33.3 ± 19.2%, $p<0.01$; sensitivity, 0.78; specificity, 0.68; positive predictive value, 0.84; negative predictive value, 0.59; **Table 3**) and PFS (mean ± standard deviation: 30.4 ± 14.3 months *vs*. 21.3 ± 7.3 months, $p<0.05$). Complete/optimal IDS cases in the high-CA 125 group and suboptimal IDS cases in the low-CA 125 group were similar to the other cases with respect to age, histopathological type, stage, and frequency of NACT. The survival rate also tended to be higher in the low-CA 125 group, although a statistically significant difference was not detected for OS (**Fig. 1**).

Discussion

The prognosis of ovarian cancer is related to cytoreduction, which represents one of the most important treatment factors related to surgery and may even be important in cases of recurrent disease[12,13]. Quality of life, efficacy of subsequent chemotherapy, and median survival each depend on residual tumor volume after cytoreductive surgery[14,15]. To achieve maximum cytoreduction, NACT followed by IDS is often selected as the first treatment for advanced EOC.

No studies have included extensive investigations of the optimal timing of IDS during NACT and, indeed, this optimal timing remains to be clarified. However, some researchers have investigated correlations between the achievement of cytoreduction and changes in serum CA 125 levels. Rodriguez et al.[16] evaluated the relation-

Table 2 Characteristics of patients with suspected International Federation of Gynecology and Obstetrics (FIGO) Stage III/IV ovarian cancer (N=107) according to post-neoadjuvant chemotherapy (NACT) cancer antigen 125 (CA 125) levels (<35 *vs.*>100 U/mL)

Patient characteristics	Low-CA 125 group (<35 U/mL; N=41)	High-CA 125 group (>100 U/mL; N=19)	*p*-value
Age, years (range)	58 (36–77)	52.5 (38–75)	
FIGO Stage, N (%)			
III	19 (46.3)	13 (68.5)	
IV	22 (53.7)	6 (31.5)	
Histopathological type, N (%)			
HGSC	34 (83.0)	13 (68.4)	
EC	0 (0.0)	1 (5.3)	
MC	3 (7.3)	0 (0.0)	
CCC	1 (2.4)	4 (21.0)	
UC	3 (7.3)	1 (5.3)	
Courses of NACT, N (%)			
6	29 (70.7)	16 (84.2)	$p>0.05$
≤5	12 (29.3)	3 (15.8)	
Pre-NACT CA 125 levels (U/mL)*	2,260.1±618.3	2,606.1±1,421.2	$p>0.05$
IDS, N (%)			
Complete/optimal	32 (78.1)	6 (31.6)	0.0029
Suboptimal	9 (21.9)	13 (68.4)	
PFS, months*	30.4±14.3	21.3±7.3	0.047
OS, months*	41.7±10.2	30.8±11.3	$p>0.05$

HGSC, high-grade serous carcinoma; EC, endometrioid carcinoma; MC, mucinous carcinoma; CCC, clear cell carcinoma; UC, undifferentiated carcinoma; IDS, interval debulking surgery; OS, overall survival; PFS, progression-free survival.
*mean±standard deviation (SD) was used for summary statistics.

Table 3 Cancer antigen 125 (CA 125) levels after neoadjuvant chemotherapy (NACT) in patients with suspected International Federation of Gynecology and Obstetrics Stage III/IV ovarian cancer undergoing interval debulking surgery (IDS; N=60) according to residual disease

Post-NACT CA 125 levels (U/mL)	Complete/optimal IDS (N=38)	Suboptimal IDS (N=22)	Total
<35	32	9	41
>100	6	13	19

Sensitivity, 0.78; specificity, 0.68; positive predictive value, 0.84; negative predictive value, 0.59.

ship between mean serum CA 125 levels and surgical outcomes in a study of 103 patients with Stage IIIC/IV EOC who were treated with platinum-based NACT followed by IDS. The mean serum CA 125 levels prior to IDS differed significantly between the complete/optimal and suboptimal surgery groups (92 *vs.* 233 U/mL; $p<0.01$). However, surgery groups did not differ significantly in terms of CA 125 levels at diagnosis (1,566 *vs.* 2,077 U/mL; $p>0.05$). Rodriguez et al. also noted that 38 patients (80%) in the complete surgery group had preoperative CA 125 levels of ≤100 U/mL, as compared to 33 patients (63.4%) in the optimal surgery group ($p<0.05$). The results of the present study unequivocally support these prior findings. Additionally, we have shown that the mean CA 125 level prior to IDS is strongly associated with OS, as is particularly illustrated by our comparison of the high-CA 125 (>100 U/mL) and low-CA 125 (<35 U/mL) groups. The CA 125 cut-off value used by Rodriguez et al.[16] was substantially greater than that of the present study because Rodriguez et al.[16] included a median of 3 courses of NACT, whereas our study included a median of 6 courses.

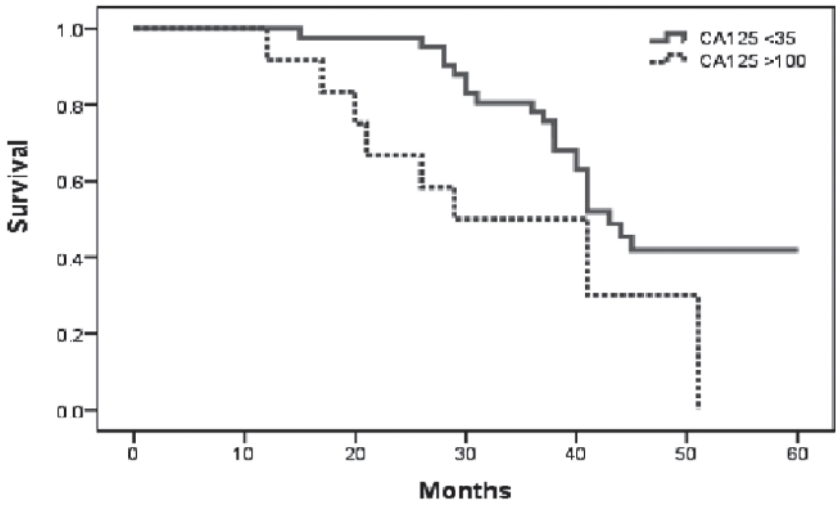

Fig. 1 Survival curves for patients with ovarian cancer according to CA 125 serum concentration before interval debulking surgery.

Prat et al.[17] used a different approach to assess the associations between CA 125 levels, PFS, and OS. They reviewed 96 patients with FIGO Stage III/IV ovarian cancer who were treated with optimal PDS and achieved complete responses with normalized CA 125 levels. Patients with nadir CA 125 levels (≤10 U/mL) had a longer PFS (42 *vs*. 20 months, $p<0.01$) and OS (84 *vs*. 43 months, $p<0.0001$) as compared to patients with CA 125 levels in the range of 11–35 U/mL. Accordingly, the authors concluded that a nadir CA 125 level is a strong independent prognostic factor for patients who have advanced ovarian cancer with complete response to primary treatment. Vasudev et al.[18] reported that the regression rate of serum CA 125 levels during NACT had both prognostic and predictive value. However, our results do not support these prior findings, because we observed that the number of NACT courses required for serum CA 125 levels to halve or reduce to <35 U/mL was similar between the optimal/complete and the suboptimal surgery groups. Therefore, we conclude that the pre-IDS value of serum CA 125 levels is more clinically important that the CA 125 reduction rate for successful cytoreduction after NACT.

Arits et al.[19] have questioned the ability of serum CA 125 levels to predict the outcomes of PDS, finding that the AUC for pre-operative CA 125-based predictions of suboptimal surgery in FIGO Stage III/IV disease was only 0.576 ($p>0.05$). They affirmed that marked weight loss and large quantities of ascites were independent risk factors for suboptimal cytoreduction in patients with EOC, showing an AUC of 0.76 ($p<0.001$), and additionally noted that patients with these factors may be considered candidates for NACT.

In the present study, all patients were treated with taxane and platinum-based NACT, receiving 2–6 courses (median, 6 courses) pre-IDS. Ten patients received 3 courses of NACT or less, 7 of whom received optimal/complete cytoreductive surgery. All 7 of these patients had pre-IDS CA 125 levels of <35 U/mL. Each of the other 3 patients who received <3 courses of NACT were confirmed as having progressive disease that resulted in suboptimal surgery. These data suggest that, as compared to the number of NACT courses, the pre-IDS CA 125 level is a better predictor of IDS outcome.

There is no evidence to suggest that IDS is indicated immediately for patients with CA 125 levels that remain static or rise during NACT, unless a contraindication is present. If a patient has already received 6 courses of NACT with decreasing CA 125 levels, but still has a serum CA 125 level of >35 U/mL, then the best therapeutic strategy remains unclear and is controversial. From a medical oncology perspective, it is worth noting that several large clinical trials have found that maintenance chemotherapy is not efficacious after a predetermined 6 courses of administration[20]. Accordingly, an indication of NACT in excess of 6 courses should be considered with care.

Although our study is limited by its rather small sample size, these findings could be instrumental in selecting the timing for IDS that is most likely to lead to an improved prognosis. Overall, our data suggest that post-NACT CA 125 levels of <35 U/mL can be used as a

prognostic factor of a higher likelihood of optimal/complete IDS, which is known to be an independent predictor of survival for EOC patients with FIGO Stage III/IV regardless of the frequency of NACT administration. However, it should be noted that the patients with post-NACT CA 125 levels of >100 U/mL are still candidates for IDS and hold a possibility of remission, because 6 patients out of 19 in the high-CA 125 group had achieved optimal/complete IDS. We hope that our data will contribute to further improvements in the prognosis of patients with advanced EOC, which accounts for >60% of all ovarian cancers, and who represent potential candidates for NACT-IDS. More investigation, however, will be required to further clarify these issues.

Conflict of Interest: The authors declare no conflict of interest.

References

1. Elattar A, Bryant A, Winter-Roach BA, Hatem M, Naik R: Optimal primary surgical treatment for advanced epithelial ovarian cancer. Cochrane Database Syst Rev 2011; CD007565.
2. Leamon CP, Lovejoy CD, Nguyen B: Patient selection and targeted treatment in the management of platinum-resistant ovarian cancer. Pharmgenomics Pers Med 2013; 6: 113–125.
3. Kehoe S, Hook J, Nankivell M, Jayson GC, Kitchener H, Lopes T, Luesley D, Perren T, Bannoo S, Mascarenhas M, Dobbs S, Essapen S, Twigg J, Herod J, McCluggage G, Parmar M, Swart AM: Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial. Lancet 2015; 386: 249–257.
4. Vergote I, Tropé CG, Amant F, Kristensen GB, Ehlen T, Johnson N, Verheijen RH, van der Burg ME, Lacave AJ, Panici PB, Kenter GG, Casado A, Mendiola C, Coens C, Verleye L, Stuart GC, Pecorelli S, Reed NS: Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. N Engl J Med 2010; 363: 943–953.
5. Chi DS, Musa F, Dao F, Zivanovic O, Sonoda Y, Leitao MM, Levine DA, Gardner GJ, Abu-Rustum NR, Barakat RR: An analysis of patients with bulky advanced stage ovarian, tubal, and peritoneal carcinoma treated with primary debulking surgery (PDS) during an identical time period as the randomized EORTC-NCIC trial of PDS vs neoadjuvant chemotherapy (NACT). Gynecol Oncol 2012; 124: 10–14.
6. Singh AP, Senapati S, Ponnusamy MP, Jain M, Lele SM, Davis JS, Remmenga S, Batra SK: Clinical potential of mucins in diagnosis, prognosis, and therapy of ovarian cancer. Lancet Oncol 2008; 9: 1076–1085.
7. Fu Y, Wang X, Pan Z, Xie X: Clinical outcomes and prognostic factors of patients with epithelial ovarian cancer subjected to first-line treatment: a retrospective study of 251 cases. Front Med 2014; 8: 91–95.
8. Juretzka MM, Barakat RR, Chi DS, Iasonos A, Dupont J, Abu-Rustum NR, Poynor EA, Aghajanian C, Spriggs D, Hensley ML, Sabbatini P: CA125 level as a predictor of progression-free survival and overall survival in ovarian cancer patients with surgically defined disease status prior to the initiation of intraperitoneal consolidation therapy. Gynecol Oncol 2007; 104: 176–180.
9. Tian C, Markman M, Zaino R, Ozols RF, McGuire WP, Muggia FM, Rose PG, Spriggs D, Armstrong DK: CA-125 change after chemotherapy in prediction of treatment outcome among advanced mucinous and clear cell epithelial ovarian cancers: a Gynecologic Oncology Group study. Cancer 2009; 115: 1395–1403.
10. van Altena AM, Kolwijck E, Spanjer MJ, Hendriks JC, Massuger LF, de Hullu JA: CA125 nadir concentration is an independent predictor of tumor recurrence in patients with ovarian cancer: a population-based study. Gynecol Oncol 2010; 119: 265–269.
11. Rocconi RP, Matthews KS, Kemper MK, Hoskins KE, Huh WK, Straughn JM Jr: The timing of normalization of CA-125 levels during primary chemotherapy is predictive of survival in patients with epithelial ovarian cancer. Gynecol Oncol 2009; 114: 242–245.
12. Rafii A, Stoeckle E, Jean-Laurent M, Ferron G, Morice P, Houvenaeghel G, Lecuru F, Leblanc E, Querleu D: Multicenter evaluation of post-operative morbidity and mortality after optimal cytoreductive surgery for advanced ovarian cancer. PLoS One 2012; 7: e39415.
13. Luyckx M, Leblanc E, Filleron T, Morice P, Darai E, Classe JM, Ferron G, Stoeckle E, Pomel C, Vinet B, Chereau E, Bergzoll C, Querleu D: Maximal cytoreduction in patients with FIGO stage IIIC to stage IV ovarian, fallopian, and peritoneal cancer in day-to-day practice: a Retrospective French Multicentric Study. Int J Gynecol Cancer 2012; 22: 1337–1343.
14. Chi DS, Eisenhauer EL, Zivanovic O, Sonoda Y, Abu-Rustum NR, Levine DA, Guile MW, Bristow RE, Aghajanian C, Barakat RR: Improved progression-free and overall survival in advanced ovarian cancer as a result of a change in surgical paradigm. Gynecol Oncol 2009; 114: 26–31.
15. du Bois A, Reuss A, Pujade-Lauraine E, Harter P, Ray-Coquard I, Pfisterer J: Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: a combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials: by the Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and the Groupe d'Investigateurs Nationaux Pour les Etudes des Cancers de l'Ovaire (GINECO). Cancer 2009; 115: 1234–1244.
16. Rodriguez N, Rauh-Hain JA, Shoni M, Berkowitz RS, Muto MG, Feltmate C, Schorge JO, Del Carmen MG, Matulonis UA, Horowitz NS: 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 2012; 125: 362–366.
17. Prat A, Parera M, Peralta S, Perez-Benavente MA, Garcia A, Gil-Moreno A, Martinez-Palones JM, Roxana I, Baselga J, Del Campo JM: Nadir CA-125 concentration in the normal range as an independent prognostic factor for optimally treated advanced epithelial ovarian cancer. Ann Oncol 2008; 19: 327–331.
18. Vasudev NS, Trigonis I, Cairns DA, Hall GD, Jackson DP, Broadhead T, Buxton J, Hutson R, Nugent D, Perren TJ: The prognostic and predictive value of CA-125 regression during neoadjuvant chemotherapy for advanced ovarian or primary peritoneal carcinoma. Arch Gynecol Obstet 2011; 284: 221–227.

19. Arits AH, Stoot JE, Botterweck AA, Roumen FJ, Voogd AC: Preoperative serum CA125 levels do not predict suboptimal cytoreductive surgery in epithelial ovarian cancer. Int J Gynecol Cancer 2008; 18: 621–628.
20. Mei L, Chen H, Wei DM, Fang F, Liu GJ, Xie HY, Wang X, Zou J, Han X, Feng D: Maintenance chemotherapy for ovarian cancer. Cochrane Database Syst Rev 2013; 6: CD007414.

(Received, March 7, 2017)
(Accepted, June 7, 2017)