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Association between chemotherapy and disease-specific survival in women with borderline ovarian tumors: A SEER-based study

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ABSTRACT

Background: The impact of chemotherapy on disease-specific survival in patients with borderline ovarian tumors (BOTs) has not been studied previously.
Methods: Patients with BOTs were identified from The Surveillance, Epidemiology, and End Results (SEER) database. Associations of chemotherapy and other risk factors with disease-specific survival were analyzed using Cox proportion hazards regression models.
Results: A total of 6065 patients diagnosed during 1988–2000 were selected. The mean age at diagnosis was 48.0 ± 16.5 with a median follow-up time of 190.0 ± 72.5 months. The majority of BOTs were at stage I (86.7%) and treated with surgery (99.3%). Chemotherapy and radiotherapy were given to 343 patients (5.7%) and 33 (0.5%) patients, respectively. A total of 296 patients (4.9%) died from this disease. Both univariate and multivariate survival analysis showed that chemotherapy, older age, bilateral tumor, advanced stage, non-surgery and radiotherapy were associated with worse disease-specific survival. The comprised effect of chemotherapy remained after patients were stratified by age, histology and stage.
Conclusions: Chemotherapy is associated with worse disease-specific survival in patients with BOTs. Tumor laterality, age, stage and other treatments are also prognostic factors for this disease.

Introduction

Borderline ovarian tumors (BOTs) comprise 10–15% of all epithelial ovarian cancers [1]. The disease is commonly diagnosed at early stages and in women of childbearing ages [2,3]. The majority of patients are managed with surgery alone with an excellent prognosis. Chemotherapy is recommended for patients with high-risk BOTs, such as those with invasive implants and/or unresectable residual tumors. Most previous studies found that chemotherapy brought no benefit, or even a detrimental effect to overall survival or progression free survival in these patients [4–6]. It is noted that the number of patients receiving chemotherapy reported in these studies was very limited. Due to the excellent prognosis, the majority of patients with BOTs die from other diseases. The effect of chemotherapy on disease-specific survival has not been reported in these previous studies. The endpoint of disease-specific survival may better reflect the outcome of the treatment. Using a large population from a publicly available database, this study was conducted to examine the association between chemotherapy and disease-specific survival in women with BOTs.

Materials and methods

This study utilized data from the Surveillance, Epidemiology, and End Results (SEER) database. The SEER*Stat version 8.3.4. was used to identify patients with BOTs from SEER18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2016 Sub (1973–2014 varying) [7] using the method described previously [8–10]. The inclusion criteria was comprised of all patients diagnosed with BOTs based on the histopathology codes (serous 8442-1, 8451-1, and 8462-1; and mucinous 8472-1, 8473-1). A total of 6295 patients were initially identified from the SEER database. The stages were defined based upon the codes of SEER modified American Joint Committee on Cancer (AJCC) stage 3 (1988–2003). Patients with tumors whose primary sites were not at the ovary (n = 79), or with unknown stage or surgery status (n = 117), or

Abbreviations: AJCC, American Joint Committee on Cancer; BOTs, borderline ovarian tumors; SEER, The Surveillance, Epidemiology, and End Results.

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unknown survival time (n = 34) were then excluded. The flow chart shows the detailed procedure for selecting patients (Fig. 1). Based on our inclusion and exclusion criteria, 6065 patients with BOTs were included in this study.

The following variables were extracted from the database: patients' demographics (age, year of diagnosis, ethnicity and marital status), treatments (lymphadenectomy, surgery, chemotherapy and radiotherapy), tumor information (laterality, size, histology and stage), follow-up time and endpoint (disease-specific death). Information concerning lymphadenectomy was collected using coding for the Regional Nodes introduced in the 1988 database. Disease specific survival was defined as the time interval between the date of diagnosis with BOT and the date of death due to the disease.

The SAS software V9.3 (SAS Institute, Inc., Cary, N.C.) was applied for statistical analysis. The ordinal/categorical data were examined using the χ^2 test. Mean follow-up time of two groups was compared by t-Test. The change in prevalence of chemotherapy at each year was analyzed by linear regression. Univariate or multivariate Cox proportional hazards models were used to determine the effect of chemotherapy and other risk factors on disease-specific survival. The Kaplan-Meier survival curves were generated to compare the differential effects of treatments and other risk factors on survival. The statistical differences were analyzed by the log-rank test. Two-sided P values < 0.05 were considered to be statistically significant.

Results

The characteristics of patients with BOTs are listed in Table 1. The mean age of these patients was 48.0 ± 16.5 years. Among these patients, most patients were white (85.0%) and diagnosed at stage I (83.6%). Serous and mucinous BOTs accounted for 63.1% and 36.9%, respectively. Surgery was performed in 99.3% patients; however, chemotherapy was administered to only 343 patients (5.7%). Radiotherapy was given to 33 patients (0.5%). The mean follow-up time was 190.0 ± 72.5 months. At the end of the follow-up year, 296 patients (4.9%) died from this disease.

The prevalence of chemotherapy in each year was calculated (Fig. 2). The results revealed that in 1988, chemotherapy was given to 8.7% patients, while only 4.8% patients received the treatment in 2000. Thus demonstrating there was a significant decline in the use of chemotherapy in patients with BOTs ($P = 0.0013$).

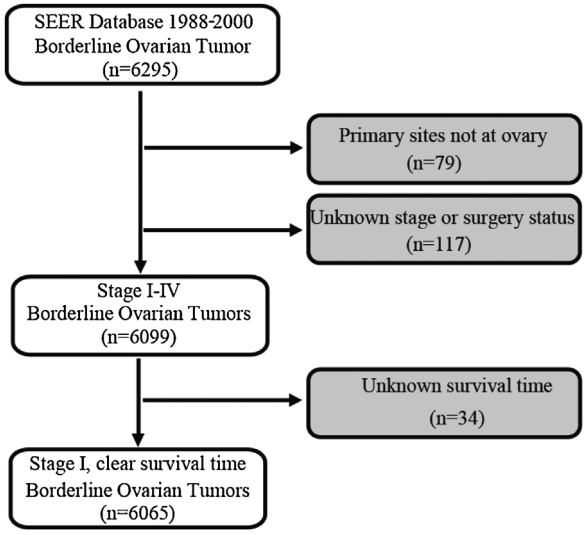

Fig. 1. Flow chart of selecting patients with BOTs.

Table 1
Demographic and pathoclinical features of patients with BOT (n = 6065).

Variables		n (%)
Age (years)		
	Mean ± SD	48.0 ± 16.5
	≤ 40	2192 (36.1)
	> 40	3873 (63.9)
Race		
	White	5162 (85.1)
	Black	410 (6.8)
	Others	493 (8.1)
Marital status		
	Single*	2575 (42.5)
	Married	3239 (53.4)
	Unknown	251 (4.1)
Laterality		
	Unilateral	4794 (79.0)
	Bilateral	1271 (21.0)
Histology		
	Serous	3826 (63.1)
	Mucinous	2239 (36.9)
Lymphadenectomy		
	No	4209 (69.4)
	Yes	1840 (30.3)
	Unknown	16 (0.3)
Stage		
	I	5070 (83.6)
	II	341 (5.6)
	III	536 (8.8)
	IV	118 (2.0)
Tumor size		
	≤ 5 cm	779 (12.8)
	> 5cm	1402 (23.1)
	unknown	3884 (64.1)
Surgery	No	42 (0.7)
	Yes	6023 (99.3)
Chemotherapy	No	5722 (84.3)
	Yes	343 (5.7)
Radiotherapy	No	6032 (99.5)
	Yes	33 (0.5)
Death	No	5769 (95.1)
	Yes	296 (4.9)
Follow-up time (months)		
Median (range)		196 (1-323)
Mean ± SD		190.0 ± 72.5

* including never married, divorced, separated and widowed.

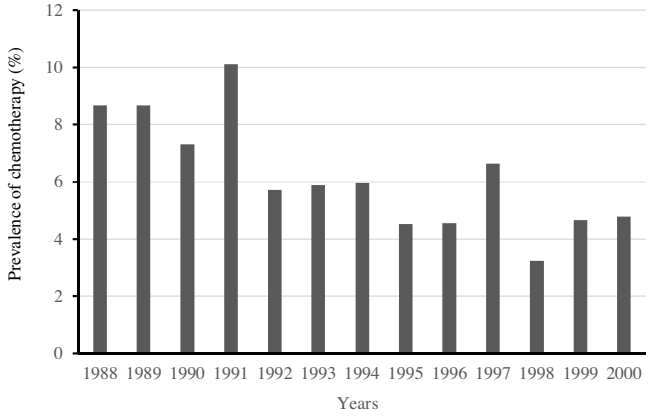

Fig. 2. The prevalence of chemotherapy used for patients with BOTs from 1988 to 2000.

The features of patients receiving chemotherapy are presented in Table 2. Patients with serous, bilateral BOTs, at advanced stages, receiving lymphadenectomy or radiotherapy were more likely to receive chemotherapy. The vast majority of chemotherapy was given with surgery (98.8%). Only 6 patients received both

Table 2
Characteristics of BOT patients with or without chemotherapy.

Variables		No chemotherapy (n = 5722)	Chemotherapy (n = 343)	*P* value
Age (years)				
	Mean ± SD	48.0 ± 16.6	48.9 ± 15.4	0.3110
	≤ 40	2074 (26.3)	118 (34.4)	0.4900
	> 40	3648 (63.7)	225 (65.6)	
Race	White	4865 (85.0)	297 (86.6)	0.0464
	Black	381 (6.7)	29 (8.5)	
	Others	476 (8.3)	17 (5.0)	
Histology	Serous	3558 (62.2)	268 (78.1)	<0.0001
	Mucinous	2164 (37.8)	75 (21.9)	
Marital status Single*		2442 (42.7)	133 (38.8)	0.0815
	Married	3038 (53.1)	201 (58.6)	
	Unknown	242 (4.2)	9 (2.6)	
Laterality				
	Unilateral	4639 (81.1)	155 (45.2)	<0.0001
	Bilateral	1083 (18.9)	188 (54.8)	
Lymphadenectomy No		4011 (70.1)	198 (57.7)	<0.0001
	Yes	1696 (29.6)	167 (42.0)	
	Unknown	15 (0.3)	1 (0.3)	
Stage	I	4962 (86.7)	108 (31.5)	<0.0001
	II	299 (5.2)	42 (12.2)	
	III	390 (6.8)	146 (42.6)	
	IV	71 (1.2)	47 (13.7)	
Tumor size	≤ 5 cm	740 (12.9)	39 (11.4)	0.7002
	> 5cm	1322 (23.1)	80 (23.3)	
	unknown	3660 (64.0)	224 (65.3)	
Surgery	No	38 (0.7)	4 (1.2)	<0.2761
	Yes	5684 (99.3)	339 (98.8)	
Radiotherapy	No	5695 (99.5)	337 (98.2)	0.0018
	Yes	27 (0.5)	6 (1.8)	
Death	No	5521 (96.5)	248 (72.3)	<0.0001
	Yes	201 (3.5)	95 (27.7)	
Follow-up time (months)				
Mean ± SD		191.7 ± 70.8	162.1 ± 92.7	<0.0001

* including never married, divorced, separated and widowed.

Table 3
Univariate and multivariate survival analysis in patients with BOTs.

Variables		Univariate		Multivariate	
		HR (95%CI)	*P* value	HR (95%CI)	*P* value
Age		1.04 (1.03-1.04)	<0.0001	1.04 (1.03-1.05)	<0.0001
	≤ 40	1			
	> 40	2.58 (1.95-3.43)	<0.0001		
Race					
	White	1			
	Black	1.40 (0.93-2.09)	0.1063		
	Other	0.83 (0.53-1.31)	0.4281		
Marital status					
	Single*	1			
	Married	0.91 (0.72-1.15)	0.4402		
	unknown	0.47 (0.21-1.07)	0.0720		
Histology	Serous	1			
	Mucinous	0.88 (0.69-1.12)	0.2865		
Stage					
	I	1			
	II	2.95 (1.97-4.42)	<0.0001	2.23 (1.46-3.41)	0.0002
	III	5.70 (4.34-7.48)	<0.0001	3.53 (2.54-4.91)	<.0001
	IV	16.44 (11.7-23.12)	<0.0001	7.58 (5.11-11.25)	<.0001
Laterality	Unilateral	1			
	Bilateral	3.23 (2.57-4.06)	<0.0001	1.47 (1.13-1.91)	0.0043
Tumor size	≤ 5 cm	1			
	>5 cm	1.25 (0.80-1.96)	0.3321		
	Unknown	1.50 (1.01-2.22)	0.0442		
Lymphadenectomy					
	No	1			
	Yes	1.17 (0.92-1.49)	0.2019		
	Unknown	1.74 (0.24-12.39)	0.5822		

Table 3 (*Continued*)

Variables		Univariate		Multivariate	
		HR (95%CI)	*P* value	HR (95%CI)	*P* value
Surgery					
	No	1		1	
	Yes	0.16 (0.08-0.34)	<0.0001	0.14 (0.07-0.29)	<0.0001
Chemotherapy					
	No	1		1	
	Yes	9.26 (7.25-11.83)	<0.0001	3.78 (2.82-5.04)	<0.0001
Radiotherapy					
No		1			
Yes		4.94 (2.44-9.97)	<0.0001	2.63 (1.30-5.32)	0.0073

* including never married, divorced, separated and widowed.

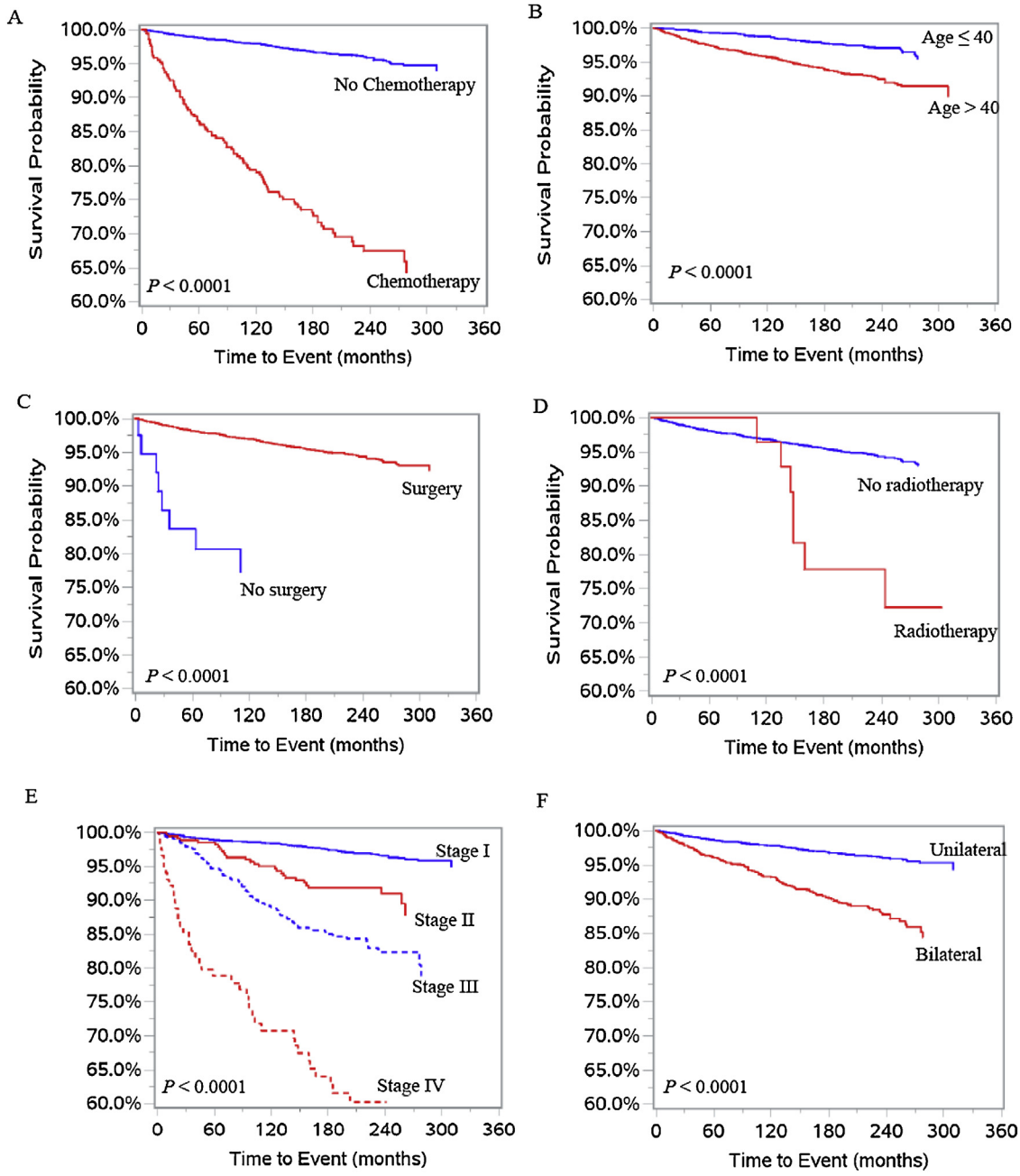

Fig. 3. Survival curves for patients with BOTs: chemotherapy (A), age (B), surgery (C), radiotherapy (D), stage (E) and laterality (F).

chemotherapy and radiotherapy. Mean follow-up time was 162.1 ± 92.7 months for the chemotherapy group, which was significantly shorter than the non-chemotherapy group (191.7 ± 70.8.months). A significantly higher proportion of patients died of the disease in the chemotherapy group ($P < 0.0001$).

Univariate survival analysis found that age, stage, laterality, surgery, chemotherapy and radiotherapy were prognostic factors significantly associated with disease-specific survival (Table 3). The survival curves for the risk factors are presented in Fig. 3.

Multivariate survival analysis showed that increased age (hazard ratio (HR) = 1.04, 95% confidence interval (CI): 1.03–1.05, $P < 0.0001$), higher stages (compared to stage I, HR = 2.23 for stage II, 95% CI: 1.46–3.41, $P = 0.0002$; HR = 3.53 for stage III, 95% CI: 2.54–4.91, $P < 0.0001$; HR = 7.58 for stage IV, 95% CI: 5.11–11.25, $P < 0.0001$), bilateral (HR = 1.47, 95% CI: 1.13–1.91, $P = 0.0043$), surgery (HR = 0.14, 95% CI: 0.07-0.29, $P < 0.0001$), chemotherapy (HR = 3.78, 95% CI: 2.82–5.04, $P < 0.0001$) and radiotherapy (HR = 2.63, 95% CI: 1.30–5.32, $P = 0.0073$) were significantly associated with disease-specific survival (Table 3).

The association between chemotherapy and disease-specific survival was further analyzed after stratification of patients by age (≤ 40 and >40 years), histology (serous and mucinous) and stage

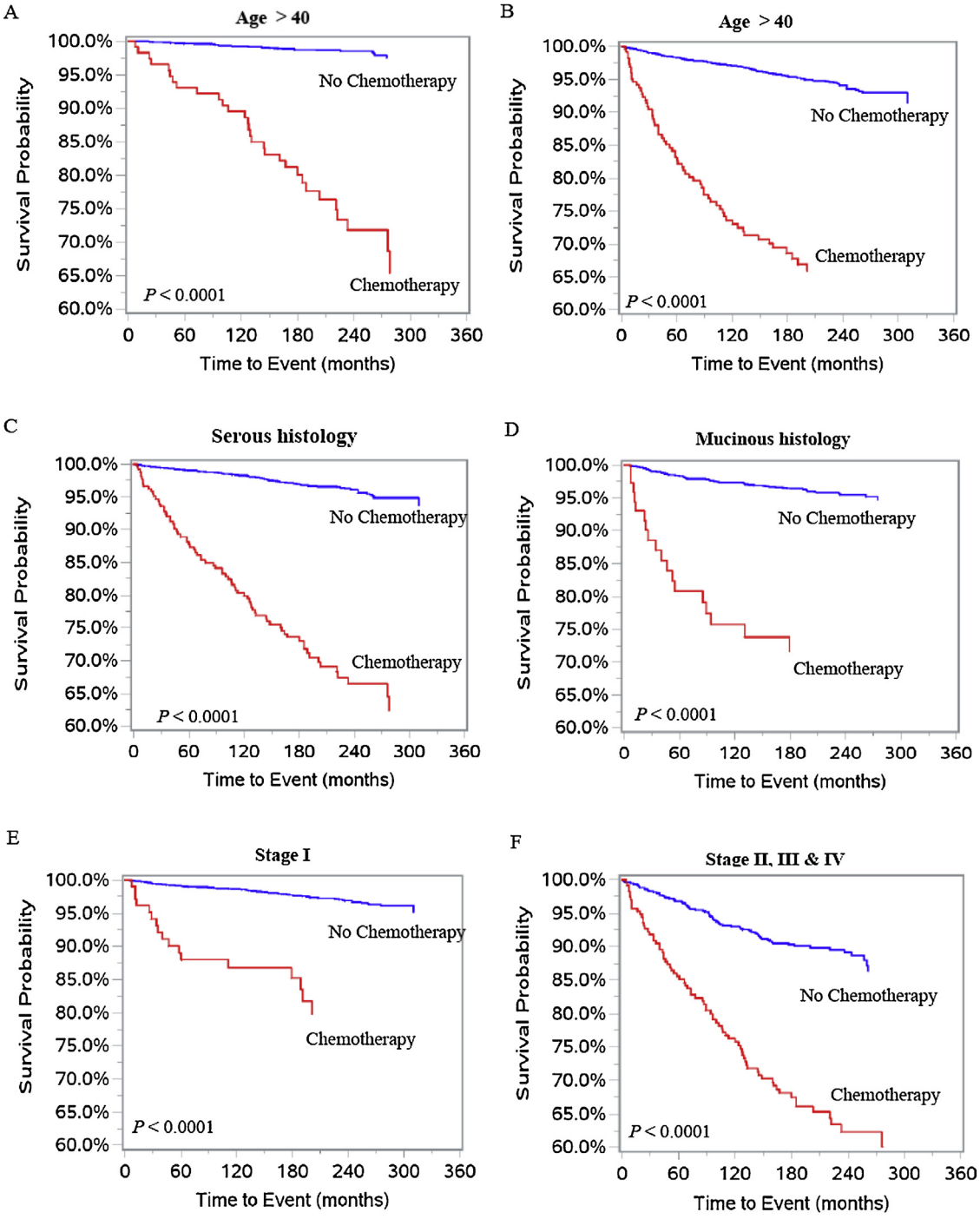

Fig. 4. Survival curves for patients with BOTs after stratification: age (A and B), histology (C and D) and stage (E and F).

(I and II, III & IV). After the stratifications, the results revealed that chemotherapy was still significantly associated with a worse disease-specific survival in these patients (Fig. 4).

Discussion

Previous studies have shown no beneficial effects of chemotherapy on overall survival or progression-free survival in patients with BOTs. In a database from 14 gynecological oncology departments in Turkey and Germany, 364 patients with BOTs were recorded during 1998-2015. Both univariate and multivariate analyses found that adjuvant chemotherapy was not associated with progression-free survival and overall survival in these patients [11]. Using data from our hospital, our recent study has revealed that chemotherapy was associated with a poorer progression free survival in univariate survival analysis, but was not a prognostic factor in a multivariate survival model [12]. Another study reported that adjuvant chemotherapy was not associated with recurrence and subsequent pregnancy rate in patients with BOTs [13]. Vasconcelos [4] and Abascal-Saiz [6] have summarized older studies and concluded there is no benefit from adjuvant chemotherapy in the treatment of patients with BOT.

This population based study is the first to examine the impact of chemotherapy on disease-specific survival in patients with BOTs. With a cohort size of 6065 patients, our result showed that chemotherapy was associated with poorer disease-specific survival. The compromised effects were still significant after controlling with confounding factors of age, tumor laterality, stage, surgery and radiotherapy, or after stratifying patients by age, histology and stage. Chemotherapy is recommended for patients with high-risk BOTs, such as those with invasive implants and/or residual tumors. However, the database does not include information concerning those high-risk factors. More studies must be conducted to corroborate the negative effect of chemotherapy on disease specific survival in these patients.

New histopathological, molecular, and genetic studies have proposed dividing ovarian cancer into type I and II broad categories [14–16]. BOTs are considered to be the intermediate step for type I tumors to develop into ovarian cancer. Type I ovarian tumors are clinically indolent, confined to the ovary and relatively genetically stable; therefore, are resistant to routine chemotherapy. This may explain why chemotherapy has no survival benefit in patients with BOTs.

Our study showed that there was a significant decline in the use of chemotherapy in patients with BOTs during the study period of 1988–2000. A recent population-based study included 7113 patients diagnosed with BOTs between 1993 and 2016 from the Netherlands Cancer Registry (NCR). Their study reported that 4.4% patients received chemotherapy during 1993-1998. The rate of patients treated with chemotherapy declined 0.7% from 2011 to 2016 [17]. The decreased use of chemotherapy may indirectly reflect no beneficial effect of chemotherapy.

In this study, only 33 patients (0.5%) received radiotherapy. All patients who were treated with radiotherapy also received surgery. The majority of patients (n = 30) received radiotherapy after surgery. Six patients received both radiotherapy and chemotherapy. Despite a limited number of patients receiving radiotherapy, this study revealed that radiotherapy was significantly associated with a worse disease-specific survival in both univariate and multivariate survival analysis. Similar to our finding, previous studies reported no beneficial effect of adjuvant radiotherapy in patients with BOTs [18,19].

The literature reported that 15–40% of serous BOTs are demonstrated to be bilateral [20]. This study showed that 21.0% of overall patients had bilateral BOTs. Among the serous BOTs, 29.6% were bilateral. Serous BOTs with a micropapillary pattern tended to be bilateral [20], which was associated with a poor prognosis [21,22]. The micropapillary information was not available in the SEER database. Interestingly, our results revealed that bilateral BOTs were associated with worse disease-specific survival when compared to unilateral ones. This finding implies that patients with bilateral BOTs may be at higher risk.

Using the same SEER database, a recent study investigated the effect of lymphadenectomy on disease-specific survival only in patients with BOTs at stage I. Their results revealed that lymphadenectomy was not associated with disease-specific survival [9]. Although patients of all stages were included in this study, our results also showed that lymphadenectomy is not a risk factor associated with disease specific survival. Other studies reported no benefit of lymphadenectomy on progression free survival or overall survival in these patients [22–27]; however, our previous study reported improved progression free survival after lymphadenectomy [12].

One limitation of this study is due to its retrospective study design. Patients were not randomly assigned to a treatment, they were simply grouped into surgery or no surgery. It was unknown whether there was a residual tumor after surgery. Many important pathological features of the tumors, such as invasive implants and micropapillary patterns, were not available for these patients. The information about recurrences and the types of relapses were not presented in the database. The regimens and duration of chemotherapy, the toxicity and other side effects of chemotherapy were not recorded. The strength of this study is the large sample size, long follow-up time and using the disease-specific survival as the endpoint.

Conclusions

Chemotherapy is associated with poorer disease specific survival in patients with BOTs. More attention should be paid to its effect on patients with high-risk BOTs. In addition, tumor laterality, age, stage, surgery and radiotherapy are also prognostic factors for this disease.

Statement of ethics

Due to the retrospective nature of the study and data being from a public database, this study was exempt from review by the Medical Ethics Committee of Zhejiang Cancer Hospital.

Authorship & contributors

WY and CX conceived the concept. WY, SH, ZT YA and CX collected and analyzed data. CX, ZT and YA participated in interpretation of results. WY and CX wrote the manuscript. All authors have read and approved the final version of the manuscript.

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Declaration of Competing Interest

None.

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