ANTICANCER RESEARCH *40*: 6003-6008 (2020)
doi:10.21873/anticanres.14621

Review

Survival After Primary Surgery Compared With Neoadjuvant Chemotherapy in Early-stage Ovarian Cancer

DEANNA HUFFMAN[1], RODNEY WEGNER[2], AMJAD JALIL[3], THOMAS KRIVAK[4] and EIRWEN MILLER[4]

[1]*Department of Internal Medicine, Allegheny Health Network, Pittsburgh, PA, U.S.A.;*
[2]*Division of Radiation Oncology, Allegheny Health Network Cancer Institute, Pittsburgh, PA, U.S.A.;*
[3]*Allegheny Health Network Cancer Institute, Pittsburgh, PA, U.S.A.;*
[4]*Division of Gynecologic Oncology, Allegheny Health Network Cancer Institute, Pittsburgh, PA, U.S.A.*

Abstract. *Background/Aim: Our study evaluated the survival of women with early-stage ovarian cancer treated with neoadjuvant chemotherapy (NAC) vs. primary debulking surgery (PDS). Patients and Methods: We used the 2004-2015 National Cancer Database to identify women with early ovarian cancer treated with multiagent chemotherapy or surgery. Logistic regression was used to identify predictors of NAC. Overall survival estimates were compared using Kaplan–Meier analysis and Cox proportional hazards regression models were used to examine variables. Results: In total, 14,627 women were included. The majority (96%) underwent PDS while (4%) underwent NAC. Median survival time was 40 months (95%CI=37.190-47.280, p<0.0001) in the NAC group and 91 months (95%CI=84.4-110.290, p<0.0001) in the PDS group. Five-year overall survival was 36% for the NAC cohort and 65% for the PDS cohort. Conclusion: Women treated with neoadjuvant chemotherapy (NAC) had worse overall and 5-year survival. This finding agrees with the accepted convention of reserving NAC for women with advanced, unresectable disease.*

Ovarian cancer has the highest mortality of all gynecological cancers and is the fifth leading cause of cancer-related death in women (1). It is typically diagnosed in advanced stages, and the initial treatment involves either neoadjuvant chemotherapy (NAC) or primary debulking surgery (PDS). The goal of NAC is to reduce tumor burden to improve surgical results, and reduce postoperative complications in surgeries than can be otherwise complicated and carry high morbidity (2). The use of NAC in ovarian cancer was first introduced in the 2000s, but randomized controlled trials have failed to demonstrate a clear mortality benefit, and controversy remains about its role in the treatment of ovarian cancer (2-5). Currently the use of NAC, as recommended by the American Society of Clinical Oncology (ASCO), is reserved for women with high peri-operative risk or those with low likelihood of optimal debulking surgery (6). Treatment trends show increasing use of NAC, and some studies suggest that the benefit of NAC may extend beyond current recommendations, although further research is needed to identify the ideal patient pool (2, 7). This paper aimed to use the National Cancer Database to evaluate the use of NAC in patients with early stage ovarian cancer who are more likely to undergo PDS, and examine overall mortality among these two treatment modalities.

Correspondence to: Rodney Wegner, MD, Division of Radiation Oncology, Allegheny General Hospital, Allegheny Health Network Cancer Institute, Level 02, 320 E. North Avenue, Pittsburgh, PA 15212, U.S.A. Tel: +1 4123593400, Fax: +1 4123593171, e-mail: Rodney.wegner@ahn.org

Key Words: Ovarian cancer, primary debulking surgery, neoadjuvant chemotherapy, review.

Patients and Methods

Our patient subset was generated from the National Cancer Database (NCDB). Created by the American Cancer Society and the American College of Surgeons, the NCDB is a near-totally comprehensive collection of data representing 70% of all newly diagnosed cancers in the United States (6). Patient data are de-identified and logged by registrars, therefore our data pool is exempt from oversight by the institutional review board. Our population of interest was patients 18 years and older diagnosed with early-stage (I and II) ovarian cancer from 2004-2015. Cohort selection is outlined in the CONSORT diagram seen in Figure 1. Excluded patients included those who did not receive any treatment and those who could not be followed up. The neoadjuvant chemotherapy cohort (NAC) was defined as patients receiving chemotherapy any number of days prior to surgery. The primary debulking surgery cohort (PDS) was defined as patients who underwent a definitive surgery any number of days prior to administration of chemotherapy.

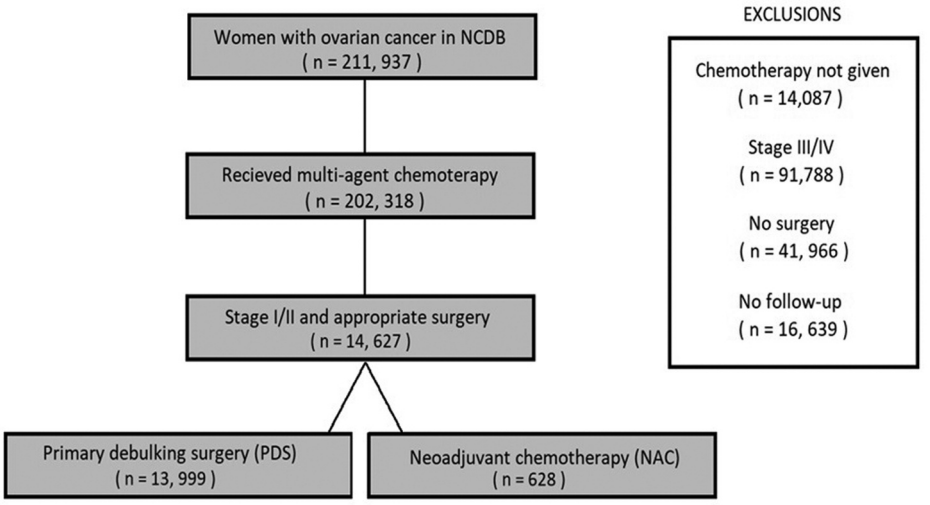

Figure 1. *CONSORT diagram for study cohort selection.*

Age at diagnosis was divided using the cutoff of 60 years, which was the median. Race was categorized as white, African American, or other. Comorbidity severity was classified using the Charlson/Deyo comorbidity index (7). Clinical and pathological staging definitions are in accordance with the International Federation of Gynecology and Obstetrics (8). Insurance data were pulled from patient's admission page. Median household income was reported as quartiles from 2012 census data, based on patient zip code. Facility type was assigned according to the Commission on Cancer accreditation category.

Data were analyzed with Medcalc (Ostend, Belgium). Any cases with missing variables were excluded from regression analyses. To prevent immortal time bias, we excluded patient from survival analyses who did not live a minimum of 3.0 months from treatment initiation. Overall survival (OS) was defined as total months from diagnosis to the date of death or last contact. A standard Kaplan–Meier curve was used to calculate probability of survival of the propensity score-matched cohorts. Nearest neighbor one-to-one propensity matched pairs were generated to overcome indication bias. A cox proportional hazards model was also used for multivariable survival groups.

Results

Of women diagnosed with ovarian cancer from 2004-2015 who are registered in the NCDB, 14,627 women with stage I or II disease received multiagent chemotherapy and a stage-appropriate surgical procedure. Baseline characteristics of our population are outlined in Table I. In summary, 64% of patients had stage I disease at the time of diagnosis and the mean patient age at diagnosis was 60 years. Most patients (96%) were in the PDS cohort, as is expected from current practice trends. Characteristics that were most significantly associated with receiving NAC included age 60 years or older and stage II disease. Odds ratios for downstaging after treatment are outlined in Table II. Downstaging was defined as a decrease in numerical staging from initial clinical stage to final pathological stage after undergoing initial treatment. Women who underwent NAC were less likely to achieve downstaging than women who received PDS (OR=0.7314, 95%CI=0.5984-0.8941, p=0.0023). Odds ratios for downstaging increased with more recent year of diagnosis.

Median follow-up time was 47 months and there were 3,877 deaths in the survival outcome cohort. As described in methods, a propensity score was generated using logistic regression analysis. A matched cohort was created using an exact match on the propensity score, resulting in 613 pairs. Kaplan–Meier curves for propensity-matched cohorts are shown in Figure 2. Women who underwent NAC had an increased hazard of death (HR=1.79, 95%CI=1.5795-2.0186, p<0.0001) as seen in Table III. Other characteristics associated with increased hazard of death included age 60 years or older, African American race, stage II disease, and carcinosarcoma histology. Hazard of death increased with increasing comorbidity score and pathologic stage. Clear cell or serous histologic subtype had a negative association with HR of death, as did having private insurance. Estimated 5-year OS rate for NAC and PDS were 36% and 65%, respectively (Table IV). Median survival time was 40 months for NAC (95%CI=37-47) and 91 months for PDS (95%CI=84-110).

Discussion

Treatment of ovarian cancer remains a controversial subject. Current strategies include primary surgery with or without

Table I. *Patient demographics and odds ratios for receiving neoadjuvant chemotherapy (N=14,627).*

Characteristic	PDS (N=13,999) No. (%)	NAC (N=628) No. (%)	OR (95%CI)	*p*-Value
Age, y				
<60	7,627 (54.5)	191 (30.4)	1 (reference)	
≥60	6,372 (45.5)	437 (69.6)	1.7413 (1.4130-2.1460)	<0.0001
Race				
White	12,397 (88.6)	522 ((83.1)	1 (reference)	
African American	827 (5.9)	69 (11.0)	1.7014 (1.2696 to 2.2798)	0.0004
Other	775 (5.5)	37 (5.9)	1.4882 (1.0340 to 2.1418)	0.0323
Comorbidity score				
0	11,420 (81.6)	467 (74.4)	1 (reference)	
1	2,115 (15.1)	123 (19.6)	1.3505 (1.0880-1.6765)	0.0064
2	464 (3.3)	38 (6.1)	1.5489 (1.0755-2.2308)	0.0187
Stage				
I	9,076 (64.9)	239 (38.1)	1 (reference)	
II	4,923 (35.1)	389 (61.9)	2.1459 (1.8027-2.5544)	<0.0001
Grade				
1	1,420 (10.1)	17 (2.7)	1 (reference)	
2	2,871 (20.1)	56 (8.9)	1.2364 (0.7081-2.1588)	0.4556
3	7,472 (53.4)	357 (56.8)	1.5585 (0.7081-2.1588)	0.0874
Unknown	2,236 (16.0)	198 (31.5)	3.8436 (2.2849-6.4653)	<0.0001
Histology				
Adenocarcinoma	1,010 (7.2)	132 (21.0)	1 (reference)	
Clear cell	2,039 (14.6)	45 (7.2)	0.2090 (0.1456-0.3002)	<0.0001
Endometroid	3,887 (27.8)	46 (7.3)	0.1273 (0.0877-0.1846)	<0.0001
Serous	5,250 (3.8)	367 (58.4)	0.5440 (0.4340 to 0.6819)	<0.0001
Mucinous	923 (6.6)	10 (1.6)	0.1292 (0.0664-0.2514)	<0.0001
Carcinosarcoma	775 (5.5)	26 (4.1)	0.1835 (0.1174-0.2867)	<0.0001
Other	115 (0.8)	2 (0.3)	0.1356 (0.0328 to 0.5606)	<0.0001
Insurance status				
Uninsured	569 (4.1)	21 (3.3)	1 (reference)	
Private	8,168 (58.3)	231 (36.8)	0.9232 (0.7003-1.2170)	0.5707
Government	5,008 (35.8)	365 (58.1)	0.8767 (0.6522-1.1786)	0.3834
Unknown	254 (1.8)	11 (1.8)	0.8644 (0.6100-1.2249)	0.4126
Income quartile, $				
<38,000	1,944 (13.9)	114 (18.2)	1 (reference)	
38,000-47,999	3,104 (22.2)	160 (25.5)	1.0388 (0.7823-1.3793)	0.7926
48,000-62,999	3,809 (27.2)	163 (26.0)	0.9841(0.7237-1.3381)	0.9186
>63,000	5,142 (36.7)	191 (30.4)	0.9750 (0.6896-1.3787)	0.8863
Cancer center type				
Community	589 (4.2)	23 (3.7)	1 (reference)	
Comprehensive community	5,255 (37.5)	260 (41.4)	1.2191 (0.7720-1.9252)	0.3953
Academic/Research center	8,155 (58.3)	345 (54.9)	1.0407 (0.6594-1.6427)	0.8639

NAC: Neoadjuvant chemotherapy; PDS: primary debulking surgery; y: years.

adjuvant or neoadjuvant chemotherapy, as well as systemic chemotherapy and hormonal treatments (9). Despite advances in treatment modalities, it is unclear if the recent decline in ovarian cancer mortality is significant when compared to the recent decline in incidence (10). Although early-stage ovarian cancer is consistently treated with a primarily surgical approach, real-word data do not consistently identify the most effective treatment strategy. The rationale behind the surgical approach to treatment is that complete and accurate surgical staging of early ovarian cancer has been shown to predict disease-free and overall survival and is used to determine the need for adjuvant chemotherapy (11). The use of neoadjuvant chemotherapy has been traditionally reserved for unresectable cases. Randomized clinical trials have finally been able to demonstrate the benefit of neoadjuvant chemotherapy in advanced-stage ovarian cancer (12), but no such trials have been conducted for stage I and II disease.

The first two randomized controlled trials to compare PDS and NAC in ovarian cancer were EORTC (European

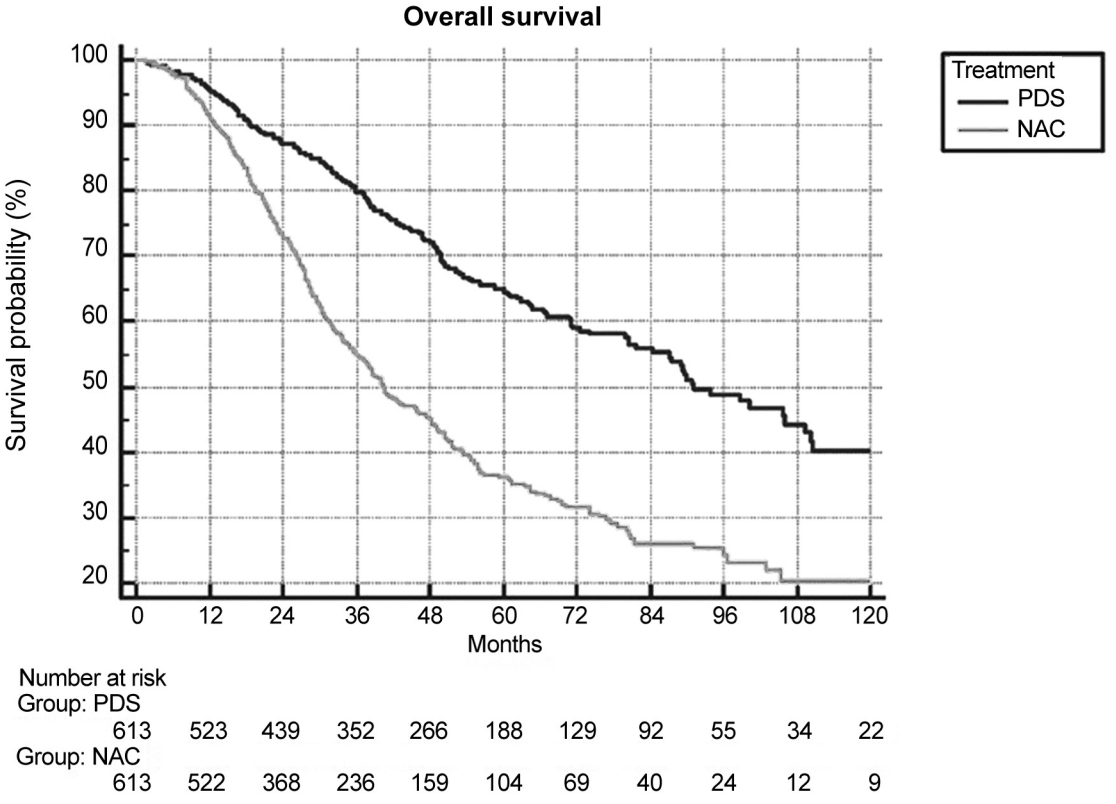

Figure 2. *Kaplan–Meier curves for propensity-matched cohorts.*

Table II. *Odds ratios (OR) for downstaging.*

Characteristic	OR (95%CI)	*p*-Value
Stage		
I	1 (reference)	
II	0.8266 (0.7623-0.8963)	<0.0001
Cancer center type		
Community	1 (reference)	
Comprehensive community	1.4676 (1.1853-1.8172)	0.0004
Academic/Research center	1.3064 (1.0580-1.6130)	0.0130
Year of diagnosis		
2004-2007	1 (reference)	
2008-2010	1.9953 (1.6450-2.4202)	<0.0001
2011-2013	3.7689 (3.1406-4.5228)	<0.0001
2014-2016	4.1364 (3.4476-4.9628)	<0.0001
NAC vs. PDS		
Primary debulking surgery	1 (reference)	
Neoadjuvant chemotherapy	0.7314 (0.5984-0.8941)	0.0023

Organization for Research and Treatment of Cancer) in 2010 and CHORUS (Medical Research Council Chemotherapy or Upfront Surgery) in 2015 (4, 5). EORTC was designed to show non-inferiority of NAC compared to PDS on the basis of overall survival in patients diagnosed with stage IIIC or IV epithelial ovarian carcinoma, fallopian tube carcinoma or primary peritoneal carcinoma from 1998-2006. Overall survival did not differ significantly between the two groups (5). The CHORUS trial was designed similarly using patients from 2005-2010. Again, no significant difference in overall survival was found, nor were patient populations identified who might benefit from one treatment over the other in terms of age, stage, performance status or histology (4). In 2016, JCOG (Japan Clinical Oncology Group) and SCORPION (Survival analyses from a randomized trial of primary debulking surgery *versus* neoadjuvant chemotherapy for advanced epithelial ovarian cancer with high tumor load) trials evaluated surgical outcomes in patients treated with PDS and NAC (12, 13). JCOG included patients with stage III and IV disease randomized to receive either PDS or NAC with carboplatin and paclitaxel every 3 weeks. Morbidity endpoints were defined as frequency of adverse events, duration of surgery, amount of blood loss and frequency of blood transfusions. In this trial, grade III and IV adverse events were significantly less frequent in the NAC cohort (5%) compared to the PDS cohort (16%) and peri-operative deaths were not significantly different (12). SCORPION similarly evaluated surgical morbidity and progression-free survival (PFS) in stage IIIC and IV ovarian cancer. Again, stage III and IV adverse events varied significantly between

Table III. *Cox proportional hazard models for overall survival.*

Characteristic	Hazard of death (95%CI)	*p*-Value
Age, y		
<60	1 (reference)	
≥60	1.3046 (1.20560-1.4116)	<0.0001
Race		
White	1 (reference)	
African American	1.1685 (1.0302-1.3253)	0.0154
Other	0.7778 (0.6562-0.9219)	0.0038
Comorbidity score		
0	1 (reference)	
1	1.0973 (1.0055-1.1975)	0.0373
2	1.5227 (1.3127-1.7662)	<0.0001
Stage		
I	1 (reference)	
II	1.1764 (1.0868-1.2735)	0.0001
Grade		
1	1 (reference)	
2	1.6996 (1.4191-2.0356)	<0.0001
3	2.1056 (1.7730-2.5005)	<0.0001
Unknown	1.8897 (1.5712-2.2729)	<0.0001
Histology		
Adenocarcinoma	1 (reference)	
Clear cell	0.9234 (0.8004-1.0652)	0.2744
Endometroid	0.6416 (0.5614-0.7332)	<0.0001
Serous	0.8530 (0.7633-0.9532)	0.0050
Mucinous	0.9937 (0.8312-1.1880)	0.9451
Carcinosarcoma	1.3804 (1.1817-1.6126)	<0.0001
Other	1.0728 (0.7343-1.5672)	0.7165
Insurance status		
Uninsured	1 (reference)	
Private	0.7973 (0.6696-0.9493)	0.0109
Government	1.1009 (0.9205-1.3166)	0.2924
Unknown	0.8699 (0.6310-1.1993)	0.3950
NAC vs. PDS		
Primary debulking surgery	1 (reference)	
Neoadjuvant chemotherapy	1.7856 (1.5795-2.0186)	<0.0001
Surgical margins		
Positive	1 (reference)	
Negative	1.4579 (1.3494-1.5751)	<0.0001
Unknown or NA	1.1527 (1.0463-1.2699)	0.0040
Pathologic stage		
I	1 (reference)	
II	1.5177 (1.3575-1.6967)	<0.0001
III	2.9230 (2.6282-3.2508)	<0.0001
IV	4.0561 (3.3911-4.8516)	<0.0001
Unknown	1.8066 (1.6192-2.0157)	<0.0001

NAC: Neoadjuvant chemotherapy; PDS: primary debulking surgery; y: years.

Table IV. *Mean, median and overall survival data.*

Treatment cohort	Median survival time in months	95%CI, *p*<0.0001
PDS	91.010	84.400-110.290
NAC	40.380	37.190-47.280
Overall	61.040	53.620-70.080
5-Year overall survival		
PDS	65%	
NAC	36%	

NAC: Neoadjuvant chemotherapy; PDS: primary debulking surgery.

the two cohorts with 52.7% suffering such an event in the PDS group and only 5.7 in the NAC group (13). CHORUS, JCOG and SCORPION all evaluated frequency of severe adverse effects related to chemotherapy and in each case no difference was found between treatment groups (3, 4, 14-16). The summation of these studies demonstrates reduced morbidity and no change in overall survival with the use of NAC when compared to PDS; however, as mentioned prior, there are no such RCT's that demonstrate these same benefits in earlier-stage disease.

In our study, the paucity of use of NAC compared with PDS is on par with current treatment trends. Women who were more likely to receive NAC were older and had more advanced disease on initial clinical staging. Patients who underwent treatment with NAC were less likely to be downstaged on final surgical pathology than those who underwent PDS. Additionally, overall survival was much lower in those patients who received NAC. Our data seem to suggest that NAC is still being reserved for patients with more severe disease, even among early stages. The use of NAC in older patients likely reflects a hesitancy to proceed with surgery in these patients. Interestingly, there were no socioeconomic factors that predicted one treatment over the other. As expected, older patients and those with a higher comorbidity score had a higher risk of death.

Limitations of this study include the large number of women who had to be excluded due to missing data or incomplete follow-up. In addition, given the retrospective nature of the study there is a heavy selection bias, which we attempted to mitigate by using a propensity match. In addition, there are no data on the specific chemotherapy agents or number of cycles delivered. There is also no information on toxicity, local recurrence, or distant recurrence, all of which are important outcomes in a study such as the present. Along those lines, the NCDB also lacks information regarding residual disease or salvage therapies. A strength of using data from the NCDB is that the data are representative and generalizable across the entire nation, making it useful for examining and identifying treatment trends.

In conclusion, women with early stage ovarian cancer in the United States who underwent neoadjuvant chemotherapy rather than primary debulking surgery had a higher hazard of death and worse 5-year overall survival. These patients were also older and had more advanced disease. These findings tend to agree with current treatment trends that

heavily favor PDS in these patients. It is clear that more work needs to be done to define the appropriate category of women with ovarian cancer who may benefit from NAC in the future.

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

Authors' Contributions

Study concept and design: DH, RW. Analysis and interpretation of data: DH, RW. Drafting of manuscript: DH. Critical revision of the manuscript for important intellectual content: all authors. Administrative, technical or material support: RW.

References

1 Ozga M, Aghajanian C, Myers-Virtue S, McDonnell G, Jhanwar S, Hichenberg S and Sulimanoff I: A systematic review of ovarian cancer and fear of recurrence. Palliat Support Care *13(6)*: 1771-1780, 2015. PMID: 25728373. DOI: 10.1017/S1478951515000127

2 Elies A, Rivière S, Pouget N, Becette V, Dubot C, Donnadieu A, Rouzier R and Bonneau C: The role of neoadjuvant chemotherapy in ovarian cancer. Expert Rev Anticancer Ther *18(6)*: 555-566, 2018. PMID: 29633903. DOI: 10.1080/14737140.2018.1458614

3 Elies A, Rivière S, Pouget N, Becette V, Dubot C, Donnadieu A, Rouzier R and Bonneau C: The role of neoadjuvant chemotherapy in ovarian cancer. Expert Rev Anticancer Ther *18(6)*: 555-566, 2018. PMID: 29633903. DOI: 10.1080/14737140.2018.1458614

4 Kehoe S, Hook J, Nankivell M, Jayson CG, Kitchener H, Lopes T, Luesley D, Perren T, Banoo S, Mascarenhas M, Dobbs S, Essapen S, Twigg J, Herod J, McCluggage G, Parmar M and Swart A: Primary chemotherapy *versus* primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomized, controlled, non-inferiority trial. Lancet *386(9990)*: 249-257, 2015. PMID: 26002111. DOI: 10.1016/S0140-6736(14)62223-6

5 Vergote I, Tropé CG, Amant F, Kristensen GB, Ehlen T, Johnson N, Verheijen RHM, van der Burg MEL, Lacave, AJ, Panici PB, Kenter GG, Casado A, Mendiola C, Coens C, Verleye L, Stuart GCE, Percorelli S and Reed NS: Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. N Engl J Med *363(10)*: 943-953, 2010. PMID: 20818904. DOI: 10.1056/NEJMoa0908806

6 Wright AA, Bohlke K, Armstrong DK, Bookman M, Cliby WA, Coleman RL, Dizon DS, Kash JJ, Meyer LA, Moore KN, Olawaiye AB, Oldman J, Salani R, Sparacia D, Tew W, Vergote I and Edelson MI: Neoadjuvant chemotherapy for newly diagnosed, advanced ovarian cancer: Society of Gynecologic Oncology and American Society of Clinical Oncology Clinical Practice Guideline. Gynecol Oncol *143(1)*: 3460-3473, 2016. PMID: 27502591. DOI: 10.1200/JCO.2016.68.6907

7 Cho JH, Kim S and Song YS: Neoadjuvant chemotherapy in advanced ovarian cancer: optimal patient selection and response evaluation. Chin Clin Oncol *7(6)*: 58, 2018. PMID: 30509079. DOI: 10.21037/cco.2018.10.11

8 Deyo RA, Cherkin DC and Ciol MA: Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol *45(6)*: 613-619, 1992. PMID: 1607900. DOI: 10.1016/0895-4356(92)90133-8

9 Orr B and Edwards RP: Diagnosis and treatment of ovarian cancer. Hematol Oncol Clin North Am *32(6)*: 943-964, 2018. PMID: 30390767. DOI: 10.1016/j.hoc.2018.07.010

10 Eisenhauer EA: Real-world evidence in the treatment of ovarian cancer: Ann Oncol *28(suppl_8)*: viii61-viii65, 2017. PMID: 29232466. DOI: 10.1093/annonc/mdx443

11 Trimbos JB: Surgical treatment of early-stage ovarian cancer: Best Pract Res Clin Obstet Gynaecol *41*: 60-70, 2017. PMID: 27894705. DOI: 10.1016/j.bpobgyn.2016.10.001

12 Onda T, Matsumoto K, Shibata T, Sato A, Fukuda H, Konishi I, Kamura T and Yoshikawa H: Phase III trial of upfront debulking surgery *versus* neoadjuvant chemotherapy for stage III/IV ovarian, tubal and peritoneal cancers: Japan Clinical Oncology Group Study JCOG0602. Jpn J Clin Oncol *38(1)*: 74-77, 2008. PMID: 18258715. DOI: 10.1093/jjco/hym145

13 Fagotti A, Ferrandina G, Vizzielli G, Fanfani F, Gallotta V, Chiantera V, Costantini B, Margariti PA, Alletti SG, Cosentino F, Tortorella L and Scambia G: Phase III randomised clinical trial comparing primary surgery *versus* neoadjuvant chemotherapy in advanced epithelial ovarian cancer with high tumor load (SCORPION trial): Final analysis of peri-operative outcome. Eur J Cancer *59*: 22-33, 2016. PMID: 26998845. DOI: 10.1016/j.ejca.2016.01.017

14 Seagle BL, Graves S, Strohl AE and Shahabi S: Survival after primary debulking surgery compared with neoadjuvant chemotherapy in advanced ovarian cancer: A National Cancer Database Study. Int J Gynecol Cancer *27(8)*: 1610-1618, 2017. PMID: 28763362. DOI: 10.1097/IGC.0000000000001072

15 Bilimoria KY, Stewart AK, Winchester DP and Ko CY: The National Cancer Data Base: a powerful initiative to improve cancer care in the United States. Ann Surg Oncol *15(3)*: 683-690, 2008. PMID: 18183467. DOI: 10.1245/s10434-007-9747-3

16 Matsuo K, Machida H, Mandelbaum RS, Konishi I and Mikami M: Validation of the 2018 FIGO cervical cancer staging system. Gynecol Oncol *152(1)*: 87-93, 2019. PMID: 30389105. DOI: 10.1016/j.ygyno.2018.10.026

Received July 26, 2020
Revised September 19, 2020
Accepted September 27, 2020