Current Problems in Cancer 45 (2021) 100621

Contents lists available at ScienceDirect

Current Problems in Cancer

journal homepage: www.elsevier.com/locate/cpcancer

Impact of nonspecific death on overall survival in early-stage epithelial ovarian cancer patients

Danian Dai[a,b,#], Ting Deng[b,#], Bin Wang[c,#], Shangqiu Chen[a,#], Zhimin Liu[b], Xiaolin Luo[b], Feng Wang[a], He Huang[b,**], Jihong Liu[a,b,*]

[a] *Department of Gynecology and Obstetrics, The Fifth Affiliated Hospital of Sun Yat-Sen University, Zhuhai, Guangdong, 519000, China*

[b] *Department of Gynecologic Oncology, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Guangzhou, Guangdong, 510060, China*

[c] *Institute of Life Sciences, Chongqing Medical University, Chongqing, 400016, China*

ABSTRACT

Objective: To estimate the impacts of nonovarian cancer-specific death (non-OCSD) and ovarian cancer-specific death (OCSD) on early-stage patients, and to determine which statistical method yielded survival results most similar to real-world situations. *Methods:* Data of patients with early-stage epithelial ovarian cancer from 1988 to 2015 registered in the Surveillance, Epidemiology, and End Results database were ana-

Abbreviations: OCSD, ovarian cancer-specific death; non-OCSD, nonovarian cancer-specific death; SEER, surveillance, epidemiology, and end results; OS, overall survival; ACD, all causes of death; AJCC, American Joint Committee on Cancer; DC, death certificate; COD, cause of death; G1, well differentiated; G2, moderately differentiated; G3, poorly differentiated; G4, undifferentiated; HR, hazard ratio; SHR, subdistribution hazard ratio; OR, odds ratio; CI, confidence interval.

☆ **Funding:** This work was supported by the National Natural Science Foundation of China (grant number 81772782).

☆☆ **Ethics approval and consent to participate:** The institutional review boards of The Fifth Affiliated Hospital Sun Yat-Sen University approved the study. The need for individual consent was waived by the committee since the data obtained from the SEER database.

★ **Author Contributions:** DD, TD, BW, SC, HH and JL contributed to the conception and design of the study. DD, TD, BW, SC, ZL, XL and FW contributed to data collection. DD, TD, BW, SC, ZL, XL and FW analyzed and interpreted the data. DD, TD, and BW drafted the report, which was critically revised for valuable intellectual content by HH and JL. All authors approved the final version of the report.

★★ **Conflicts of Interest:** The authors declare no potential conflict of interest.

* Correspondence to: Jihong Liu, Department of Gynecologic Oncology, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Guangzhou, China.

** Correspondence to: He Huang, Department of Gynecologic Oncology, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Guangzhou, China.

E-mail addresses: huangh@sysucc.org.cn (H. Huang), liujih@mail.sysu.edu.cn (J. Liu).

# These authors contributed equally to this work.

https://doi.org/10.1016/j.currproblcancer.2020.100621

lyzed. The primary outcome events of epithelial ovarian cancer were OCSD, non-OCSD, or alive. Incidences of non-OCSD and OCSD with different clinicopathological factors, cumulative incidences of non-OCSD and OCSD, and overall survival impact of non-OCSD were analyzed. *Results:* A total of 1606 non-OCSD (8.9%) and 3022 OCSDs (16.8%) were analyzed. Several independent features were associated with non-OCSD, including age (>60 years), radiotherapy, and marital status. In patients with histology (eg, endometrioid or mucinous), well-differentiated cells, stage I disease, or widowed marital status, as well as age older than 60, non-OCSD rates of all causes of death notably distorted overall survival, resulting in inaccurate and biased interpretations. *Conclusions:* Overall survival was greatly influenced by non-OCSD in early epithelial ovarian cancer. Future clinical trials should consider non-OCSD as a competing risk event, especially among patients older than 60 years and those with well-differentiated cells, no chemotherapy, and widowed marital status.

ARTICLE INFO

Keywords: Competing risk; Survival rate; Nonovarian cancer-specific death; Ovarian cancer; Risk factors

Background

Ovarian cancer is the fifth leading cause of cancer-related death among women and is the most lethal gynecologic malignancy in the United States.[1] The latest cancer statistics show that in 2019 approximately 22,530 women will be diagnosed, and 13,980 will die from this cancer.[1] Epithelial ovarian cancer accounts for nearly 90% of all types of ovarian cancer; most women diagnosed with ovarian cancer are in the advanced stage and have poor prognosis.[2] Less than 30% of patients are diagnosed in the early-stage, and their 5-year survival rate is significantly higher.[3]

For epithelial ovarian carcinoma, surgery remains the cornerstone of treatment,[4] supplemented by chemotherapy and targeted therapy.[5-8] Overall survival (OS) is considered the most critical and direct benefit indicator for all kinds of clinical studies.[9] However, inconsistencies in observed OS in the existing literature have led to multiple controversies. Two large European studies (ACTION and ICON1) previously demonstrated the vital value of adjuvant chemotherapy in early-stage ovarian cancer.[5,6] Chemotherapy based on platinum could lead to an improvement of OS and an absolute benefit in disease-free survival at 5 years. Nevertheless, the results of this treatment in subgroups of women with early ovarian cancer according to the level of risk are inconsistent. Previous studies[10] reported that ICON1 showed no significant difference in OS between those who did and did not receive adjuvant chemotherapy among women at low (stage IA, G1) and medium risk (stage IA, G2, and stage IB/IC G1). However, Chatterjee et al. found that the association between chemotherapy and improved survival among intermediate-risk (stage IA or IB, G2) patients remained significant.[11] Hence, the precise role of adjuvant therapy in subgroups of patients with early ovarian cancer is still controversial.[11-13]

For most patients with solid tumors, causes of death apart from cancer become more common as the time from treatment to follow up increases. This phenomenon can be observed in patients with pediatric cancer,[14] head and neck cancer,[15] breast cancer [16] and so on. Dinkelspiel et al.[17] found that the probability of mortality due to ovarian cancer decreases with time, and nonovarian cancer-specific death (non-OCSD) increases notably in all stage ovarian cancer patients. OS based on all causes of death (ACD), which fails to consider the interference of non-cancer deaths, may lead to huge biases between research results and facts. Moreover, the potential factors that contribute to non-OCSD in early-stage patients are still undefined. Therefore, competitive risk models were advocated to obtain reliable results that are similar to real-world situations, and help physicians in designing more targeted studies and survival strategies for treatment.[18,19] In this large-scale population-based study, the impacts of non-OCSD and ovarian

cancer-specific death (OCSD) in early-stage patients were estimated through a comparison of Cox regression model and competing risk model to identify a more suitable statistically approach for obtaining more accurate survival results.

Methods

Inclusion and Exclusion Criteria

The data for this analysis was obtained from the surveillance, epidemiology, and end results (SEER) database by the National Cancer Institute (reference number 14047-Nov2017). The study was approved by the ethics committee of The Fifth Affiliated Hospital Sun Yat-sen University. Patients diagnosed with ovarian cancer from January 1988 to December 2015 were identified and collected using the SEER*Stat software. The year and age at diagnosis, sex, race recode, tumor grade, histological type, American Joint Committee on Cancer (AJCC) stage, radiation status, chemotherapy status, surgery status, cause of death, months of survival, sequence number, first malignant primary indicator, and marital status at diagnosis were retrieved from the SEER database. The specific inclusion criteria were as follows: (1) ovarian cancer site record of the third revision of International Classification of Diseases for Oncology (ICD-O-3) was C56.9; (2) histological type (ICD-O-3) limited to epithelial ovarian tumors based on the World Health Organization criteria, including serous, mucinous, endometrioid, clear-cell, and epithelial tumors not otherwise specified; (3) AJCC stage (3rd edition or 7th edition) limited to stage I-II; 4) ovarian cancer as the first primary cancer. The exclusion criteria were survival for less than 1 month or cause of death recorded as not available or unspecified cause of death. Median follow-up was 67 months (interquartile range, 28-128).

Patient Characteristics

Age was categorized into youngest (<40 years), older (40-60 years), or oldest (>60 years). Race was recorded as white, black, other, and unknown. Histology included serous, endometrioid, mucinous, clear-cell, and epithelial tumors not otherwise specified. The grade was recorded as G1 (well-differentiated), G2 (moderately differentiated), G3 (poorly differentiated), G4 (undifferentiated), and unknown. Surgery, chemotherapy, and radiotherapy were respectively classified as yes (with administration) or no (without administration). The marital status was recorded as married, single, divorced, widowed, and unknown. Cases were considered as OCSD if the cause of death was reported as ovarian cancer. Non-OCSD causes included all malignant tumors with the exception of ovarian cancer, cardiovascular diseases (disease of heart, hypertension without heart disease, cerebrovascular diseases, atherosclerosis, aortic aneurysm, and dissection), other chronic diseases (diabetes mellitus, Alzheimer's disease, chronic obstructive pulmonary disease and allied conditions, chronic liver disease and cirrhosis, nephritis, nephrotic syndrome, nephrosis etc.), and other deaths of specified causes (none of the above categories). All finally included cases were regrouped according to the AJCC staging system (7th edition).

Statistical Analysis

The incidence rate between non-OCSD and variables was analyzed using binary logistic regression. The Kaplan-Meier method was used to assess the 5-year and 10-year non-OCSD rates and the cumulative incidence of ACD. The effect of non-OCSD on OS was evaluated by non-OCSD to ACD ratio. The cumulative incidence of OCSD or non-OCSD was calculated using the Gray test.[20] Specific causes of death were showed by stacked cumulative incidence function plots. Cox

regression model was used to analyze the hazard ratio (HR) of risk factors for ACD and the sub-distribution hazard ratio (SHR) of risk factors for cause-specific death was calculated using the competing regression model.[21] Both the Cox regression model and the competing model were performed using STATA 15.0 software. All plots were developed by *cmprsk* and *survival* packages in R software (R-3.5.3) (http://www.r-project.org). All statistical tests were 2-sided and *P* values less than 0.05 were considered statistically significant.

Results

Characteristics of Patients

A total of 18,037 eligible patients with early-stage epithelial ovarian cancer were identified between 1988 and 2015. The cohort included 13,263 stage I and 4774 stage II patients. Median follow-up was 74 months (interquartile range, 3-136) for patients with stage I and 51 months (interquartile range, 21-104) for patients with stage II. Overall, 1606 (8.9%) and 3022 (16.8%) patients underwent non-OCSD and OCSD, respectively (74.3% of the cases were considered as censored events). A censored event is data obtained during the observation that a death event has not been observed. The median age was 55 (interquartile range, 47-66) years.

Association of Patients' Clinicopathological Characteristics with Non-OCSD

Univariate binary logistic regression analysis indicated that non-OCSD was associated more with age, endometrioid or mucinous histological type, well-differentiated tumor, stage I, the administration of surgery, no chemotherapy, and widowed marital status. The association between AJCC sub-stagings and non-OSCD is presented in Supplementary Table 1. The above variables were mostly preserved in the multiple regression model, except for the mucinous histological type. Alternatively, divorced marital status was had a higher association with non-OCSDs in the multiple regression model. The results indicated that age, histology, pathological grade, AJCC stage, surgery, chemotherapy, and marital status were the dominating independent prognostic factors of non-OCSD (Table 1).

The other causes of death are listed and stratified by the therapy method (for more details see, Table 2). The leading causes of non-OCSDs were cardiovascular diseases. Other chronic diseases and other deaths of specified causes were also common causes of non-OCSD. More patients died of cardiovascular diseases and other chronic diseases in the no-radiotherapy or no-chemotherapy subgroup vs the radiotherapy or chemotherapy subgroups. On the contrary, most of the patients with surgery died from these 2 causes (Table 2). The detailed results of treatment in AJCC sub-stagings are shown in Supplementary Table 2.

Cumulative Incidence of Non-OCSD With Clinicopathological Characteristics (Competing Model)

The Gray test showed that the cumulative incidence of non-OCSD was higher in the following variables: oldest age (Fig 1a), with radiotherapy (Fig 1b), no chemotherapy (Fig 1c), and divorced or widowed status (Fig 1d). The cumulative incidence of non-OCSD was higher in the no-surgery group than in the surgery group before 200 months (Supplementary Fig 1d). The univariate analysis indicated that age, race, histology, surgery, radiotherapy, chemotherapy, and marital status were associated with non-OCSD (Table 3). The multivariate analyses displayed that age, race, radiotherapy, chemotherapy, and marital status were the most important independent predictors of the cumulative incidence of non-OCSD (Table 3). Interestingly, there was no significant difference between stage I and stage II in the cumulative incidence of non-OCSD (Fig 2a). Relative to stage II, the cumulative incidence was higher at stage I with SHRs of 1.416 (95% CI, 1.249-1.607,

Table 1
Associations patients' clinicopathological characteristics with nonovarian cancer-specific death

Variables	Total (n = 18,037)	No. (%)		Univariate analysis		Multivariate analysis	
		OCSD (n = 3022 [16.8%])	Non-OCSD (n = 1606 [8.9%])	OR (95% CI)	*P*	OR (95% CI)	*P*
Age							
<40 (Yongest)	2160	196 (9.1)	38 (1.8)	1	–	1	–
40-60 (Older)	9467	1332 (14.1)	379 (4.0)	1.468 (1.018-2.116)	0.04	2.036 (1.375-3.014)	<0.001
>60 (Oldest)	6410	1494 (23.3)	1189 (18.5)	4.105 (2.876-5.858)	<0.001	5.612 (3.791-8.308)	<0.001
Race							
Black	1057	248 (23.5)	116 (11.0)	1	–		–
White	14,787	2503 (16.9)	1375 (9.3)	1.174 (0.933-1.478)	0.171	–	–
Other	2084	269 (12.9)	114 (5.5)	0.906 (0.664-1.236)	0.534	–	–
Unknown	109	2 (1.8)	1 (0.9)	1.069 (0.096-11.908)	0.957	–	–
Histology							
Serous	5236	1154 (22.0)	502 (9.6)	1	–	1	–
Endometrioid	4317	447 (10.4)	396 (9.2)	2.037 (1.716-2.417)	<0.001	1.713 (1.409-2.082)	<0.001
Mucinous	3009	281 (9.3)	312 (10.4)	2.552 (2.106-3.093)	<0.001	1.658 (1.316-2.088)	0.537
Clear-cell	3611	563 (15.6)	204 (5.6)	0.833 (0.688-1.009)	0.061	0.933 (0.750-1.162)	0.283
Not otherwise specified	1864	577 (31.0)	192 (10.3)	0.765 (0.630-0.929)	0.007	0.883 (0.703-1.109)	<0.001
Grade							
G1	3338	214 (6.4)	288 (8.6)	1	–	1	–
G2	4251	592 (13.9)	419 (9.9)	0.526 (0.423-0.653)	<0.001	0.663 (0.518-0.848)	0.001
G3	4471	1096 (24.5)	384 (8.6)	0.260 (0.211-0.322)	<0.001	0.463 (0.360-0.595)	<0.001
G4	1869	366 (19.6)	96 (5.1)	0.195 (0.146-0.259)	<0.001	0.412 (0.296-0.572)	<0.001
Unknown	4108	754 (18.4)	419 (10.2)	0.413 (0.334-0.511)	<0.001	0.726 (0.561-0.940)	<0.001
AJCC stage							
I	13,263	1561 (11.8)	1177 (8.9)	1	–	1	–
II	4774	1461 (30.6)	429 (9.0)	0.389 (0.341-0.444)	<0.001	0.525 (0.452-0.611)	<0.001
Surgery							
No	422	287 (68.0)	68 (16.1)	1	–	1	–
Yes	17,615	2735 (15.5)	1538 (8.7)	2.373 (1.809-3.114)	<0.001	2.404 (1.710-3.378)	<0.001
Radiotherapy							
No	17,837	2944 (16.5)	1574 (8.8)	1	–	–	–
Yes	200	78 (39.0)	32 (16.0)	0.767 (0.506-1.163)	0.212	–	–
Chemotherapy							
No	8240	982 (11.9)	993 (12.1)	1	–	1	
Yes	9797	2040 (20.8)	613 (6.3)	0.297 (0.262-0.337)	<0.001	0.457 (0.397-0.527)	<0.001
Marital status							
Married	9685	1477 (15.3)	652 (6.7)	1	–	1	–
Single	4004	597 (14.9)	243 (6.1)	0.922 (0.774-1.099)	0.364	1.080 (0.885-1.320)	0.448
Divorced	1648	285 (17.3)	154 (9.3)	1.224 (0.986-1.520)	0.067	1.284 (1.005-1.640)	0.046
Widowed	2016	562 (27.9)	507 (25.1)	2.044 (1.757-2.378)	<0.001	1.338 (1.119-1.601)	0.001
Unknown	684	101 (14.8)	50 (7.3)	1.121 (0.789-1.593)	0.522	1.198 (0.809-1.773)	0.368

Notes: The univariate and multivariate analyses were conducted with the binary logistic regression model.
Abbreviations: CI, confidence interval; G1, well differentiated; G2, moderately differentiated; G3, Poorly differentiated; G4, undifferentiated.; Non-OCSD, Nonovarian cancer specific death; OCSD, ovarian cancer-specific death; OR, odds ratio.

Table 2
Detailed causes of death

	Total, No. (%)	Administration of radiotherapy, No. (%)		Administration of chemotherapy, No. (%)		Administration of surgery, No. (%)	
		Without	With	Without	With	Without	With
Alive	13,409 (74.3)	13,319 (74.7)	90 (45.0)	6265 (76.0)	7144 (72.9)	67 (15.9)	13,342 (75.7)
OCSD	3022 (16.8)	2944 (16.5)	78 (39.0)	982 (11.9)	2040 (20.8)	287 (68.0)	2735 (15.5)
Non-OCSD	1606 (8.9)	1574 (8.8)	32 (16.0)	993 (12.1)	613 (6.3)	68 (16.1)	1538 (8.7)
Other cancers	78 (0.4)	76 (0.4)	2 (1.0)	42 (0.5)	36 (0.4)	15 (3.6)	63 (0.4)
Cardiovascular diseases	646 (3.6)	635 (3.6)	11 (5.5)	419 (5.1)	227 (2.3)	18 (4.3)	628 (3.6)
Other chronic diseases	488 (2.7)	476 (2.7)	12 (6.0)	292 (3.5)	196 (2.0)	24 (5.7)	464 (2.6)
Other deaths of specified causes	394 (2.2)	387 (2.2)	7 (3.5)	240 (2.9)	154 (1.6)	11 (2.6)	383 (2.2)

Abbreviations: Non-OCSD, Nonovarian cancer specific death; OCSD, ovarian cancer-specific death.

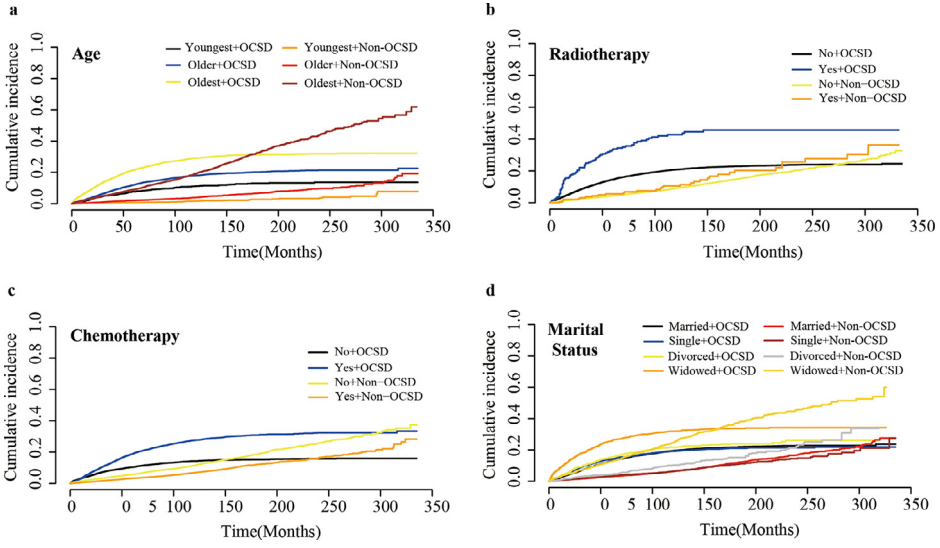

Fig. 1. Effects of age, radiotherapy, chemotherapy, and marital status on non-OCSD and OCSD according to the Gray method. (a) The youngest patients with epithelial ovarian cancer (<40 years) were used as the reference; the oldest patients (>60 years) and the older patients (40-60 years) had more non-OCSDs with SHRs of 13.610 (95% CI, 9.860-18.785) and 2.551 (95% CI, 1.828-3.559), respectively ($P < 0.001$), and also had more OCSDs, with SHRs of 2.920 (95% CI, 2.517-3.388) and 1.623 (95% CI, 1.398-1.884), respectively ($P < 0.001$). (b) The administration of radiotherapy corresponded to a risk of more non-OCSD (SHR, 1.455; 95% CI, 1.039-2.038; $P = 0.029$) and more OCSD (SHR, 2.440; 95 %CI, 1.940-3.069; $P < 0.001$). (c) With the administration of chemotherapy, the risk of non-OCSD was lower (SHR, 0.569; 95% CI, 0.515-0.629; $P < 0.001$), but the risk of OCSD was higher (SHR, 1.992; 95%CI, 1.844-2.151; $P < 0.001$). (d) Divorced and widowed patients had more non-OCSDs with SHRs of 1.478 (95% CI, 1.242-1.760) and 4.027 (95% CI, 3.592-4.515), respectively ($P < 0.001$). Divorced and widowed patients had more OCSDs with SHRs of 1.172 (95% CI, 1.033-1.330; $P = 0.014$) and 1.940 (95% CI, 1.758-2.143; $P < 0.001$), respectively. Married patients were used as the reference. OCSD, ovarian cancer-specific death; non-OCSD, nonovarian cancer-specific death; CI, confidence interval; SHR, subdistribution hazard ratio.

$P < 0.001$) in the oldest subgroup (Fig 2b). See Table 3 and Supplementary Figure 1 for the plots and other detailed variables related to the cumulative incidence of non-OCSD.

Comparison of Cox Regression Model and Competing Risk Model

Cox regression model presented that the oldest subgroup had a more adverse outcome than the youngest one that used as the reference and the odds ratio (OR) of ACD was 5.443(95% CI, 4.760-6.224) for the oldest one. The cumulative incidence of ACD for 3 age groups is presented in Figure 2d. The AJCC stage of ACD for stage II patients (vs stage I patients) was 2.402(95% CI, 2.265-2.548), and there was a much higher risk of ACD for stage II patients vs the stage I patients based on the Kaplan-Meier curves (Fig 2c). Univariate and multivariate analyses for ACD were calculated by Cox regression model, and other detailed data are shown in Supplementary Table 3, and Supplementary Figures 1-3.

However, outcomes from the competing model were noteworthy. The risk of oldest subgroup increased significantly for non-OCSD compared with the youngest one 13.610 (95% CI, 9.860-18.785), and the risk of OCSD (vs youngest) was 2.920 (95% CI, 2.517-3.388). The cumulative incidence curves of non-OCSD, according to the Gray test, crossed closely for stage I and stage II (Fig 2a), while 2 lines clearly separated after adjustment of age (Fig 2b). The SHR of non-OCSD (vs stage I) was 1.051 (95% CI, 0.941-1.174, $P = 0.376$) without adjustments, whereas the SHR after adjustments for age was 1.416 (95% CI, 1.249-1.607, $P < 0.001$). Moreover, the chemotherapy group had a lower non-OCSD rate (SHR, 0.569; 95% CI, 0.515-0.629, $P < 0.001$) but a higher

Table 3
Nonovarian cancer specific death in univariate and multivariate analyses: a competing risk regression model

Variables	Univariate analysis		Multivariate analysis	
	SHR (95% CI)	*P*	SHR (95% CI)	*P*
Age (year)				
<40 (Yongest)	1	—	1	—
40-60 (Older)	2.551 (1.828-3.559)	<0.001	3.003 (2.137-4.218)	<0.001
>60 (Oldest)	13.610 (9.860-18.785)	<0.001	13.762 (9.844-19.239)	<0.001
Race				
Black	1	—	1	—
White	0.864 (0.714-1.044)	0.131	0.861 (0.715-1.038)	0.118
Other	0.528 (0.408-0.684)	<0.001	0.689 (0.533-0.892)	0.005
Unknown	0.119 (0.016-0.862)	0.035	0.144 (0.019-1.068)	0.058
Histology				
Serous	1	—	—	—
Endometrioid	0.948 (0.832-1.081)	0.426	—	—
Mucinous	1.035 (0.890-1.190)	0.634	—	—
Clear-cell	0.658 (0.560-0.773)	<0.001	—	—
Not otherwise specified	1.033 (0.874-1.222)	0.701	—	—
Grade				
G1	1	—	—	—
G2	1.129 (0.973-1.310)	0.110	—	—
G3	1.074 (0.923-1.250)	0.359	—	—
G4	0.825 (0.655-1.038)	0.100	—	—
Unknown	1.162 (1.000-1.349)	0.049	—	—
AJCC stage				
I	1	—	1	—
II	1.051 (0.941-1.174)	0.376		
Surgery				
No	1	—	1	—
Yes	0.516 (0.398-0.669)	<0.001	1.010 (0.759-1.345)	0.945
Radiotherapy				
No	1	—	1	—
Yes	1.455 (1.039-2.038)	0.029	1.539 (1.107-2.139)	0.010
Chemotherapy				
No	1	—	1	—
Yes	0.569 (0.515-0.629)	<0.001	0.603 (0.545-0.667)	<0.001
Marital status				
Married	1	—	1	—
Single	0.957 (0.826-1.108)	0.552	1.283 (1.107-1.487)	0.001
Divorced	1.478 (1.242-1.760)	<0.001	1.298 (1.090-1.545)	0.003
Widowed	4.027 (3.592-4.515)	<0.001	1.883 (1.670-2.122)	<0.001
Unknown	1.315 (0.985-1.756)	0.063	1.241 (0.934-1.649)	0.137

*Notes:*The univariate and multivariate analyses were performed with the Gray method and the Fine-Gray proportional hazards model.
*Abbreviations:*AJCC, American Joint Committee on Cancer; CI, confidence interval; G1, well differentiated; G2, moderately differentiated; G3, Poorly differentiated; G4, undifferentiated; SHR, subdistribution hazard ratio.

OCSD rate (SHR, 1.992; 95% CI, 1.844-2.151, $P < 0.001$) than the no-chemotherapy group. Other detailed results of OCSD for the competing risk model are shown in Supplementary Table 4.

Impact of Non-OCSD on OS

A Kaplan-Meier failure function was used to analyze the 5-year and 10-year probabilities of non-OCSD and ACD (Table 4). The ratio of non-OCSDs to ACD was higher than 0.5 for patients in the oldest subgroup, as well as for patients with well-differentiated tumor cells, no chemotherapy, and widowed status. Whereas, the ratio was lower than 0.3 for patients with stage II and poorly differentiated tumors (Table 4).

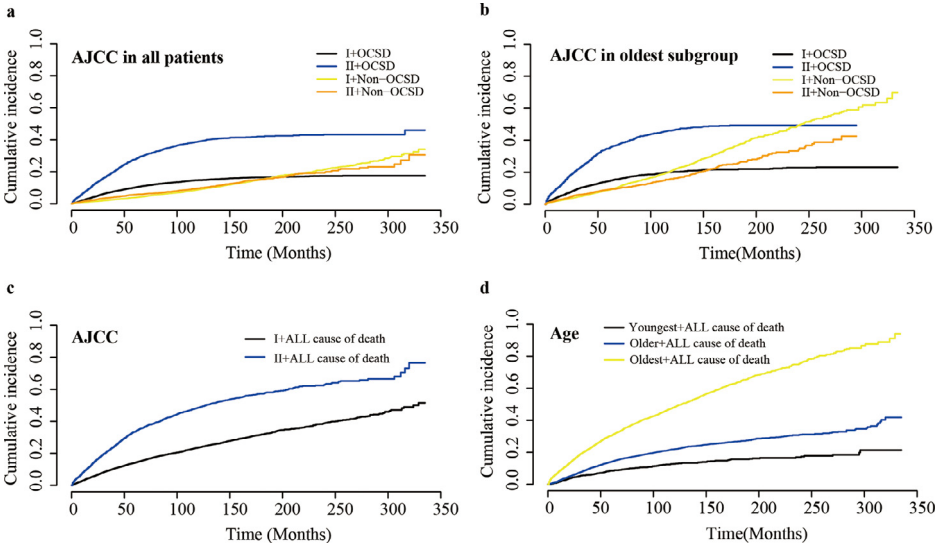

Fig. 2. Influences of the clinical staging on non-OCSD and OCSD according to the Gray method and influences of the clinical staging and age on all causes of death according to the Kaplan-Meier method. (a) The cumulative incidence function of non-OCSD was not related to the clinical staging (SHR, 1.051; 95% CI, 0.941-1.174; $P = 0.376$), but was related to a higher number of OCSDs (SHR, 3.014; 95% CI, 2.807-3.236; $P < 0.001$). (b) Patients with stage II ovarian cancer had fewer non-OCSDs (SHR, 0.706; 95% CI, 0.622-0.801; $P < 0.001$) than stage I patients in the subgroup with the oldest patients, but more OCSDs (SHR, 2.681; 95% CI, 2.422-2.968; $P < 0.001$). (c) The hazard ratio (based on the Cox regression model) of all causes of death for the AJCC staging (with stage I as the reference) was 2.402 (95% CI, 2.265-2.548), and the 2 curves of all causes of death (based on the Kaplan-Meier method) for stage I and stage II patients were clearly separated. (d) The curves based on the Kaplan-Meier method showed that the eldest patients had the most deaths than the other groups. The hazard ratio (based on the Cox regression model) of all causes of death was 1.877 (95% CI, 1.637-2.152) for elderly patients (with younger patients as the reference). OCSD, ovarian cancer-specific death; non-OCSD, nonovarian cancer-specific death; CI, confidence interval; SHR, subdistribution hazard ratio; AJCC, American Joint Committee on Cancer.

The stacked cumulative incidence function plots presented the risk of cause-specific death. For the oldest subgroup (Fig 3a), endometrioid ovarian cancer patients (Fig 3b) and patients with stage I (Fig 3e), the risk of non-OCSD exceeded OCSD at approximately 175 months. Likewise, the 2 curves crossed at about 150 months for the mucinous subgroup (Fig 3c) and widowed patients (Fig 3f). For the well-differentiated subgroup, the risk of non-OCSD exceeded OCSD at 100 months (Fig 3d).

Discussion

Principal Findings

This study demonstrates that nonspecific death is a predominant confounding factor in the calculation of OS, so non-OCSD is of great significance to the prognosis assessment of patients with early epithelial ovarian cancer. According to the competing risk model, the outcome of the OS could reflect the impact of the observed disease itself. However, the use of the OS-based Kaplan-Meier method would result in biased outcomes, and under- or over-estimate the efficacies of treatment approaches determined by ACD as the primary observation ending of survival rates. This has triggered many controversial issues related to survival, which in turn negatively affect clinical decision-making.

This was the large-scale study focusing on risk factors of non-OCSD on OS, comparing survival analyses, and comparing competing risk analyses for early-stage epithelial ovarian cancer.

Table 4
Impact of non-OCSD on all causes of death

Variables	No.	Non-OCSD at 5 y (%)	ACD at 5 y (%)	Non-OCSD/ ACD at 5 y	Non-OCSD at 10 y (%)	ACD at 10 y (%)	Non-OCSD/ ACD at 10 y
Total	18,037	4.78	19.24	0.25	10.56	30.18	0.35
Age							
<40 (Yongest)	2160	0.81	8.47	0.10	1.80	12.82	0.14
40-60 (Older)	9467	2.23	14.11	0.16	4.42	21.97	0.20
>60 (Oldest)	6410	10.32	30.46	0.34	24.53	48.36	0.51
Race							
Black	1057	7.01	27.39	0.26	13.32	39.58	0.34
White	14,787	4.93	19.37	0.25	11.03	30.66	0.36
Other	2084	2.68	14.70	0.18	6.16	22.47	0.27
Unknown	109	1.52	3.18	0.48	1.52	5.55	0.27
Histology							
Serous	5236	5.37	23.19	0.23	11.70	38.12	0.31
Endometrioid	4317	4.56	12.36	0.37	10.83	23.10	0.47
Mucinous	3009	4.34	12.81	0.34	10.80	21.60	0.50
Clear-cell	3611	3.22	18.42	0.17	7.02	26.42	0.27
Not otherwise specified	1864	7.42	35.65	0.21	12.45	44.37	0.28
Grade							
G1	3338	3.55	8.83	0.40	9.28	16.48	0.56
G2	4251	4.54	15.35	0.30	10.49	26.66	0.39
G3	4471	4.93	25.39	0.19	11.59	40.61	0.29
G4	1869	4.18	24.93	0.17	9.81	37.80	0.26
Unknown	4108	6.15	22.76	0.27	11.04	31.00	0.36
AJCC stage							
I	13,263	4.14	14.13	0.29	9.83	23.59	0.42
II	4774	6.75	33.48	0.20	12.95	48.57	0.27
Surgery							
No	422	30.73	86.17	0.36	38.92	89.02	0.44
Yes	17,615	4.44	17.61	0.25	10.22	28.74	0.36
Radiotherapy							
No	17,837	4.76	19.00	0.25	10.51	29.88	0.35
Yes	200	6.93	39.25	0.18	15.37	53.28	0.29
Chemotherapy							
No	8240	6.07	16.08	0.38	12.74	25.57	0.50
Yes	9797	3.63	22.10	0.16	8.39	34.40	0.24
Marital status							
Married	9685	3.21	15.80	0.20	7.28	25.87	0.28
Single	4004	3.70	17.49	0.21	7.15	25.41	0.28
Divorced	1648	4.78	19.75	0.24	12.08	31.98	0.38
Widowed	2016	14.95	38.36	0.39	32.86	56.60	0.58
Unknown	684	4.97	18.35	0.27	11.05	29.25	0.38

Notes: The univariate and multivariate analyses were conducted with the binary logistic regression model.
*Abbreviations:*CI, confidence interval; G1, well differentiated; G2, moderately differentiated; G3, poorly differentiated; G4, undifferentiated; Non-OCSD, Nonovarian cancer specific death; OCSD, ovarian cancer-specific death; OR, odds ratio.

Our results showed that the impact of confounding causes of death could be balanced using a competing risk regression model, which could help to obtain results more similar to those of the real world and to solve some of the controversies caused by differences in survival outcomes. The risk factors of nonspecific death, which have not been sufficiently investigated by previous studies, should receive more attention in future follow-up research on high-risk populations.

Results of the Study in the Context of Previous Research

At present, a multitude of clinical studies still use ACD as the primary observation endpoint of OS, and evaluation criteria is based on whether the difference of OS is significant.[22-25] Some researchers have questioned whether the OS calculated by ACD could be used to correctly interpret real results.[16,26,27] Therefore, the impact of other causes of death on the entire survival

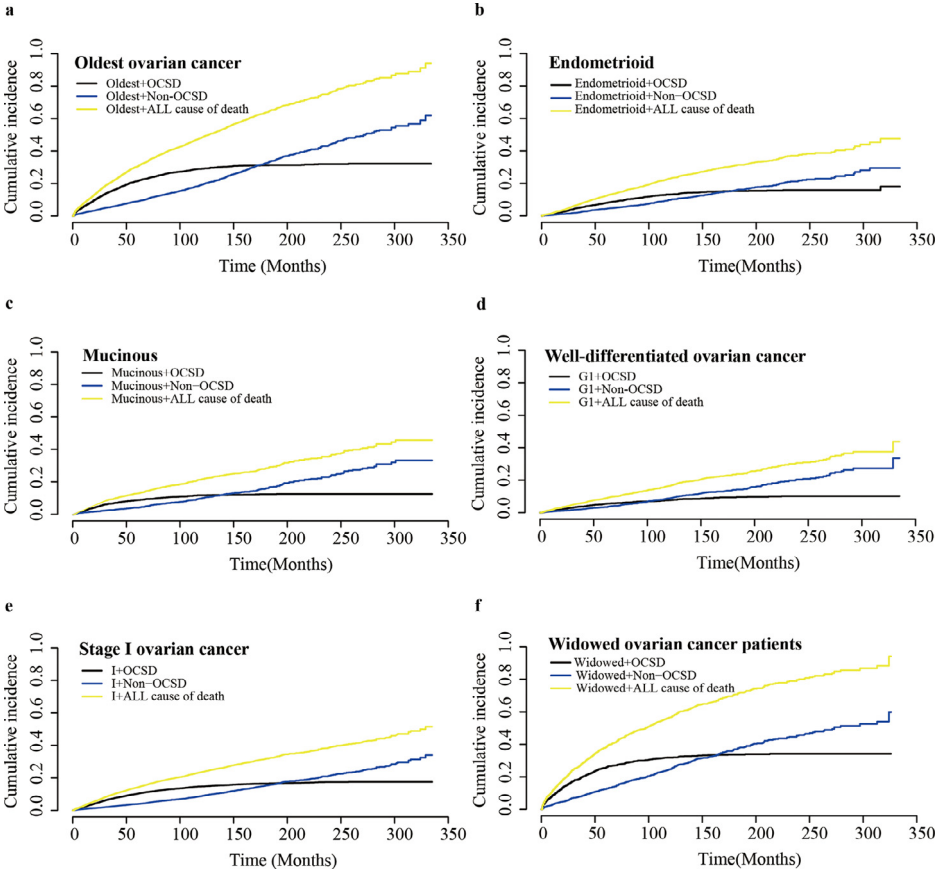

Fig. 3. Stacked cumulative incidence plots. (a) For the oldest subgroup, the non-OCSD and OCSD curves crossed at approximately 175 months. (b) For patients with endometrioid ovarian cancer, the risk of non-OCSD increased rapidly after almost 175 months. (c) For the mucinous subgroup, the non-OCSD curve exceeded the OCSD at 150 months, and the 2 curves clearly separated. (d) For the well-differentiated subgroup, the risk of OCSD was exceeded by the risk of non-OCSD at the beginning of follow-up. (E) In stage I, the non-OCSD and OCSD curves crossed at approximately 200 months. (F) For widowed patients, the risk of non-OCSD surpassed the OCSD at approximately 150 months. OCSD, ovarian cancer-specific death; non-OCSD, nonovarian cancer-specific death.

spectrum should not be underestimated. Previous literature implied that cardiovascular mortality and other chronic diseases cannot be ignored, as they contribute to a significant number of deaths in women with early-stage ovarian cancer [17]; our study revealed a similar situation.

Another major issue is the impact of effect of nonspecific death on OS of patients undergoing adjuvant chemotherapy. The ICON7 trial previously reported [28] that the addition of bevacizumab to standard chemotherapy could improve progression-free survival in patients with advanced ovarian cancer, whereas the whole population analysis failed to show an improvement in OS.[29] It is noteworthy that in subgroup analyses, an OS benefit was observed in high-risk patients, but not in non-high-risk patients. The reason that the benefit of progression-free survival cannot be translated into an improvement of OS is not clear. Moreover, another study found that in high-risk patients (stage IC/IIA and grade 2 or 3), the administration of 6 cycles paclitaxel/carboplatin chemotherapy was associated with a significantly lower relapse rate vs 4 cycles of chemotherapy; this benefit was only observed after 2 years (3% vs 18%; $P = 0.013$), and vanished at 5 years (23% vs 25%; $P = 0.797$).[30] Nevertheless, in this study, significantly increment of non-OCSD was observed in patients with well-differentiated tumors and stage I patients over time; this change

was more significant in the oldest subgroup. That is, the mortality risks of non-high-risk patients from other causes were found to outweigh the risk from ovarian cancer. This indicates that OS may be diluted by non-OCSD and may partly explain why there was no statistical difference in OS for the above studies.

In addition, our study also showed that non-OCSD was more significantly associated with no chemotherapy, cardiovascular diseases in particular, and other chronic diseases. This is consistent with a previous study, which reported that patients with early-stage ovarian cancer with adequate surgical staging might not need adjuvant chemotherapy.[31] Meanwhile, early-stage tumors typically respond well to treatment, and some histological subtypes have greater than 90% 5-year survival rates.[32] Deaths from other causes would be more frequent than ovarian cancer for patients with stage I tumors 7 years after diagnosis, and patients with stage II tumors 10 years after diagnosis.[17] This may be related to the phenomenon of nonchemotherapy patients having more non-OCSD.

Interestingly, in the current study, marital status was also one of the primary influence factors for non-OCSD; this is a factor that has frequently been ignored in previous research. A previous SEER study reported that married patients were less likely to die after being diagnosed with cancer, based on an identification of 1,260,898 patients with the top ten 10 causes of cancer-related deaths.[33] However, the association of non-OCSD with clinicopathological factors did not to be confirmed by further analysis in the abovementioned studies.

In this study, the independent prognostic factors of OS in the Cox regression model were not associated with chemotherapy. However, the competing risk model yielded completely different results, showing that chemotherapy was an independent prognostic factor of OS regardless of non-OCSD or OCSD. This contradictory result is useful for understanding why the benefits of disease-free survival could not be translated into OS benefits in the aforementioned studies. More importantly, variations of OS results from the clinical studies could directly lead to changes in clinical practice, which has great impacts on the effectiveness of treatment. Thus, a competing risk model should preferably be applied rather than a Cox regression model.

Clinical Implications

For early epithelial ovarian cancer, non-OCSD events are non-negligible competing risks. In particular, prospective clinical studies should require long-term follow-up that pays more attention to the impact of non-OCSD in real-world outcomes. Our study results imply that the survival curves of the observation object may not be statistically different due to the confounding of non-OSCD. Without an adequate sample size or follow-up time, such curves will be more notably affected by the cumulative incidence of non-OCSD than that of OCSD. OS will be inevitably impaired by non-OCSD. The fact that the absolute risk of ACD could be overestimated has been confirmed in a variety of tumors, including breast cancer,[16] malignant brain tumor,[34] lung cancer,[35] and head and neck cancer.[15]

Previous studies indicated that the leading cause of death for patients with early-stage ovarian cancer would dramatically change 7 years after diagnosis.[17] Ward et al.[36] also found that endometrial cancer was the most prevalent cause of death during the first 5 years, after which the predominant cause of death was cardiovascular mortality. Therefore, our study indicated that the competing risk estimate might be better able to present the real-world situation of deaths caused by ovarian cancer in the analysis of OCSD. Additionally, the risk factors identified in this study as related to non-OCSD highlight the need for researchers to more closely observe ovarian cancer populations during follow-up.

Strengths and Limitations

The strengths of the study were the large sample size, which was systematically analyzed to determine non-OCSD risk factors, and the comparison of Cox survival analysis and competing

risk models for OS calculations. The significant finding of the study is that the risk of non-OCSD gradually exceeds the risk of OCSD over time. The ratios of non-OCSD to ACD among different risk factors at 5 and 10 years were also shown for patients with early-stage ovarian cancer. Moreover, this study provides reasonable explanations for the phenomenon of the absence of statistical differences in OS.

There are several potential limitations of this study. First, there was some degree of misclassification for the death certificate data and algorithms used to determine the cause of death, resulting in biases to some extent.[37-39] However, the potential biases were minimized as far as possible by using large sample size and verifying the specific cause of death. Second, the values of some factors in the SEER database were missing; hence, statistical efficiency may be partially impaired. For example, the detailed records of treatment methods, such as chemotherapy, were missing from the SEER database; analysis of this incomplete data would likely result in decreased reliability of the findings. Third, these results to patients who did not receive chemotherapy (biologically low risk or better sub-staging) may not be appropriate. Finally, because of the small number of patients with early ovarian cancer, prognostic factors in sub-staging were not analyzed to ensure statistical efficacy.

Conclusions

At present, ACD remains the primary indicator used for calculating OS in many clinical studies. However, incorrect and biased interpretation yielded by Cox regression models might mislead clinicians in the treatment decision process. In the present study, our comprehensive analysis of non-OCSD distribution among patients concerning clinicopathologic factors found that the impacts of non-OCSD on OS were predominant in many specific situations. In future clinical trials, the application of competing risk models is recommended, especially for patients with factors that place them at high risk for non-OCSD.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.currproblcancer.2020.100621.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA: Cancer J Clin*. 2019;69:7–34 Jan.
2. Hayat MJ, Howlader N, Reichman ME, Edwards BK. Cancer statistics, trends, and multiple primary cancer analyses from the Surveillance, Epidemiology, and End Results (SEER) Program. *Oncologist*. 2007;12:20.
3. Hennessy BT, Coleman RL, Markman M. Ovarian cancer. *Lancet*. 2009;374:1371–1382.
4. González-Martín A, Toledo G, Chiva L. Epithelial ovarian carcinoma: current evidences and future perspectives in the first-line setting. *Clin Transl Oncol*. 2010;12:418–430.
5. Colombo N, Guthrie D, Chiari S, et al. International Collaborative Ovarian Neoplasm trial 1: a randomized trial of adjuvant chemotherapy in women with early-stage ovarian cancer. *J Natl Cancer Inst*. 2003;95:125.
6. Trimbos JB, Vergote I, Bolis G, et al. impact of adjuvant chemotherapy and surgical staging in early-stage ovarian carcinoma: European Organisation for Research and Treatment of Cancer–Adjuvant ChemoTherapy in Ovarian Neoplasm Trial. *J Natl Cancer Inst*. 2003;95:113–125.
7. Bolis G, Colombo N, Pecorelli S, et al. Adjuvant treatment for early epithelial ovarian cancer: results of two randomised clinical trials comparing cisplatin to no further treatment or chromic phosphate (32P). G.I.C.O.G.: Gruppo Interregionale Collaborativo in Ginecologia Oncologica. *Ann Oncol*. 1995;6:887–893.
8. Dean E, El-Helw L, Hasan J. targeted therapies in epithelial ovarian cancer. *Cancers*. 2010;2:88–113.
9. Mckee AE, Farrell AT, Pazdur R, Woodcock J. The role of the U.S. Food and Drug Administration review process: clinical trial endpoints in oncology. *Oncologist*. 2010;15(Suppl 1):13–18.
10. Neilson JP. Adjuvant (post-surgery) chemotherapy for early stage epithelial ovarian cancer. *Cochrane Database Syst Rev*. 2012;3 CD004706.
11. Chatterjee S, Chen L, Tergas AI, et al. Utilization and outcomes of chemotherapy in women with intermediate-risk, early-stage ovarian cancer. *Obstetr Gynecol*. 2016;127:992.
12. Dinkelspiel HE, Tergas AI, Zimmerman LA, et al. Use and duration of chemotherapy and its impact on survival in early-stage ovarian cancer. *Gynecol Oncol*. 2015;137:203–209.

13. Trimbos B, Timmers P, Pecorelli S, et al. surgical staging and treatment of early ovarian cancer: long-term analysis from a randomized trial. *J Natl Cancer Inst*. 2010;102:982.
14. Mertens AC, Jian Y, Dietz AC, et al. Conditional survival in pediatric malignancies: analysis of data from the Childhood Cancer Survivor Study and the Surveillance, Epidemiology, and End Results Program. *Cancer*. 2015;121:1108–1117.
15. Baxi SS, Pinheiro LC, Patil SM, Pfister DG, Oeffinger KC, Elkin EB. Causes of death in long-term survivors of head and neck cancer. *Cancer*. 2014;120:1507–1513.
16. Glas NAD, Kiderlen M, Vandenbroucke JP, et al. Performing survival analyses in the presence of competing risks: a clinical example in older breast cancer patients. *J Natl Cancer Inst*. 2015;108 djv366.
17. Dinkelspiel HE, Miriam C, June H, et al. Long-term mortality among women with epithelial ovarian cancer. *Gynecol Oncol*. 2015;138:421–428.
18. Skuladottir H, Olsen JH. Conditional survival of patients with the four major histologic subgroups of lung cancer in Denmark. *J Clin Oncol*. 2003;21:3035–3040.
19. Howlader N, Mariotto AB, Woloshin S, Schwartz LM. Providing clinicians and patients with actual prognosis: cancer in the context of competing causes of death. *J Natl Cancer Inst Monogr*. 2014;2014:255–264.
20. Rouzier R, Bergzoll C, Brun JL, et al. The role of lymph node resection in ovarian cancer: analysis of the surveillance, epidemiology, and end results (SEER) database. *Bjog Int J Obst Gynaecol*. 2010;117:1451–1458.
21. Fine JP, Gray RJ. Taylor & Francis online:: a proportional hazards model for the subdistribution of a competing risk - J Am Stat Assoc - Volume 94, Issue . *Taylor & Francis*.
22. Tomasello G, Petrelli F, Ghidini M, et al. Tumor regression grade and survival after neoadjuvant treatment in gastro-esophageal cancer: a meta-analysis of 17 published studies. *Eur J Surg Oncol J Eur Soc Surg Oncol Brit Assoc Surg Oncol*. 2017;43 S0748798317303670.
23. Kaufman JL, Mina R, Jakubowiak AJ, et al. Combining carfilzomib and panobinostat to treat relapsed/refractory multiple myeloma: results of a Multiple Myeloma Research Consortium Phase I Study. *Blood Cancer J*. 2019;9:3.
24. Cutsem EV, Hidalgo M, Canon JL, et al. Phase I/II trial of pimasertib plus gemcitabine in patients with metastatic pancreatic cancer: Pimasertib plus gemcitabine in pancreatic cancer. *Int J Cancer*. 2018;143.
25. McGuire WP, Penson RT, Gore M, et al. Randomized phase II study of the PDGFRα antibody olaratumab plus liposomal doxorubicin versus liposomal doxorubicin alone in patients with platinum-refractory or platinum-resistant advanced ovarian cancer. *BMC Cancer*. 2018;18:1292.
26. He C, Zhang Y, Cai Z, Lin X. Competing risk analyses of overall survival and cancer-specific survival in patients with combined hepatocellular cholangiocarcinoma after surgery. *BMC Cancer*. 2019;19:178.
27. Chappell R. Competing risk analyses: how are they different and why should you care. *Clini Cancer Res*. 2012;18:2127–2129.
28. Perren TJ, Swart AM, Pfisterer J, et al. A phase 3 trial of bevacizumab in ovarian cancer. *N Engl J Med*. 2011;365:2484–2496.
29. Oza AM, Cook AD, Pfisterer J, et al. Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial. *Lancet Oncol*. 2015;16:928–936.
30. Bamias A, Bamia C, Karadimou A, et al. A risk-adapted strategy of adjuvant paclitaxel/carboplatin in early-stage ovarian cancer: time-dependent effect of 4 versus 6 cycles on outcome. *Oncology*. 2011;81:365–371.
31. Claes T, Janne K. Adjuvant chemotherapy for early-stage ovarian cancer: review of the literature. *J Clin Oncol Off J Am Soc Clin Oncol*. 2007;25:2909.
32. Heintz AP, Odicino F, Maisonneuve P, et al. Carcinoma of the ovary. FIGO 26th annual report on the results of treatment in gynecological cancer. *Int J Gynaecol Obstetr*. 2006;95(Suppl 1):S161–S192.
33. Aizer AA, Chen MH, McCarthy EP, et al. Marital status and survival in patients with cancer. *J Clin Oncol*. 2013;31:3869–3876.
34. Tai BC, Grundy R, Machin D. On the importance of accounting for competing risks in pediatric brain cancer: II. regression modeling and sample size. *Int J Radiat Oncol Biol Phys*. 2011;79:1139–1146.
35. Eguchi T, Bains S, Lee MC, et al. impact of increasing age on cause-specific mortality and morbidity in patients with stage I non-small-cell lung cancer: a competing risks analysis. *J Clin Oncol*. 2017;35:281–290.
36. Ward KK, Shah NR, Saenz CC, Mchale MT, Alvarez EA, Plaxe SC. Cardiovascular disease is the leading cause of death among endometrial cancer patients. *Gynecol Oncol*. 2012;126:176–179.
37. Robert R, Fink, Aliza K, et al. The accuracy of cancer mortality statistics based on death certificates in the United States. *Cancer Epidemiol*. 2011;35:126–131.
38. Hinchliffe SR, Abrams KR, Lambert PC. The impact of under and over-recording of cancer on death certificates in a competing risks analysis: a simulation study. *Cancer Epidemiol*. 2013;37:11–19.
39. Hu CY, Xing Y, Cormier JN, Chang GJ. Assessing the utility of cancer-registry–processed cause of death in calculating cancer-specific survival. *Cancer*. 2013;119:1900–1907.