

# Chemotherapy is not Necessary for Early-Stage Serous and Endometrioid Ovarian Cancer After Undergoing Comprehensive Staging Surgery

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## Research

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# Abstract

**Background:** To investigate whether adjuvant chemotherapy was essential for patients with early-stage serous and endometrioid epithelial ovarian cancer, we collected data from the US Surveillance, Epidemiology, and End Results database between 2004 and 2015. All subjects underwent comprehensive staging surgery and their pathological diagnoses were stage IA-IIA, grade 1-2. Ultimately, a total of 2,644 patients were enrolled in the study, among which 1,589 patients received platinum-based chemotherapy. Comparisons of categorical data were done by chi-square tests. Variables with  $P < 0.05$  in univariate analysis were further analyzed using multiple logistic regression. Selection bias from the heterogeneity of demographic and clinical characteristics were avoided by propensity score matching. Cox proportional hazards models were applied to estimate hazard ratios (HR) and 95% confidence intervals (CI), exploring the relationship between variables and 5-year overall survival.

**Results:** After propensity score matching, patients with or without chemotherapy were equal number ( $n=925$ ). Our results indicated that 65 years of age or older increased the hazard and was related to poor prognostic (HR = 1.486, CI = 1.208- 1.827,  $P < 0.001$ ). Endometrioid carcinoma was associated with better 5-year overall survival than serous cystadenocarcinoma (HR = 0.697, CI = 0.584-0.833,  $P < 0.001$ ). Chemotherapy could not prolong 5-year overall survival of early-stage serous and endometrioid ovarian cancer patients (HR = 1.092, CI = 0.954-1.249,  $P = 0.201$ ).

**Conclusions:** These results demonstrated that adjuvant chemotherapy was unnecessary for patients with early-stage serous and endometrioid ovarian cancer after they underwent comprehensive staging surgery.

## Background

Ovarian cancer is the leading cause of death from gynecological malignancies worldwide. Data from the Surveillance, Epidemiology, and End Results (SEER) database indicate that distant stage of epithelial ovarian cancer (EOC) accounts for 59%, regional stage for 20%, and localized stage merely for 15%. A great majority of patients with advanced epithelial ovarian cancer undergo surgery and receive platinum-based chemotherapy, which has been recommended by National Comprehensive Cancer Network (NCCN) guidelines throughout the ages (Coleman et al. 2017; Ledermann et al. 2016; Parmar et al. 2002). However, it remains controversial whether adjuvant chemotherapy should be used for early-stage ovarian cancer patients after they have underwent surgery, of which 5-year recurrence rate is approximately 15%-25% (Neilson 2009; Prendergast et al. 2017; Zhang et al. 2018).

Paclitaxel/carboplatin regimen forms the cornerstone of chemotherapy in epithelial ovarian cancer over the past two decades and have achieved a well clinical response (Agarwal and Kaye 2003; Narod 2016). Nevertheless, both agents have considerable side effects, ranging from anticipated myelosuppression, alopecia and gastrointestinal symptoms to occasional severe neurotoxicity (Kudlowitz et al. 2018; Gornstein and Schwarz 2014). More importantly, patients gradually develop chemoresistance with diminishing benefit from subsequent regimens (Chen et al. 2015; Yu et al. 2015; Jayson et al. 2014; Rizvi et al. 2010). Therefore, avoiding unnecessary chemotherapy will decrease the risk of drug resistance, increase the chance of secondary surgery and effectively prolong 5-year survival of early-stage patients. Besides, it undoubtedly lightens the psychological pressure and economic burden, improving their life quality obviously. Taking these needs into account, there is an urgent need to better understand the significance of chemotherapy for early-stage patients and to provide more current information for clinical practice.

Serous cystadenocarcinoma and endometrioid carcinoma, which are the two most frequent subtypes of epithelial ovarian cancer, will be focused on in this study (Hirst et al. 2018). The study cohort was designed to enroll patients with stage IA-IIA, grade 1–2 serous and endometrioid ovarian cancer. They all underwent comprehensive staging surgery and had active follow-up. Patients were divided into chemotherapy and nonchemotherapy groups. The chemotherapy groups received paclitaxel/carboplatin regimen every 3 weeks for 3–6 cycles. The present study was designed with the objective of identifying the necessity of adjuvant chemotherapy in early-stage serous and endometrioid ovarian cancer, which may provide a reference for gynecologic oncologists.

## Results

### Patient demographics

Study entry criteria were met by 2,644 eligible patients (1,055 nonchemotherapy and 1,589 chemotherapy). In this population, only 16.4 percent were younger than 45 years, 56.1 percent aged 45 to 65 years, and 27.5 percent aged 65 years or older. A great majority of patients were the white race (n = 2243, 84.8%). Stage IA accounted for 44.2%, stage IB for 5.7%, stage IC for 38.4%, and stage IIA for 11.7%. Of the 2,644 patients, 59.1% were diagnosed with grade 1, and 40.9% with grade 2. Tumor laterality consisted of right (n = 1112, 42.1%), left (n = 1121, 42.4%) and other/unknown (n = 411, 15.5%). There were 44.3% of patients who had tumors smaller than 10 cm, 42.3% larger than 10 cm. In our study, endometrioid carcinoma accounted for 68.9%, and serous cystadenocarcinoma for 31.1%. Patients characteristics were presented in Table 1.

Table 1  
Patient demographics

Characteristics	No.	%
Chemotherapy		
No/Unknown	1055	39.9
Yes	1589	60.1
Age		
≤ 45y	434	16.4
45-65y	1484	56.1
> 65y	726	27.5
Race		
White	2243	84.8
Nonwhite	401	15.2
Stage		
IA	1170	44.2
IB	152	5.7
IC	1014	38.4
IIA	308	11.7
Grade		
1	1562	59.1
2	1082	40.9
Laterality		
Right	1112	42.1
Left	1121	42.4
Other/Unknown	411	15.5
Tumor size		
≤ 10 cm	1171	44.3
> 10 cm	1119	42.3
Unknown	354	13.4
Histology		
Serous	821	31.1

**Note:** No. number; % percent.

Characteristics	No.	%
Endometrioid	1823	68.9
<b>Note:</b> No. number; % percent.		

## Comparison Of Univariate Covariates

Before propensity score matching, chemotherapy groups tended to be younger than nonchemotherapy groups ( $\leq$  45 years: 17.2% vs 15.3%; 45 to 65 years: 59.5% vs 51.0%,  $P < 0.001$ ). They were less likely to be in stage IA (34.2% vs 59.3%,  $P < 0.001$ ), more likely in stage IB (5.8% vs 5.7%,  $P < 0.001$ ) and stage IC (46.0% vs 26.8%,  $P < 0.001$ ). Compared with nonchemotherapy groups, grade 1 cases were less among chemotherapy groups (52.9% vs 68.3%,  $P < 0.001$ ) and grade 2 cases were more (47.1% vs 31.7%,  $P < 0.001$ ). More patients were serous cystadenocarcinoma in chemotherapy groups (33.5% vs 27.4%,  $P = 0.001$ ). To eliminate the heterogeneity and imbalance between groups, we performed propensity score matching and logistic regression analysis. Results demonstrated that the two groups were equal number of patients and all clinical factors were well balanced without significant differences, indicating the potential covariates between groups were greatly decreased (Table 2).

Table 2  
Comparison of univariate covariates

Characteristics	Before PSM			After PSM		
	Chemotherapy- (n = 1055)	Chemotherapy+ (n = 1589)	P	Chemotherapy- (n = 925)	Chemotherapy+ (n = 925)	P
Age			< 0.001			0.254
≤ 45y	161 (15.3)	273 (17.2)		159 (17.2)	183 (19.8)	
45-65y	538 (51.0)	946 (59.5)		504 (54.5)	503(54.4)	
> 65y	356 (33.7)	370 (23.3)		262 (28.3)	239 (25.8)	
Race			0.086			0.124
White	911 (86.4)	1332 (83.8)		793 (85.7)	768 (83.0)	
Nonwhite	144 (13.6)	257 (16.2)		132 (14.3)	157 (17.0)	
Stage			< 0.001			0.328
IA	626 (59.3)	544 (34.2)		499 (53.9)	475 (51.4)	
IB	60 (5.7)	92 (5.8)		57 (6.2)	49 (5.3)	
IC	283 (26.8)	731 (46.0)		283 (30.6)	319 (34.5)	
IIA	86 (8.2)	222 (14.0)		86 (9.3)	82 (8.9)	
Grade			< 0.001			0.530
1	721 (68.3)	841 (52.9)		595 (64.3)	581 (62.8)	
2	334 (31.7)	748 (47.1)		330 (35.7)	344 (37.2)	
Laterality			< 0.001			0.147
Right	477 (45.2)	635 (40.0)		407 (44.0)	383 (41.4)	
Left	461 (43.7)	660 (41.5)		405 (43.8)	401 (43.4)	
Other/Unknown	117 (11.1)	294 (18.5)		113 (12.2)	141 (15.2)	
Tumor size			0.044			0.888
≤ 10 cm	464 (44.0)	707 (44.5)		414 (44.8)	416 (45.0)	
> 10 cm	429 (40.7)	690 (43.4)		386 (41.7)	391 (42.3)	
Unknown	162 (15.4)	192 (12.1)		125 (13.5)	118 (12.8)	

**Note:** Data are expressed as n (%). P-value < 0.05 is regarded as statistically significant. PSM propensity score matching.

	Before PSM		After PSM	
Histology			0.001	0.226
Serous	289 (27.4)	532 (33.5)	257 (27.8)	233 (25.2)
Endometrioid	766 (72.6)	1057 (66.5)	668 (72.2)	692 (74.8)

**Note:** Data are expressed as n (%). P-value < 0.05 is regarded as statistically significant. PSM propensity score matching.

## Association Of Chemotherapy With Survival

We analyzed the association between chemotherapy and 5-year OS for stage IA-IIA. There were no statistically significant differences between chemotherapy and nonchemotherapy groups (stage IA: 46.5% vs 53.7%, P = 0.110; stage IB: 49.0% vs 49.1%, P = 0.059; stage IC: 46.1% vs 48.1%, P = 0.750; stage IIA: 39.0% vs 37.2%, P = 0.249). Early-stage patients could not benefit from chemotherapy to prolong their 5-year OS (Table 3 & Fig. 2).

Table 3  
Association of chemotherapy with 5-year OS

Stage	Chemotherapy- (n = 925)	Chemotherapy+ (n = 925)	P
IA	53.7%	46.5%	0.110
IB	49.1%	49.0%	0.059
IC	48.1%	46.1%	0.750
IIA	37.2%	39.0%	0.249

**Note:** P-value < 0.05 is regarded as statistically significant. OS overall survival.

## Univariate Analysis Of Clinical Factors With Survival

We conducted univariate analysis of the matched population to explore prognostic effect of the clinical factors. No significant differences were found between chemotherapy and nonchemotherapy groups in 5-year OS (P = 0.245). Older age was a hazard factor for 5-year OS (P < 0.001). Tumors larger than 10 cm had lower 5-year OS (P = 0.014). Moreover, 5-year OS of endometrioid carcinoma was higher than serous cystadenocarcinoma (P < 0.001) (Table 4 & Fig. 3).

Table 4  
Univariate analysis of clinical factors with 5-year OS

Characteristics	No.	5-year OS (%)	P
Chemotherapy			0.245
No/Unknown	925	50.2	
Yes	925	45.8	
Age			< 0.001
≤ 45y	342	51.5	
45-65y	1007	49.3	
> 65y	501	43.1	
Race			0.833
White	1561	48.9	
Nonwhite	289	43.3	
Stage			0.354
IA	974	50.2	
IB	106	49.1	
IC	602	47.0	
IIA	168	38.1	
Grade			0.908
1	1176	51.2	
2	674	42.4	
Laterality			0.163
Right	790	46.7	
Left	806	50.5	
Other/Unknown	254	44.1	
Tumor size			0.014
≤ 10 cm	830	45.5	
> 10 cm	777	44.8	
Unknown	243	66.7	
Histology			< 0.001
Serous	490	38.4%	

**Note:** P-value < 0.05 is regarded as statistically significant. OS overall survival.

Characteristics	No.	5-year OS (%)	P
Endometrioid	1360	51.5%	
<b>Note:</b> P-value < 0.05 is regarded as statistically significant. OS overall survival.			

## Cox Proportional Hazards Model

The cox proportional hazards model is often used in medical research to investigate the association between survival time of patients and one or more predictive variables. The Kaplan-Meier method and log-rank tests describe survival according to one factor under investigation, but ignore the impact of any others. Additionally, they are available only when the predictive variables are categorical, and don't work easily for quantitative predictors such as age. Given these problems, an alternative method is the cox proportional hazards regression analysis, which works for both quantitative predictive variables and categorical variables. Furthermore, the cox regression model extends survival analysis methods to assess simultaneously the effect of several risk factors on survival time.

To explore how clinical factors jointly impact on survival, we took all the factors associated with survival into a multivariate cox regression analysis. The results were shown in Table 5. Our analysis showed that elderly patients ( $\geq$  age 65) had higher risk and worse prognostic (HR = 1.486, CI = 1.208–1.827,  $P < 0.001$ ). Endometrioid carcinoma was related to better 5-year OS (HR = 0.697, CI = 0.584–0.833,  $P < 0.001$ ). Chemotherapy still had no statistically significant effect on the 5-year OS after excluding the influence of all the confounding factors (HR = 1.092, CI = 0.954–1.249,  $P = 0.201$ ).

Table 5  
Multivariate cox regression analysis for 5-year OS

Characteristics	HR (95% CI)	P
Chemotherapy		
No/Unknown	Ref	
Yes	1.092(0.954–1.249)	0.201
Age		
≤ 45y	Ref	
45-65y	1.044(0.877–1.244)	0.627
> 65y	1.486(1.208–1.827)	< 0.001
Race		
White	Ref	
Nonwhite	0.984(0.810–1.195)	0.872
Stage		
IA	Ref	
IB	0.967(0.689–1.359)	0.848
IC	1.063(0.910–1.241)	0.441
IIA	1.128(0.862–1.475)	0.381
Grade		
1	Ref	
2	0.865(0.743–1.008)	0.063
Laterality		
Right	Ref	
Left	0.984(0.852–1.136)	0.824
Other/Unknown	1.115(0.862–1.443)	0.407
Tumor size		
≤ 10 cm	Ref	
> 10 cm	0.984(0.848–1.141)	0.830
Unknown	0.760(0.630–0.918)	0.004
Histology		

**Note:** P-value < 0.05 is regarded as statistically significant. HR hazard ratios; CI confidence intervals; Ref reference.

Characteristics	HR (95% CI)	P
Serous	Ref	
Endometrioid	0.697(0.584–0.833)	< 0.001
<b>Note:</b> P-value < 0.05 is regarded as statistically significant. HR hazard ratios; CI confidence intervals; Ref reference.		

## Discussion

Our study was based on a large and unique population-based cohort. The large size of our study gave us the statistical power to investigate the necessity of adjuvant chemotherapy for early-stage serous and endometrioid ovarian cancer. The unique feature was that each patient had undergone comprehensive staging surgery, which was paramount for survival (Kozłowska et al. 2018; Yap et al. 2009; Dizon et al. 2008). However, several limitations should be noted, which were inherent to all SEER database analyses. We could not acquire the details of primary surgery. We clearly understood the importance of residual disease as a significant prognostic factor for outcome, but accurate surgical data were difficult to obtain for most patients (Agarwal and Kaye 2003; Rustin et al. 2010). Furthermore, the dataset lacked information concerning recurrence free survival and further treatment history affecting prognosis. Therefore, treatment groups might have exhibited additional high-risk features that we were not aware of. To reduce selection bias, propensity score matching was conducted to randomize the dataset and to strengthen causal arguments. Besides, cox proportional-hazards models were recommended by the NCCN guidelines to analyze the correlation between variables and survival. Finally, our study findings supported recent publications that questioned the value of adjuvant chemotherapy in early-stage epithelial ovarian carcinoma (Bell et al. 2006; Sijmons et al. 2007; Takada et al. 2012). Adjuvant chemotherapy was not necessary for patients of early-stage serous and endometrioid epithelial ovarian cancer after undergoing surgery. Paclitaxel plus carboplatin have not been replaced in the past two decades as the first-line primary chemotherapy for epithelial ovarian cancer (Agarwal and Kaye 2003). The two canonical drugs decrease the rate of recurrence and death, but does not affect long term survival and cannot reduce the eventual likelihood of death from ovarian cancer per se (Narod 2016). Why we continue to put early-stage patients through the regimen.

## Conclusions

In summary, our study suggested that early-stage serous and endometrioid ovarian cancer patients had no need to receive adjuvant chemotherapy when comprehensive staging surgery had been performed. Further investigation is warranted to provide guidance in the management of epithelial ovarian cancer patients. Evaluation by a gynecologic oncologist is strongly recommended for all patients with suspected ovarian cancer. Primary assessment and surgery by a gynecologic oncologist results in a survival advantage. In addition, NCCN believes that the best management of any patient with cancer is in a clinical trial. So, clinical trials are urgently needed to identify patients who might benefit most from adjuvant chemotherapy and to identify the optimal therapeutic strategy.

## Methods

### Data source

Our data were extracted from the US Surveillance, Epidemiology, and End Results (SEER) database maintained by the National Cancer Institute. SEER\*Stat software, version 8.3.5 was downloaded from the official website (<https://seer.cancer.gov/>). This program collects data from population-based cancer registries that currently cover approximately 28% of the US population.

## Patient Eligibility Criteria

Study design and inclusion criteria had been detailed in the above paragraph. A total of 2,644 patients participated in the study (Fig. 1). We included the following variables: patient id, age at diagnosis, race, survival months, tumor stage, tumor grade, tumor laterality, tumor size, surgery of primary site, type of surgery, chemotherapy, vital status, cause-specific death classification, type of follow-up expected. Age at diagnosis was divided into three groups:  $\leq 45$ , 45–65, and  $> 65$  years old. Race was classified into white and nonwhite. Tumor laterality on which tumor originated was grouped into right, left and other/unknown. Tumor size was categorized into three groups:  $\leq 10$  cm,  $> 10$  cm and unknown. Administration of chemotherapy fell into yes and no/unknown in the extracted dataset. All patients were analyzed the correlation between chemotherapy and 5-year overall survival (OS).

## Statistical analysis

### Univariate analysis

There were no cases with missing data. Pearson chi-square ( $\chi^2$ ) tests were used to evaluate univariate associations between categorical variables and chemotherapy before and after propensity score matching. All tests were two-sided. A P value of less than 0.05 was considered to indicate a significant interaction. Statistical analyses were conducted with the use of R software, version 3.5.1 and SPSS software, version 25.0.0.1.

### Propensity score matching

Selection bias generally existed in retrospective studies because of demographic heterogeneity and clinical characteristics between chemotherapy and nonchemotherapy groups. To lessen the influence of selection bias on our conclusion, we conducted propensity score matching. A logistic regression model was applied to match age at diagnosis, race, tumor stage, tumor grade, tumor laterality, tumor size, histology between the two study groups. The propensity score ranged from 0 to 1. We adopted the nearest neighbor matching and 1:1 match ratio in this model.

### Survival analysis

Survival analysis were performed with the Kaplan-Meier method and differences were compared with the use of the log-rank tests. We employ cox proportional hazards models to estimate hazard ratios (HR) and 95% confidence intervals (CI).

### Declarations

Ethics approval and consent to participate: Not applicable.

Consent for publication: Yes.

Availability of data and materials: The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: LI Shuqing analyzed the data and wrote the manuscript. ZHU Zhiling was responsible for direction and proofreading.

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## Figures

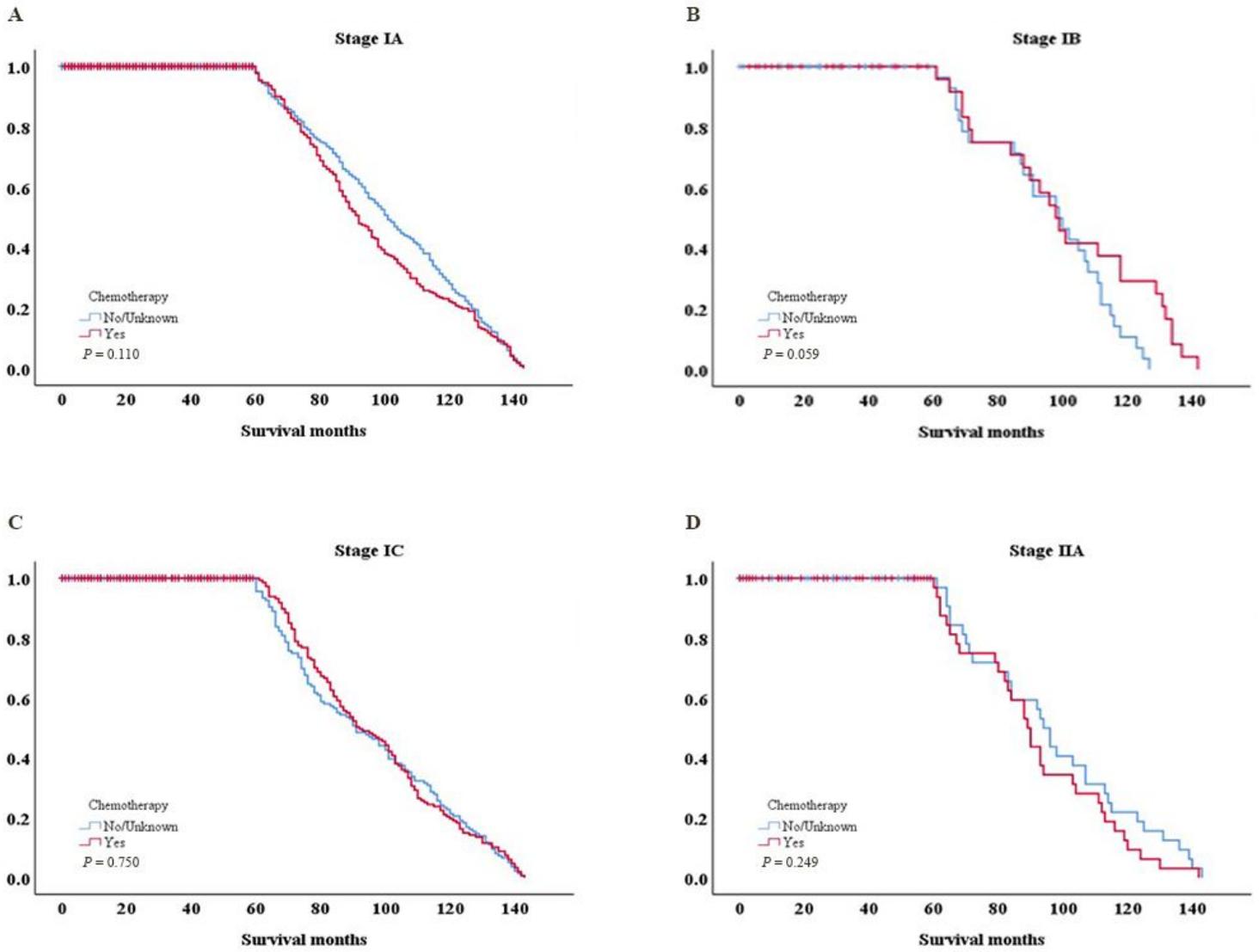


Figure 1

Consort diagram of patient selection.

**Patients diagnosed with primary ovarian cancer**

**from 2004 to 2015 (n=57,053)**

**Serous cystadenocarcinoma(n=14,651)**

**Endometrioid carcinoma(n=6,057)**

**Stage IIB, III, IV, unknown stage  
or unknown substage excluded**

**Grade 3, 4 or unknown grade  
excluded**

**No or unknown surgery excluded**

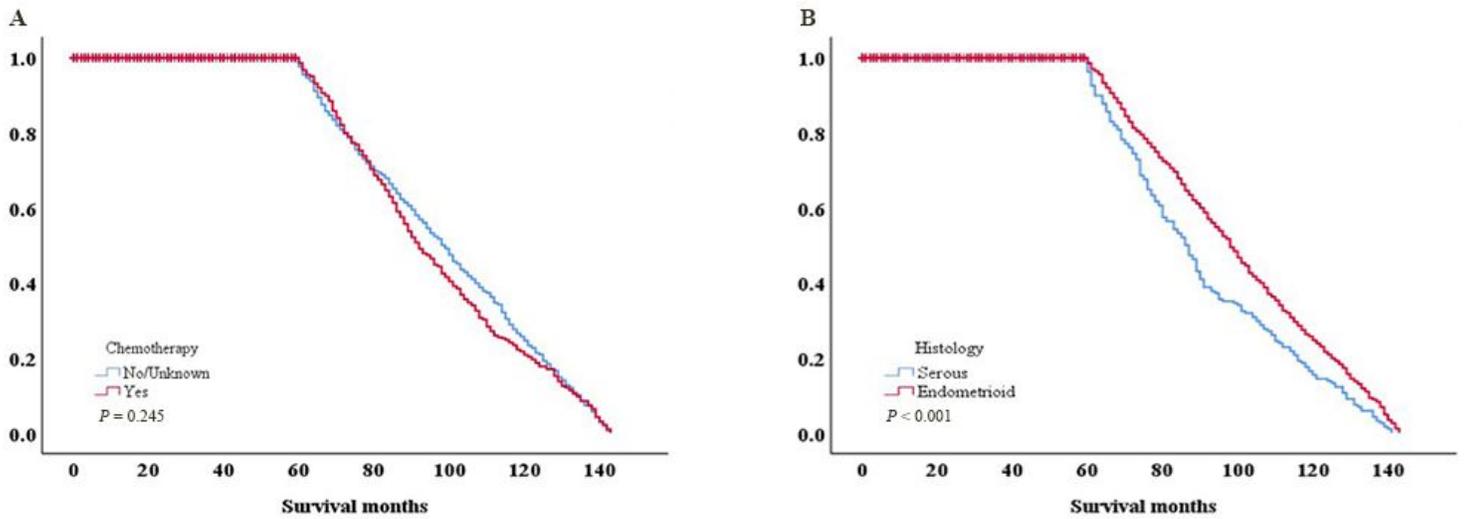
**Serous cystadenocarcinoma(n=821)**

**Endometrioid carcinoma(n=1,823)**

**Study cohort n=2,644**

**Figure 2**

Kaplan-Meier survival curves for (A) stage IA, (B) stage IB, (C) stage IC and (D) stage IIA drawing on the basis of Table 3. P-value < 0.05 is regarded as statistically significant



**Figure 3**

Kaplan-Meier survival curves for (A) chemotherapy and (B) histology drawing on the basis of Table 4. P-value < 0.05 is regarded as statistically significant

## Supplementary Files

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