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Carcinosarcoma of the Ovary: Natural History, Patterns of Treatment, and Outcome

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Abstract

Objective—Ovarian carcinosarcomas (OCS) are rare tumors composed of both malignant epithelial and mesenchymal elements. We compared the natural history and outcomes of OCS to serous carcinoma of the ovary.

Methods—Patients with OCS and serous carcinomas registered in the Surveillance, Epidemiology, and End Results (SEER) database between 1988-2007 were analyzed. Demographic and clinical characteristics were compared using chi square tests while survival was analyzed using Cox proportional hazards models and the Kaplan-Meier method.

Results—A total of 27,737 women, including 1763 (6.4%) with OCS and 25,974 (93.6%) with serous carcinomas, were identified. Patients with carcinosarcomas tended to be older and have unstaged tumors (P<0.0001). After adjusting for other prognostic factors, women with carcinosarcomas were 72% more likely to die from their tumors (HR=1.72; 95% CI, 1.52-1.96). Five-year survival for stage I carcinosarcomas was 65.2% (95% CI, 58.0-71.4%) vs. 80.6% (95% CI, 78.9-82.2%) for serous tumors. Similarly, five-year survival for stage IIIC patients was 18.2% (95% CI, 14.5-22.4%) for carcinosarcomas compared to 33.3% (95% 32.1-34.5%) for serous carcinomas.

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Conflict of Interest
The authors have no conflicts of interest.

Conclusions—Ovarian carcinosarcomas are aggressive tumors with a natural history that is distinct from serous cancers. The survival for both early and late stage carcinosarcoma is inferior to serous tumors.

Introduction

Ovarian cancer is the fifth leading cause of cancer-related death in women, with 22,280 cases and 15,500 deaths in 2012.(1) The majority of ovarian cancers are epithelial tumors, the most common of which are serous carcinomas. Ovarian carcinosarcomas are rare tumors composed of malignant epithelial and mesenchymal components.(2) It is estimated that carcinosarcomas account for 1-4% of malignant ovarian cancers.(2-7)

A number of observational studies have suggested that ovarian carcinosarcomas follow a distinct natural history compared to other more common epithelial carcinomas.(2, 5, 8) Although prospective data are lacking, the management of ovarian carcinosarcoma (OCS) is similar to other ovarian tumors and typically includes cytoreductive surgery followed by adjuvant chemotherapy for women with advanced stage disease.(2) Although platinum and taxane based chemotherapy are often used, the ideal chemotherapy regimen for OCS is not known.(2, 8-12) Based on the efficacy of ifosfamide for uterine carcinosarcoma, some studies have suggested that ifosfamide should be incorporated into the treatment of OCS. (10, 11)

Given that ovarian carcinosarcomas are rare, little is known about the disease course and outcome of women with these tumors. We performed a population-based analysis to examine the natural history and outcome of ovarian carcinosarcomas. Specifically, we compared women with serous carcinoma and carcinosarcoma of the ovary.

Methods

Data Source

The Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute was utilized for this analysis.(13-17) SEER is a population-based tumor registry that collects data on approximately 28% of the United States population.(18) SEER is composed of a number of geographically distinct registries and captures clinical and demographic data as well as tumor characteristics including stage, grade, histology, initial treatment, and follow-up. Exemption from the Columbia University Institutional Review Board was obtained.

Cohort Selection

Women with serous tumors or carcinosarcomas of the ovary diagnosed between 1988 and 2007 were included in the analysis. Clinical and pathological data, including age at diagnosis (< 50 years of age, 50-64 years of age, 65-74 years of age, and ≥75 years of age), race (white, black, other), and marital status (single, married, other), were collected. Year of diagnosis was classified as: 1988-1990, 1991-1993, 1994-1995, 1996-1997, 1998-1999, 2000-2001, 2002-2003, 2004-2005, 2006-2007. Subjects were categorized based on the geographic area of residence within the United States at the time of diagnosis: central

(Detroit, Iowa, Kentucky, Louisiana, Utah), eastern (Connecticut, New Jersey, Atlanta, rural Georgia) and western (Alaska, California, Hawaii, Los Angeles, New Mexico, San Francisco, San Jose, Seattle).(19, 20) In addition to tumor histology, tumor grade was captured and grouped as well, moderately or poorly differentiated or unknown. Staging information was derived from the American Joint Cancer Committee staging information and recorded extent of disease codes.

Statistical Analysis

Frequency distributions between categorical variables were compared using χ^2 tests. Survival was calculated as the number of months from cancer diagnosis to the date of death. Patients who were alive at last follow-up were censored. Cox proportional hazards models were developed to examine both cancer specific and overall survival after adjustment for clinical and demographic characteristics. The survival models included only women who underwent surgery as a part of their treatment. Five-year survival rates were calculated by stage and histology. Kaplan-Meier curves were developed to examine stage-specific survival and compared using the log-rank test. All hypothesis tests were two-sided. A P-value of <0.05 was considered statistically significant. All analyses were conducted using SAS version 9.2 (SAS Institute Inc, Cary, North Carolina).

Results

A total of 27,737 patients, including 1763 (6.4%) with carcinosarcomas (OCS) and 25,974 (93.6%) with serous carcinomas, were identified. The demographic and clinical characteristics of the cohort are displayed in Table 1. Patients with carcinosarcomas tended to be older than women with serous tumors; 58.6% with OCS were 65 and older compared to 45.3% with serous carcinomas ($P<0.0001$). At diagnosis, stage I tumors were noted in 11.0% of women with OCS and 10.3% of those with serous tumors, while stage IV neoplasms were documented in 22.6% of women with OCS and 28.8% of patients with serous tumors ($P<0.0001$). Stage was unknown in 15.8% of patients with OCS compared to 2.8% of women with serous tumors.

Multivariable Cox proportional hazards models including only women who underwent surgery were developed to examine survival while adjusting for other prognostic factors (Table 2). Cancer-directed surgery was performed in 93.1% of women with carcinosarcomas and 92.6% of patients with serous tumors. The hazard ratio for death for women with OCS compared to serous tumors was 1.76 (95% CI, 1.65-1.87) while the hazard ratio for death from cancer was 1.79 (95% CI, 1.68-1.91). Age, stage, area of residence, marital status and year of diagnosis were all statistically significantly associated with prognosis. Similar trends were seen in Kaplan-Meier analyses, survival was inferior for women with OCS for both early and late stage disease. Figure 1A compares survival for women with stage I tumors, while figure 1B displays survival for those with stage III neoplasms ($P<0.0001$ for both).

When five-year survival was examined, similar findings of decreased survival for women with ovarian carcinosarcomas were identified (Table 3). Among women with stage I serous tumors five-year survival was 80.6% (95% CI, 78.9-82.2%) compared to 65.2% (95% CI, 58.0-71.4%) for OCS. Five-year survival for women with stage III neoplasams was 33.3%

(95% CI, 32.1-34.5%) for serous carcinomas compared to 18.2% (95% CI, 14.5-22.4%) for ovarian carcinosarcomas. Similarly, among patients with stage IV neoplasms, five-year survival was 20.3% (95% CI, 19.2-21.3%) for serous tumors versus 11.2% (95% CI, 8.1-14.9%) for ovarian carcinosarcomas.

Discussion

Our findings suggest that ovarian carcinosarcomas are aggressive tumors with a natural history that is distinct from serous cancers. OCS tends to occur in older women and more often presents with disseminated disease. The survival for both early and late stage carcinosarcoma is inferior to serous tumors.

Prior studies have shown that ovarian carcinosarcomas are aggressive neoplasms with a predilection towards early dissemination.(2, 5, 7, 8, 21) Compared to serous and other epithelial tumors, OCS tends to occur in older women.(2, 5, 7, 8, 21) Likewise, at the time of presentation, women with OCS more often present with advanced stage disease.(2, 5, 7, 8, 21) Among women with advanced stage disease, optimal tumor cytoreduction appears to be an important determinant of survival.(4, 8, 9, 21-23) Rauh-Hain et al. found that patients with OCS who had only microscopic disease after cytoreduction had a median overall survival of 47 months compared to 18 months for those with optimal but macroscopic disease and 8 months for those with suboptimal disease after surgery.(8) We noted that OCS occurred in older women and also found that stage was unknown in a higher percentage of women with carcinosarcomas.

The optimal choice of chemotherapy for women with OCS remains to be determined. The Gynecologic Oncology Group (GOG) has undertaken several prospective studies of chemotherapy for women with OCS.(11, 12, 24) While doxorubicin appears to possess minimal activity, response rates of 20% were noted for both ifosfamide and cisplatin.(11, 12, 24) Given the activity of both cisplatin and ifosfamide, several institutional observational studies have compared outcomes of regimens containing the two agents.(2, 5, 7-9, 23, 25-28) Although limited by a small sample size, an analysis of 22 patients treated with either carboplatin and paclitaxel or cisplatin and ifosfamide found no difference in survival.(29) In contrast, Rutledge and co-workers noted improved survival in women with OCS who received ifosfamide as part of their treatment; among 31 patients with OCS the median progression free interval was 12 months in those who received carboplatin and paclitaxel but had not been reached in patients treated with a combination of cisplatin and ifosfamide.(10) Despite the potential efficacy of ifosfamide, the drug is often associated with substantial toxicity and further work is needed to examine the patterns of chemotherapy use in women with ovarian carcinosarcomas.

Regardless of treatment, outcomes appear to be poor for women with ovarian carcinosarcoma. A case-control study of 50 women with ovarian carcinosarcoma noted a median overall survival of 24 months, inferior to the 41 months noted for women with serous tumors.(8) A large study of women with OCS treated from 1988-1997 comparing survival for OCS and serous tumors noted inferior survival for OCS patients with advanced stage disease but found no statistically significant difference in survival between the two

histologic subtypes for early stage tumors.(5) We noted that survival was inferior for all stages of women with OCS compared to serous tumors. For women with stage I tumors in our cohort, survival was only 65% for carcinosarcomas compared to 81% for those with serous tumors.

While our study includes a large number of patients, we acknowledge a number of important limitations. Perhaps most importantly, centralized pathology review was not available. This is particularly important in studies examining tumors that are uncommonly seen and, as such, we cannot exclude the possibility that a small number of neoplasms were misclassified. We lacked detailed data on residual disease, an important prognostic factor for ovarian cancer. Similarly, SEER lacks data on chemotherapy treatments and patterns and timing of recurrence. Lastly, as with any study of administrative data, we are unable to capture individual patient and physician preferences that certainly influenced the allocation of treatment.

In conclusion, our data suggests that ovarian carcinosarcomas have a distinct natural history compared to serous tumors. These neoplasms are associated with a poor outcome regardless of treatment. Given the differences in outcome for carcinosarcomas compared to more common histologic subtypes, future clinical trials focusing on this rare histology and alternate chemotherapy regimens should be considered. Further studies and the development of novel agents for the treatment of ovarian carcinosarcoma are warranted.(2)

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Research Highlights

-Ovarian carcinosarcomas are aggressive tumors with a natural history that is distinct from serous cancers.

-The survival for both early and late stage carcinosarcoma is inferior to serous tumors.

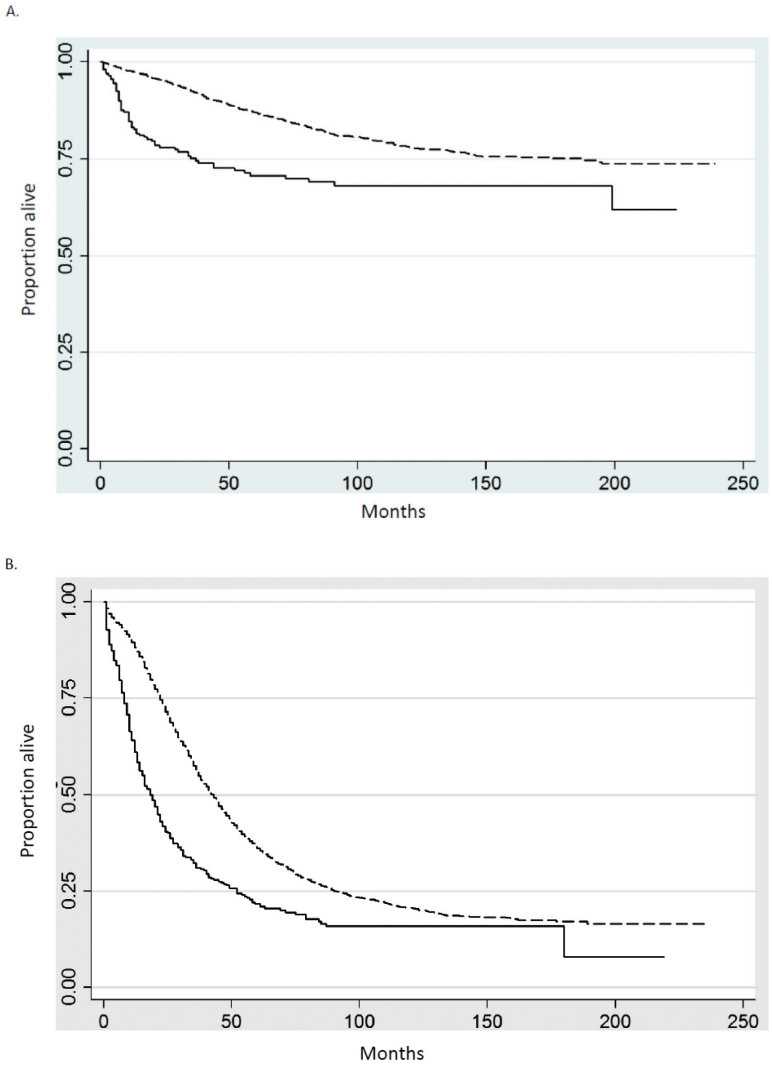

Figure 1.

Kaplan-Meier analysis of cancer-specific survival for women stratified by stage. A. Stage I (P<0.0001). B. Stage III (P<0.0001). Solid line carcinosarcoma, dashed line serous carcinoma.

Table 1

Clinical and demographic characteristics of the cohort.

	Carcinosarcoma		Serous		
	N	**(%)**	**N**	**(%)**	***P-value***
	1763		25,974		
Age (years)					<0.0001
<50	186	(10.6)	4649	(17.9)	
50-64	544	(30.9)	9566	(36.8)	
65-74	522	(29.6)	6516	(25.1)	
≥75	511	(29.0)	5243	(20.2)	
Race					0.13
White	1535	(87.1)	22,951	(88.4)	
Black	117	(6.6)	1431	(5.5)	
Other/unknown	111	(6.3)	1592	(6.1)	
Year of diagnosis					0.64
1988-1990	131	(7.4)	1685	(6.5)	
1991-1993	162	(9.2)	2294	(8.8)	
1994-1995	132	(7.5)	1762	(6.8)	
1996-1997	125	(7.1)	1868	(7.2)	
1998-1999	127	(7.2)	2018	(7.8)	
2000-2001	262	(14.9)	4104	(15.8)	
2002-2003	271	(15.4)	4010	(15.4)	
2004-2005	278	(15.8)	3988	(15.4)	
2006-2007	275	(15.6)	4245	(16.3)	
Marital status					0.002
Married	891	(50.5)	14,211	(54.7)	
Unmarried	809	(45.9)	11,028	(42.5)	
Unknown	63	(3.6)	735	(2.8)	
SEER registry					0.16
Eastern	407	(23.1)	5495	(21.2)	
Midwest	432	(24.5)	6497	(25.0)	
West	924	(52.4)	13,982	(53.8)	
Stage					<0.0001
IA	117	(6.6)	1320	(5.1)	
IB	14	(0.8)	275	(1.1)	
IC	63	(3.6)	1075	(4.1)	
INOS	18	(1.0)	107	(0.4)	
II	187	(10.6)	1850	(7.1)	
IIIA	35	(2.0)	563	(2.2)	
IIIB	49	(2.8)	936	(3.6)	
IIIC	433	(24.6)	8778	(33.8)	
IIINOS	170	(9.6)	2864	(11.0)	

	Carcinosarcoma		Serous		
	N	**(%)**	**N**	**(%)**	***P-value***
IV	398	(22.6)	7471	(28.8)	
Unknown	279	(15.8)	735	(2.8)	

Table 2

Cox proportional hazards models of cancer-specific and overall mortality.

	Cancer-specific survival	Overall survival
Histology		
Serous	Referent	Referent
Carcinosarcoma	1.79 (1.68-1.91)*	1.76 (1.65-1.87)*
Age (years)		
<50	Referent	Referent
50-64	1.36 (1.29-1.43)*	1.41 (1.34-1.49)*
65-74	1.73 (1.63-1.82)*	1.88 (1.78-1.98)*
≥75	2.39 (2.25-2.53)*	2.77 (2.62-2.93)*
Race		
White	Referent	Referent
Black	1.11 (1.03-1.20)*	1.16 (1.08-1.25)*
Other/unknown	0.96 (0.88-1.03)	0.99 (0.92-1.06)
Year of diagnosis		
1988-1990	Referent	Referent
1991-1993	0.97 (0.90-1.04)	0.94 (0.88-1.01)
1994-1995	0.90 (0.83-0.98)*	0.87 (0.81-0.94)*
1996-1997	0.89 (0.82-0.96)*	0.85 (0.79-0.92)*
1998-1999	0.90 (0.83-0.97)*	0.85 (0.79-0.92)*
2000-2001	0.89 (0.83-0.96)*	0.85 (0.80-0.91)*
2002-2003	0.82 (0.77-0.89)*	0.79 (0.74-0.85)*
2004-2005	0.81 (0.75-0.87)*	0.78 (0.73-0.84)*
2006-2007	0.76 (0.68-0.84)*	0.73 (0.66-0.80)*
Marital status		
Married	Referent	Referent
Unmarried	1.13 (1.09-1.17)*	1.16 (1.12-1.20)*
Unknown	0.99 (0.88-1.11)	1.02 (0.91-1.13)
SEER registry		
Eastern	Referent	Referent
Midwest	1.15 (1.10-1.21)*	1.14 (1.08-1.19)*
West	1.04 (1.00-1.09)	1.04 (0.99-1.08)
Stage[1]		
I	Referent	Referent
II	2.59 (2.30-2.92)*	1.91 (1.74-2.11)*
IIIA	4.02 (3.45-4.68)*	2.65 (2.32-3.03)*
IIIB	5.20 (4.57-5.91)*	3.40 (3.04-3.79)*

	Cancer-specific survival	Overall survival
IIIC	6.56 (5.95-7.23)*	4.26 (3.95-4.59)*
IIINOS	7.06 (6.36-7.84)*	4.59 (4.22-4.99)*
IV	9.18 (8.33-10.12)*	5.88 (5.45-6.34)*
Unknown	6.25 (5.41-7.22)*	4.19 (3.70-4.75)*

* P<0.05

Table 3

Five-year survival stratified by stage and histology.

	Carcinosarcoma	Serous
Stage I	65.2% (58.0-71.4%)	80.6% (78.9-82.2%)
Stage II	34.6% (27.2-42.0%)	61.7% (59.1-64.2%)
Stage IIIC	18.2% (14.5-22.4%)	33.3% (32.1-34.5%)
Stage IV	11.2% (8.1-14.9%)	20.3% (19.2-21.3%)