Comparison of Cox's Regression Model and Weibull' Parametric Model in Evaluating Factors Affecting in First Recurrence of Epithelial Ovarian Cancer

Maryam Deldar[1], Robab Anbiaee[2], Anahita Jalilian[3], Kourosh Sayehmiri[1], Shima Azimi[2]

[1] Department of Biostatistics, Faculty of Health, Ilam University of Medical Sciences, Ilam, Iran

[2] Department of Radiotherapy, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[3] School of Medicine, Ilam University of Medical Sciences, Ilam, Iran

Abstract- Ovarian cancer is one of the most deadly women's gynecological malignancies in the world, and despite the low prevalence, it accounts for about 5% of all cancer deaths in women. Survival analysis is a regression relationship between a set of variables with a specific outcome, which is considered disease survival or recurrence in medical studies. The aim of this study is to determine the important factors in the first recurrence of patients with epithelial ovarian cancer with two statistics methods. In this study, we review medical records of patients with epithelial ovarian cancer who referred to the oncology and radiotherapy department of Imam Hossein Hospital of Tehran from the beginning of 2007 to the end of 2018. Univariate and multivariate Cox regression, as well as the parametric Weibull method, were used to investigate the factors affecting patients' first recurrence. We perform all calculations with Stata Ver14. Of the 141 patients, 58 patients (41%) had a first recurrence during our follow-up. The mean time to the first recurrence was 24.88 months. Univariate Cox regression and univariate Weibull analysis showed that metastatic tumor and tumor stage had highly significant effects in the first recurrence of epithelial ovarian cancer. In multivariate Cox and multivariate Weibull analysis, the metastatic tumor had a significant effect in the first recurrence of epithelial ovarian cancer. One of the causes of ovarian cancer recurrence may be diagnosis happened at late stages. Therefore, screening programs are needed to reduce illness and death from ovarian cancer.
© 2020 Tehran University of Medical Sciences. All rights reserved.
Acta Med Iran 2020;58(9):445-451.

Keywords: Ovarian cancer; Recurrence; Predictor; Cox regression; Weibull parametric method

Introduction

Ovarian cancer is one of the leading causes of death in the women's gynecological malignancies in the world, and despite improved outcomes from surgery and chemotherapy, most women with ovarian cancer have a recurrence and eventually death in recent decades (1). Epithelial ovarian cancer is one of the leading causes of death in gynecological cancers in the western world (2). Ovarian cancer is a rare disease with a five-year survival rate of almost 47%. These characteristics make it difficult to do retrospectively study (3). It is often diagnosed in an advanced stage due to the lack of specific symptoms (4). While it accounts for 2.5% of all malignancies in women, it accounts for 5% of cancer-related deaths in women (5). There is a need to identify factors that are affected ovarian cancer (6).

Since the diagnosis of CA125 tumor marker, this marker is not only used to evaluate response to treatment widely, but it is used to diagnose ovarian cancer recurrence too (7). The primary treatment for patients with epithelial ovarian cancer is surgery followed by platinum- and taxane-based chemotherapy. Known factors that influence the prognosis of patients with ECO include age, tumor grade, tumor stage, According to" The Federation of Gynecology and Obstetrics" (FIGO), the histology of the tumor, and the outcome of the treatment involving surgery (8).

Survival analysis is a set of statistical methods used to analyze data that our favorite outcome is time to a particular event. One of the most popular survival analyses is Cox regression, as it is semi-parametric, and it can be used to investigate the effect of several variables over time to our event (9). In a study in China that the Cox regression was used to evaluate the prognosis of ovarian cancer patients (10), in the

univariate and multivariate study, disease stage, disease grade, tumor residual after surgery, and a number of chemotherapy courses were significant.

David Mysona, in his study in 2019, showed that Brain-Derived Neurotrophic Factor and Platelet-Derived Growth Factor molecules were significant in predicting high-grade serous ovarian cancer recurrence in both univariate and multivariate analysis (11). In another study in 2019, Dan Nie showed that Systemic immune-inflammation index is associated with the advanced stage of the disease and lymph node metastasis and tumor recurrence in epithelial ovarian cancer which in both univariate and multivariate Cox method, higher SII predicts less overall survival and less progression-free survival (12).

Objectives

There are many studies that have investigated the factors affecting survival or recurrence of ovarian cancer, but so far, no studies have compared factors affecting the first recurrence of ovarian cancer by two different statistical methods in Iran.

Materials and Methods

Eligibility

In this study, we investigate medical records and pathology reports of patients with ovarian cancer who referred to the oncology and radiotherapy department of Imam Hossein Hospital in Tehran for 11 years, from the beginning of 2007 to the end of 2018. Their first recurrence status at the end of 2018 was defined as failure time. In this work, we determine the time to recurrence from the patient's medical records, and in the absence of a physician's report, we consider the interval between the end of the first period of treatment and the restart of chemotherapy. The metastatic tumor is generally considered in this work, and the metastatic site is not considered due to a low sample size and incomplete physician's reports. Inclusion criteria are the initial diagnosis of ovarian cancer, and exclusion criteria are benign, borderline ovarian, germ cell and stromal tumors, Metastases to the ovary, and under the age of 18 years. Thus of 176 patients with ovarian cancer, 35 patients are excluded.

Variables

The potential prognostic variables examined in this study are as follows:

A) Patient variables include age, BMI at diagnosis,

and ascites at diagnosis.

B) tumor-related variables include tumor stage, tumor grade, tumor histology, CA125 tumor marker at diagnosis, and metastatic tumor.

C) Variables related to the types of treatment include adjuvant or neoadjuvant chemotherapy, weekly or three weeks chemotherapy courses.

D) The patient's blood parameters include hemoglobin, platelet, and white blood cells.

Statistical methods

We first use the Kaplan-Meier survival curve and life table to calculate one, two, three, four, five, and ten years disease-free survival probabilities. In the next step, we use Cox's semi-parametric method and Weibull parametric method for univariate analysis of prognostic factors in the first recurrence of ovarian cancer. In this stage, variables that have a significant impact on recurrence are investigated for the Cox proportional hazards model. Then significant variables enter the multivariate Cox survival model and multivariate Weibull model, and we compare the results. Finally, the cumulative hazard curve is plotted based on variables that are significant in Cox multivariate survival and Weibull multivariate models, then results evaluate.

Results

Descriptive data

Of the 141 patients with epithelial ovarian cancer, 58 patients (41%) recurred during our follow-up period, and the rest was censored (Right Censored). The mean time to the first recurrence was 24.88 months, the number of recurrences and the meantime to the first recurrence were analyzed separately in risk factors (Table 1).

Overall recurrence

Using the life table, disease-free survival was 0.97 in the first seven months after diagnosis, 0.82 in the first year after diagnosis, 0.55 in the first two years, 0.44 in the first three years, 0.42 in the first four years, and 0.39 in the first five years And almost to ten years it was 0.36. Kaplan-Meier survival curves were evaluated for first recurrence strata by metastatic tumor and disease stage (Figure 1). We merged stage I and stage II with respect to the low number of recurrent cases in these two-stage, and we evaluated the Cox proportional hazards.

Table 1. Clinical and demographic characteristics of ovarian cancer patients stratified by recurrence time (N=141)

Parameter		No. of patient	%	No.of first recurrence	Mean time to the first recurrence
Age at diagnosis (years)	**18–49**	62	44	30	25.88
	50–59	37	26	16	26.64
	60–69	22	15.6	5	24.76
	_70	20	14.2	7	18.66
BMI Group (kg/m2)	**Underweight/Normal (BMI < 24.9)**	28	19.9	15	19.56
	Overweight (BMI >25)	51	36	24	26.59
	Missing	62	44	…	…
Histologic type	**Serous (I)**	85	60.3	44	25.97
	Others (Endometrioid, Clear Cell, Mucinous)	30	21.2	6	22.62
	Missing	26	18.4	--	--
FIGO Stage at diagnosis	**Stage I**	34	24.1	5	31.58
	Stage II	16	11.3	8	25.35
	Stage III	44	31.2	26	23.7
	Stage IV	14	9.9	8	12.43
	Missing	33	23.4	--	--
Tumor Grade at diagnosis	**1**	24	17	7	28.36
	2	32	22.7	13	27.73
	3	37	26.2	18	26.06
	Missing	48	34	--	--
Neoadjuvant chemotherapy	**Yes**	19	13.5	9	19.77
	No	64	45.4	35	25.6
	Missing	58	41.1	--	--
Ascites at diagnosis	**Yes**	58	41.1	26	22.59
	No	78	55.3	30	26.96
	Missing	5	3.5	--	--
CA-125 prior to treatment	**< 1000 (U/mL)**	13	9	9	14.98
	> 1000 (U/mL)	42	29	18	25.38
	Missing	86	60	--	--
Metastatic tumor	**Yes**	52	36.9	32	18.47
	No	80	56.7	21	30.28
	Missing	9	6	--	--
Mean White blood cells	**<5000**	40	28.3	27	25.21
	>5000	36	25.5	11	23.52
	Missing	65	46	--	--
Mean Hemoglobin	**<11**	35	24.8	19	24.61
	>11	41	29	19	24.16
	Missing	65	46	--	--
Maximum Platelet count	**<350000**	37	26.2	18	29.73
	>350000	39	27.6	20	19.36
	Missing	65	46	--	--
Chemotherapy course	**1week**	37	26.2	22	21.52
	3week	64	45.4	30	24
	Missing	40	28.4	--	--

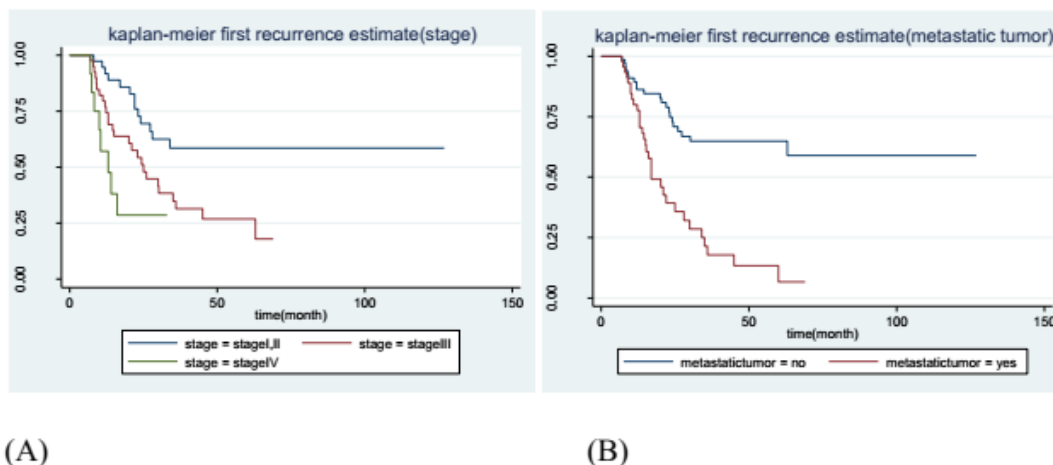BMI= body mass index; CA125 = cancer antigen 125; CI = confidence interval.

Figure 1. First recurrence estimated times strata by A) metastatic tumor B) Figo stage at diagnosis

Main results

In the next step, we first entered each of the variables into the univariate Cox model, and according to the table 2, the metastatic tumor had a hazard ratio (HR=3.617, 95%CI: 2.05_6.35, $P<0.001$), and the tumor stage had a hazard ratio (HR=1.64, 95%CI: 1.24_2.19, $P<0.001$). Thus these two variables had highly significant effects in the first recurrence of epithelial ovarian cancer. In addition to these two variables, histologic type, BMI,

CA125 tumor marker at diagnosis, ascites, mean white blood cell, and max platelet are entered into the multivariate Cox survival model because they had significantly less than 0.25 (Table 2). According to Cox's results, patients with metastasis are 3.61 times more likely to have a recurrence than those without metastasis, and individuals at the higher stages of the disease are 1.64 times more likely to have a recurrence than those at the lower stages.

Table 2. Univariate and multivariate Cox parametric method for the first recurrence of epithelial ovarian cancer

Univariate				Multivariate			
Covariate	**HR**	**95%CI**	**P**	**Covariate**	**HR**	**95%CI**	**P**
Age	0.89	0.68_1.16	0.414	FIGO Stage at diagnosis	1.56	0.88_2.76	0.12
Metastatic tumor	3.617	2.05_6.35	<0.001	Metastatic tumor	4.06	1.2_13.73	0.024
Neoadjuvant chemotherapy	0.87	0.41_1.82	0.71	Histologic type	1.23	0.29_5.22	0.77
FIGO Stage at diagnosis	1.64	1.24_2.19	<0.001	BMI	0.43	0.11_1.74	0.24
Tumor grade at diagnosis	1.22	0.82_1.85	0.32	Baseline ascites	1.68	0.52_5.48	0.38
Histologic type	1.93	0.82_4.54	0.12	CA-125 prior to treatment	1.64	0.29_5.22	0.77
BMI	0.58	0.3_1.12	0.1	Mean White blood cells	1.36	0.41_4.51	0.61
Ascites at diagnosis	1.36	0.8_2.31	0.24	Maximum Platelet count	2.62	0.78_8.84	0.11
CA-125 prior to treatment	2.65	1.16_6.04	0.02				
Chemotherapy course	0.85	0.49_1.49	0.58				
Mean White blood cells	1.77	0.87_3.57	0.11				
Mean Hemoglobin	1.08	0.57_2.05	0.71				
Maximum Platelet count	0.67	0.34_1.28	0.23				

P< 0.05 Indicating significance, HR indicating hazard ratio

We first tested the Cox proportional hazards assumption for the eight variables selected in the univariate Cox, and the results of the Harell test showed that the Cox proportional hazards assumption was valid for the eight variables. So we imported them into multivariate Cox. Finally, multivariate Cox results

showed that the metastatic tumor with a hazard ratio (HR=4.06, 95%CI: 1.2_13.73, $P=0.024$) had a significant effect in the first recurrence of epithelial ovarian cancer (Table 2). According to our results in multivariate Cox, the hazard ratio in patients with metastasis is four times more recurrence than patients

without metastasis.

Again, we entered each of the variables into the univariate Weibull parametric model, and according to table 3, the metastatic tumor (HR=4.62, 95% CI: 2.6_8.19, *P*<0.001) and tumor stage (HR= 1.87, 95% CI: 1.4_2.5, *P*<0.001) had highly significant effects in the first recurrence of epithelial ovarian cancer. In addition to these variables, variables histologic type, CA125 tumor marker at diagnosis, mean white blood cell count, and max platelet count also had a significant hazard ratio of less than 0.05. So we entered these six variables into

the multivariate Weibull model, and again according to table 3, the metastatic tumor with (HR=3.64, 95%CI: 1.19_11.14, *P*=0.023) had a highly significant effect in the first recurrence of epithelial ovarian cancer, so that metastatic tumor increases the risk of the first recurrence in epithelial ovarian cancer patients 3.91 times, and the higher stage of the tumor, increases the risk of the first recurrence 2.21 times. So the results were almost the same for both the semi-parametric Cox model and the parametric Weibull model.

Table 3. Univariate and multivariate Weibull parametric method for the first recurrence of epithelial ovarian cancer

Univariate				Multivariate			
Covariate	HR	95%CI	*P*	Covariate	HR	95%CI	*P*
Age	0.91	0.69_1.18	0.49	FIGO Stage at diagnosis	1.55	0.91_2.64	0.1
Metastatic tumor	4.62	2.6_8.19	<0.001	Metastatic tumor	3.64	1.19_11.14	0.023
Neoadjuvant chemotherapy	0.83	0.39_1.73	0.62	Histologic type	1.54	0.41_5.81	0.52
FIGO Stage at diagnosis	1.87	1.4_2.5	<0.001	CA-125 prior to treatment	2.03	0.59_6.98	0.26
Tumor grade at diagnosis	1.36	0.89_2.06	0.14	Mean White blood cells	1.71	0.54_5.43	0.35
Histologic type	2.3	0.98_5.4	0.05	Maximum Platelet count	1.84	0.61_5.56	0.27
BMI	0.62	0.32_1.19	0.15				
Ascites at diagnosis	1.42	0.84_2.41	0.18				
CA-125 Prior to treatment	3.93	1.63_9.44	0.002				
Chemotherapy course	0.65	0.37_1.14	0.14				
Mean White blood cells	2.15	1.06_4.35	0.03				
Mean Hemoglobin	1.24	0.65_2.35	0.5				
Maximum Platelet count	0.51	0.26_1	0.05				

P< 0.05 Indicating significance, HR indicating hazard ratio

The cumulative hazard function was plotted for the two variables that had a significant hazard ratio in the first recurrence of epithelial ovarian cancer (Figure 2). Figure 2(A) shows that during our follow-up period, patients with metastasis had a significantly higher

cumulative hazard than patients without metastasis, and for patients without metastasis from month 30 onwards, the cumulative hazard was almost constant. Also, figure 2(B) shows that the higher tumor stage in the first fifty months included a greater cumulative hazard.
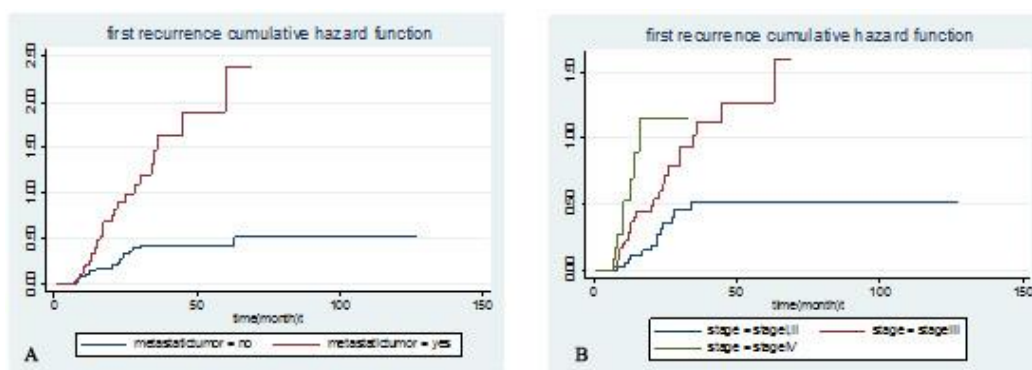

Figure 2. Cumulative hazard function of first recurrence strata by A) metastatic tumor B) Figo stage at diagnosis

Discussion

Ovarian cancer is a rare disease in Iran, as well as other areas. The median age of this cancer in our study

was 52.5 years; it is lower than the median age of Previs study in the United States in 2014, which was 59 years (13). The one-year disease-free survival rate was 82% in our study. This rate is higher than the Luvero study in

2019, which reported an 18-month disease-free survival rate of 80% (14).

In our study, it was shown that among the studied variables, metastatic tumor with a hazard ratio of 4.06 is the most important factor in the first recurrence of epithelial ovarian cancer. Further, maximum platelet count, tumor stage, BMI, presence of ascites at diagnosis, CA125 tumor marker, and white blood cell had a hazard ratio higher than 1.3, although they were not statistically significant. In the Previs study in 2014, the presence of ascites had a significant hazard ratio of 2.63 in a multivariate study of factors affecting ovarian cancer recurrence in women treated with chemotherapy and bevacizumab (13). In our study, the presence of ascites at diagnosis in the univariate cox model had a hazard ratio of 1.36 and in the multivariate cox model had a hazard ratio of 1.6 in the first recurrence of epithelial ovarian cancer.

Shinagare AB in 2018 showed that a higher rate of CA125 marker tumor increase abdominal recurrence in stage III and IV papillary serous patients, which was significant in both univariate and multivariate Cox models, but the disease stage was not significant in this study (15). Results of the present study showed the CA125 tumor marker in the univariate Cox model had a significant hazard ratio of 2.65, and in the multivariate Cox, the model had a hazard ratio of 1.64 in the first recurrence of epithelial ovarian cancer. In the Clarke CL study in 2019 that investigated long-term survival predictors of patients with grade III and IV serous ovarian cancer, lower age, lower stage, and depression significantly association with long-term survival (3). In our study, age had no significant effect on the first recurrence, but a higher tumor stage had a significant effect on the first recurrence.

In the Zheng Li study in 2017, who examined the predictors of survival of epithelial ovarian cancer patients using neutrophil-to-lymphocyte ratio and preoperative red cell distribution, in the univariate study, age, stage of the disease, and tumor histology were significant And in the multivariate study, age and stage of disease were significant (8). In the present study, tumor histology in the univariate Cox model had a hazard ratio of 1.93 with a significance of 0.12, but in the multivariate Cox, the model had a hazard ratio of 1.23.

In the Nagle study in 2015, obesity had a high hazard in ovarian cancer survival (16), and in the same year, the Tran A-Q study showed obesity had a significant hazard on ovarian cancer survival (17). Similar studies have also suggested that obesity is a risk factor for ovarian

cancer survival, but in a study (18) in Australia, BMI >25 was less risk than BMI <25 at diagnosis. It is noteworthy, at first recurrence, we found that underweight (BMI <24.9) had an approximate hazard ratio two times then (BMI >25).

One of the limitations of the present study is the percentage increase of right censoring in some variables. Of course, in the variables that were entered into the multivariate Cox analysis, and they were significant in the univariate study, the percentage of right censoring was below 50%, except for the CA125 tumor marker. Another limitation of the present study is the low incidence of ovarian cancer that makes difficult retrospective cohort studies.

Interpretation

According to a high recurrence rate of epithelial ovarian cancer and according to our results that tumor stage and metastatic tumor were identified as two important factors in the first recurrence of this cancer; one of the causes of recurrence may be diagnosis happened at late stages. Therefore, screening programs are needed to reduce illness and death from ovarian cancer.

References

1. Lindemann K, Beale PJ, Rossi E, Goh JC, Vaughan MM, Tenney ME, et al. Phase I study of BNC105P, carboplatin and gemcitabine in partially platinum-sensitive ovarian cancer patients in first or second relapse (ANZGOG-1103). Cancer Chemother Pharmacol 2019;83:97-105.

2. Marchetti C, Kristeleit R, McCormack M, Mould T, Olaitan A, Widschwendter M, et al. Outcome of patients with advanced ovarian cancer who do not undergo debulking surgery: A single institution retrospective review. Gynecol Oncol 2017;144:57-60.

3. Clarke CL, Kushi LH, Chubak J, Pawloski PA, Bulkley JE, Epstein MM, et al. Predictors of Long-Term Survival among High-Grade Serous Ovarian Cancer Patients. Cancer Epidemiol Biomarkers Prev 2019;28:996-9.

4. Sun Y, Liu S, Feng Z, Cheng J, Lu L, Wang M, et al. Preoperative omental metastasis-related maximum standardized fluorine-18-fluorodeoxyglucose uptake value can predict chemosensitivity and recurrence in advanced high-grade serous ovarian cancer patients. Nucl Med Commun 2018;39:761-7.

5. Torre LA, Trabert B, DeSantis CE, Miller KD, Samimi G, Runowicz CD, et al. Ovarian cancer statistics, 2018. CA Cancer J Clin 2018;68:284-96.

6. Moosavi AS, Tehranian A, Behtash N, Modares Gilani M, Ghaemmaghami F. Long Term Oral Etoposide As Second Line Therapy in Recurrent Epithelial Carcinoma of the Ovary Acta Med Iran 2006;44:7-12.

7. Shimizu A, Sawada K, Kimura T. Development of novel approaches to detect ovarian cancer recurrence. J Med Artif Intell 2019;2.

8. Li Z, Hong N, Robertson M, Wang C, Jiang G. Preoperative red cell distribution width and neutrophil-to-lymphocyte ratio predict survival in patients with epithelial ovarian cancer. Sci rep 2017;7:43001.

9. Omurlu IK, Ture M, Tokatli F. The comparisons of random survival forests and Cox regression analysis with simulation and an application related to breast cancer. Expert Syst Appl 2009;36:8582-8.

10. Zheng Q-Q, Wang P, Hui R, Yao A-M. Prognostic analysis of ovarian cancer patients using the Cox regression model. Chin J Cancer 2009;28:170-2.

11. Mysona D, Pyrzak A, Purohit S, Zhi W, Sharma A, Tran L, et al. A combined score of clinical factors and serum proteins can predict time to recurrence in high grade serous ovarian cancer. Gynecol Oncol 2019;152:574-80.

12. Nie D, Gong H, Mao X, Li Z. Systemic immune-inflammation index predicts prognosis in patients with epithelial ovarian cancer: A retrospective study. Gynecol Oncol 2019;152:259-64.

13. Previs R, Bevis K, Huh W, Tillmanns T, Perry L, Moore K, et al. A prognostic nomogram to predict overall survival in women with recurrent ovarian cancer treated with bevacizumab and chemotherapy. Gynecol oncol 2014;132:531-6.

14. Luvero D, Plotti F, Montera R, Terranova C, De Cicco NC, Scaletta G, et al. Ovarian cancer relapse: From the latest scientific evidence to the best practice. Crit Rev Oncol Hematol 2019;140:28-38.

15. Shinagare AB, Balthazar P, Ip IK, Lacson R, Liu J, Ramaiya N, et al. High-Grade Serous Ovarian Cancer: Use of Machine Learning to Predict Abdominopelvic Recurrence on CT on the Basis of Serial Cancer Antigen 125 Levels. J Am Coll Radiol 2018;15:1133-8.

16. Nagle C, Dixon S, Jensen A, Kjaer S, Modugno F, DeFazio A, et al. Obesity and survival among women with ovarian cancer: results from the Ovarian Cancer Association Consortium. Br J Cancer 2015;113:817-26.

17. Tran A-Q, Cohen JG, Li AJ. Impact of obesity on secondary cytoreductive surgery and overall survival in women with recurrent ovarian cancer. Gynecol Oncol 2015;138:263-6.

18. Zhang M, Xie X, Lee AH, Binns CW, Holman CAJ. Body mass index in relation to ovarian cancer survival. Cancer Epidemiol Biomarkers Prev 2005;14:1307-10.