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ORIGINAL ARTICLE

Carcinosarcoma of the ovary compared to ovarian high-grade serous carcinoma: impact of optimal cytoreduction and standard adjuvant treatment

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Abstract

Objective The purpose of this retrospective study was to compare the prognoses of women with ovarian carcinosarcoma (OCS) who had optimal cytoreductive surgery followed by platinum plus taxane combination chemotherapy to those of women with ovarian high-grade serous carcinoma (HGSC) treated in the same manner.

Methods A multicenter, retrospective department database review was performed to identify patients with OCS at eight gynecologic oncology centers in Turkey. A total of 54 women with OCS who had undergone optimal cytoreductive surgery followed by platinum plus taxane combination chemotherapy between 1999 and 2017 were included in this case–control study. Each case was matched to two women with ovarian HGSC who had undergone optimal cytoreductive surgery followed by platinum plus taxane combination chemotherapy. The Kaplan–Meier method was used to generate survival data. Factors predictive of outcome were analysed using Cox proportional hazards models.

Results Median disease-free survival (DFS) was 29 months [95% confidence interval (CI) 0–59, standard error (SE) 15.35] versus 27 months (95% CI 22.6–31.3, SE 2.22; $p = 0.765$) and median overall survival (OS) was 62 versus 82 months ($p = 0.53$) for cases and controls, respectively. For the entire cohort, the presence of ascites [hazard ratio (HR) 2.32; 95% CI 1.02–5.25, $p = 0.04$] and platinum resistance [HR 5.05; 95% CI 2.32–11, $p < 0.001$] were found to be independent risk factors for decreased OS.

Conclusion DFS and OS rates of patients with OCS and HGSC seem to be similar whenever optimal cytoreduction is achieved and followed by platinum plus taxane combination chemotherapy.

Keywords High-grade serous ovarian cancer · Optimal cytoreductive surgery · Ovarian carcinosarcoma · Platinum · Taxane

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Introduction

Ovarian carcinosarcoma (OCS) is a rare tumor that comprises between 2 and 7.5% of all ovarian carcinomas [1]. Although OCS behaves differently from more common histological subtypes of epithelial ovarian cancer (EOC), some studies have proposed similar etiopathogenetic pathways for OCS and ovarian high-grade serous carcinoma (HGSC) [2, 3]. OCS is still being treated similarly to HGSC despite a lack of good evidence [4].

HGSC is the most common type of EOC (approximately 70–80%) and it accounts for most of the deaths due to the disease [5]. Nevertheless, stage III OCS is more common than either stage III mucinous carcinoma or stage III clear cell carcinoma of the ovary [6]. Because OCS is as frequent as other uncommon types of EOC, it is crucial to define optimal treatment of these rare tumors.

To date, only a few studies have assessed the survival of women with OCS compared to other histotypes of EOC [7–10]. All studies have demonstrated significantly decreased survival in OCS when compared to that of ovarian HGSC [7–10]. However, treatment options in these studies were heterogeneous in terms of surgery and chemotherapy [7–10]. The Surveillance, Epidemiology and End Results (SEER) database from George et al. [9] emphasized the lack of data about chemotherapy regimens and detailed data on residual disease status which seemed to be important limitations associated with that study.

Given the heterogeneity in the treatment of OCS in previous reports, we wondered whether the disease free-survival (DFS) and overall survival (OS) rates of women with OCS and HGSC are different or not when they are treated similarly. The purpose of this retrospective, collaborative study was to compare the prognoses of women with OCS who had optimal cytoreductive surgery followed by platinum plus taxane combination chemotherapy to those of women with ovarian HGSC treated in the same manner.

Materials and methods

Women with a postoperative histopathological diagnosis of OCS who had been treated between 1 January 1999 and 31 December 2016 were identified in the cancer registry databases of eight gynecologic oncology centers in Turkey. The study was approved by the Institutional Review Boards. All patients provided informed consent regarding research use of their medical information at admission. All operations were performed by gynecologic oncologists.

The inclusion criterion was optimal cytoreductive surgery plus lymph node dissection (LND) with a postoperative pathology-proven OCS diagnosis followed by a combination of platinum and taxane chemotherapy. We excluded patients who received neoadjuvant chemotherapy, women with synchronous malignancies, those with incomplete clinicopathologic records, those who did not have optimal cytoreductive surgery, and women who did not undergo LND. Women with platinum-refractory disease were also excluded. Platinum-refractory disease was defined as disease that progressed or was stable during initial platinum therapy. Optimal cytoreduction was defined as ≤1 cm maximal diameter of the largest residual tumor nodule at the completion of the primary operation.

Each case was matched to two women with ovarian HGSC for the same period. Matched cases were randomly chosen from a series of 417 women who had undergone optimal cytoreductive surgery plus LND followed by platinum and taxane combination chemotherapy. Cases and controls were matched by age at diagnosis (±10 years), stage, and year of diagnosis (±10 years). Control women were selected without having information regarding the outcome of their disease. In all patients (cases and controls), a gynecologic pathologist at each participating institution confirmed the diagnosis of OCS or HGSC. Once patients were selected, the demographic and clinical data were collected retrospectively from patient medical, surgical, pathology, and chemotherapy records. All tumors were staged according to the 1988 International Federation of Gynecology and Obstetrics (FIGO) staging system [11].

The treatment policies were decided by the attending physician or by the multidisciplinary tumor board at each participating institution. Adjuvant chemotherapy was administered to all patients with OCS or HGSC. The primary chemotherapy regimen was standard for all patients and contained paclitaxel 175 mg/m^2 plus carboplatin dosed at an area under the curve of 5 or 6 every 21 days for 6 cycles. Platinum-sensitive disease included patients who had relapsed >6 months after completing prior platinum therapy. Platinum-resistant disease included patients who had relapsed <6 months of prior platinum therapy [12, 13].

Patients returned for follow-up evaluation every 3 months for the first 2 years, every 6 months for the next 3 years, and annually thereafter. Computed tomography or magnetic resonance imaging was performed annually. Survival data were last calculated on 31st December 2016. The survival status of the patients was determined as alive or dead at the time of the last follow-up. For all study subjects with a recorded death, this was confirmed by performing a social security death index search.

After initial diagnosis, recurrence was defined as documentation of metastasis with serum CA125 measurement and imaging techniques after a DFS ≥3 months. DFS was defined as the time from surgery to the first identification of recurrence by radiologic imaging and serum CA125 measurement or death from any cause, whichever occurred first,

or the date of last contact for patients remaining alive without recurrent disease. OS was calculated as the time period between initial diagnosis of OCS or HGSC to the date of death or the last contact. Surviving patients were censored at their last known follow-up.

Survival analysis was based on the Kaplan–Meier method, and the results were compared using a log-rank test. The chi-squared test and Student's *t*-test for unpaired data were used for statistical analysis. Cox regression analysis was used to determine factors affecting survival, presented as hazard ratios (HRs) and 95% confidence interval (CI), unadjusted or adjusted for all factors. All variables with a p value <0.05 in univariate analysis were included in the multivariate analysis. All statistical analyses were performed with SPSS software version 23.0 (SPSS, Inc., Chicago, IL, USA). A p value <0.05 was considered to indicate statistical significance.

Results

One hundred and two women were identified with a postoperative pathology-proven diagnosis of primary OCS at eight participating institutions during the study period. We excluded 34 women who had suboptimal cytoreductive surgery and 6 women with platinum-refractory disease. We also excluded 5 women who received neoadjuvant chemotherapy, 1 woman with synchronous colon cancer and 2 women with incomplete medical records. Therefore, the present analysis addresses the remaining 54 women with OCS. These 54 cases were compared to 108 controls with ovarian HGSC who had optimal cytoreductive surgery plus LND followed by platinum plus taxane combination chemotherapy.

The demographic and clinical characteristics of the study population are shown in Table 1. Age, baseline serum CA125 level, tumor size, presence of ascites, positive peritoneal cytology, number of LNs removed, number of metastatic LNs, recurrence rates, platinum sensitivity, and median follow-up time were similar between the cases and controls. Patients with OCS were more likely to have unilateral tumors; 59.3% of tumors with OCS histopathology were unilateral compared to 23.1% of tumors with HGSC histopathology ($p < 0.001$). In both groups, stage I, III and IV disease was noted in 14.8, 83.3 and 1.9%, respectively.

With a median follow-up of 36 months, the median DFS for women with OCS was 29 months (95% CI 0–59, SE 15.35) compared to 27 months (95% CI 22.6–31.3, SE 2.22) in the HGSC group ($p = 0.76$) (Fig. 1). OS was also similar in both groups; median OS was 62 months in the OCS group compared to 82 months in the HGSC group ($p = 0.53$) (Fig. 2). When the 5-year OS rates were examined; similar findings were identified in the OCS and HGSC groups (54.6 vs 59.5%, respectively).

For the entire cohort, univariate analysis revealed elevated baseline serum CA125 level ($p = 0.003$), positive peritoneal cytology ($p = 0.02$), presence of ascites ($p = 0.004$), bilaterality ($p < 0.001$), retroperitoneal LN involvement ($p = 0.02$), and platinum resistance ($p < 0.001$) as significant factors for decreased DFS (Table 2). At the end of multivariate analysis, bilaterality (HR 2.7, 95% CI 1.53–4.74; $p < 0.001$) and platinum resistance (HR 29.3, 95% CI 10.9–78.94; $p < 0.001$) remained as independent risk factors for decreased DFS (Table 2). For the entire cohort, univariate analysis revealed the presence of ascites ($p = 0.01$) and platinum resistance ($p < 0.001$) as significant factors for decreased OS. At the end of multivariate analysis, the presence of ascites (HR 2.32; 95% CI 1.02–5.25, $p = 0.04$) and platinum resistance (HR 5.05; 95% CI 2.32–11, $p < 0.001$) were identified as independent predictors of decreased OS as shown in Table 3.

Finally, 54 patients with OCS were separately analyzed. In the multivariate Cox regression model, only platinum resistance (HR 66.8; 95% CI 7.36–606.73, $p < 0.001$) was identified as an independent predictor of decreased OS. The OS for women with platinum resistance was significantly shorter when compared to that of the platinum-sensitive group ($p < 0.001$) as depicted in Fig. 3. The median OS of the platinum-resistant patients was 13 months, while the median OS of the platinum-sensitive women has not been reached yet ($p < 0.001$).

There were 31 (57.4%) recurrent cases among 54 women with OCS. The distribution of recurrences were—10 cases with isolated liver metastases, 8 cases with multiple upper abdominal metastases, 2 cases with para-aortic lymph node failures, 5 cases with isolated lung metastases, 3 cases with systemic recurrences (multiple organ metastases such as liver, lung and spleen at the same time), and 3 cases with pelvic failures. Of 31 women with recurrent disease, only nine (29%) underwent secondary cytoreductive surgery (3 women with pelvic recurrence, 2 women with para-aortic lymph node failure, 2 patients with isolated resectable liver metastases and 2 women with multiple upper abdominal metastases). Four of these patients had both epithelial and sarcomatous components whereas five had only sarcomatous lesions in the metastatic sites. The remaining 22 (71%) patients with recurrence were diagnosed with imaging studies and elevated serum CA125 levels. For this reason, no data are available about the recurrence patterns (epithelial, sarcomatous or both) in those cases. At the time of reporting, of 54 women with OCS, 20 were dead of disease, 16 were alive with disease, and 18 were alive with no evidence of disease.

At the time of reporting, of 108 women with HGSC, 36 (33.3%) were dead whereas 72 (66.7%) were alive. The corresponding figures were found to be 20 (37%) and 34 (63%), respectively, in the OCS group.

Table 1 Demographic and clinical characteristics of the study population

	Ovarian carcinosarcoma ($N = 54$)	Matched high-grade serous ovarian carcinoma ($N = 108$)	p
Age, years (median)	59 (37–77)	56 (28–87)	0.3
≥ 60	25 (46.3%)	40 (37%)	
< 60	29 (53.7%)	68 (63%)	
Serum CA125 (median, IU/ml)	262 (12–2322)	508 (2–5340)	0.5
≥ 250 IU/ml	27 (50%)	62 (57.4%)	
< 250 IU/ml	21 (38.9%)	38 (35.2%)	
Unknown	6 (11.1%)	8 (7.4%)	
Bilaterality, *N*			< 0.001
Bilateral	22 (40.7%)	67 (62%)	
Unilateral	32 (59.3%)	25 (23.1%)	
Unknown	–	16 (14.8%)	
Tumor size (median, cm)	12 (3–24)	12 (2–30)	0.8
≥15 cm	18 (33.3%)	32 (29.6%)	
<15 cm	34 (63%)	66 (61.1%)	
Unknown	2 (3.7%)	10 (9.3%)	
Ascites, *N*			0.9
Present	29 (53.7%)	56 (51.9%)	
Absent	15 (27.8%)	29 (26.9%)	
Unknown	10 (18.5%)	23 (21.3%)	
Peritoneal cytology, *N*			0.6
Positive	29 (53.7%)	66 (61.1%)	
Negative	23 (42.6%)	42 (38.9%)	
Unknown	2 (3.7%)	–	
Number of LNs removed (median, range)	48.5 (9–106)	53 (23–117)	0.076
Retroperitoneal LN metastases, *N*			0.21
Present	29 (53.7%)	69 (63.9%)	
Absent	25 (46.3%)	39 (36.1%)	
Recurrence, *N*			1
Present	31 (57.4%)	62 (57.4%)	
Absent	23 (42.6%)	46 (42.6%)	
Platinum sensitivity			0.06
Present	38 (70.4%)	96 (89.9%)	
Absent	11 (20.3%)	12 (11.1%)	
Unknown	5 (9.3%)	–	
Median follow-up, months	33 (1–188)	36 (6–174)	0.75
Stage, *N*			1
I	8 (14.8%)	16 (14.8%)	
III	45 (83.3%)	90 (83.3%)	
IV	1 (1.9%)	2 (1.9%)	

N number, *LN* lymph node

Discussion

This study was conducted to assess the impact of optimal cytoreductive surgery followed by platinum plus taxane combination chemotherapy on survival outcomes in patients with OCS closely matched to a control group of patients with HGSC. To the best of our knowledge, this is the first case–control study comparing the results of optimal cytoreductive surgery followed by platinum plus taxane combination chemotherapy in OCS and HGSC. Our results clearly indicated similar DFS and OS rates in patients with OCS and HGSC when treated in the same manner.

However, we should underline some limitations associated with our study. The retrospective nature of the study cannot exclude any bias. Sarcomatous growth pattern in the tumor, which might have influenced platinum sensitivity,

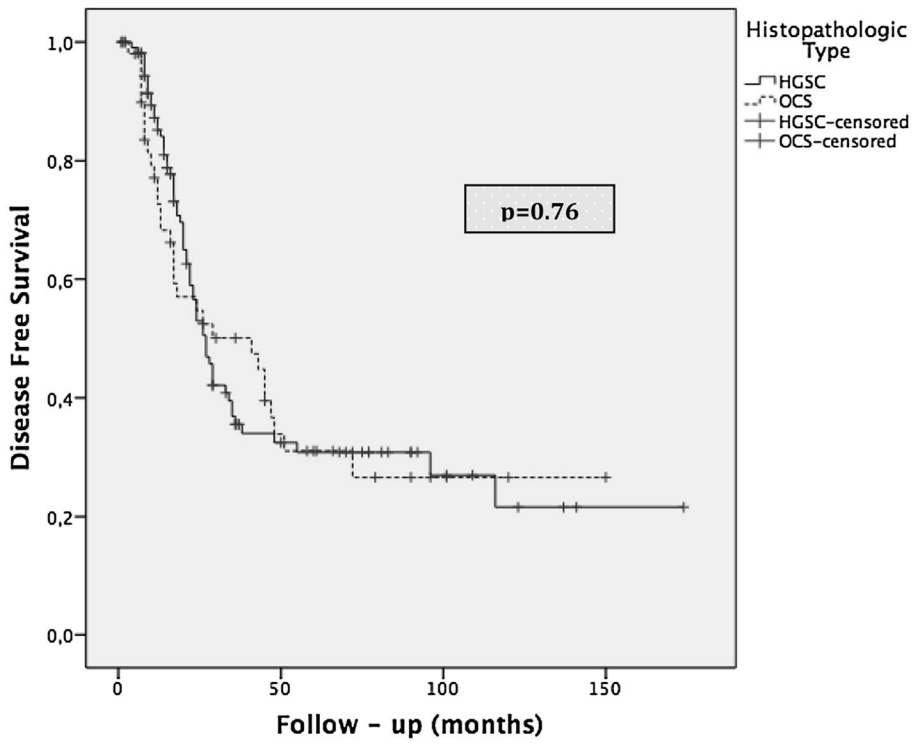

Fig. 1 Disease-free survival curve of women with ovarian carcinosarcoma ($n = 54$) compared to that of ovarian high-grade serous carcinoma ($n = 108$)

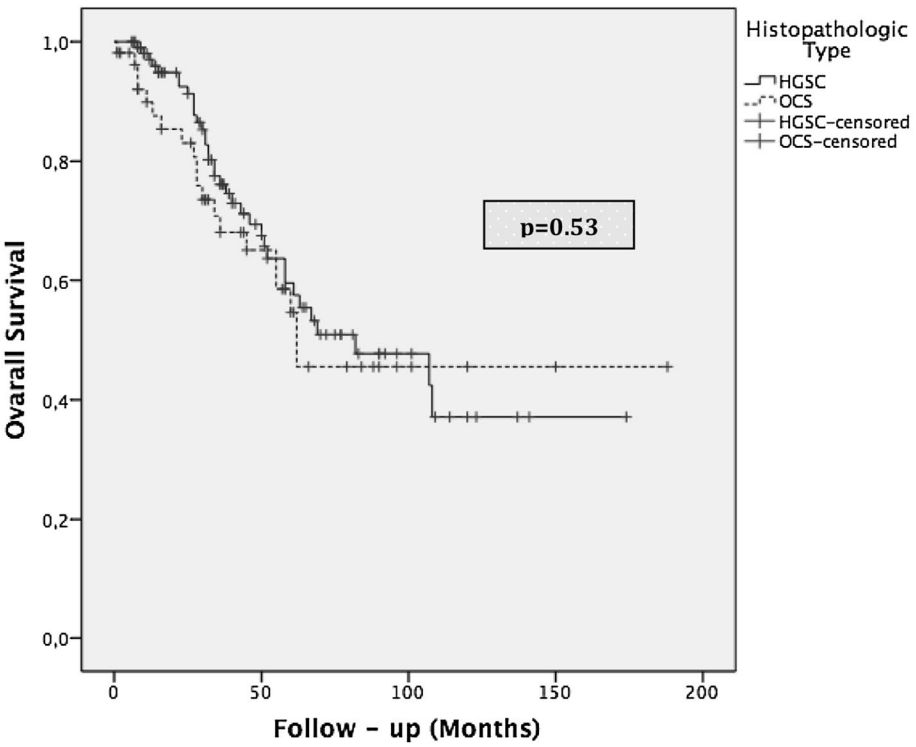

Fig. 2 Overall survival curve of women with ovarian carcinosarcoma ($n = 54$) compared to that of ovarian high-grade serous carcinoma ($n = 108$)

was not defined in the pathology reports of women with OCS. Furthermore, a small number of patients in the early stages in both groups might have influenced survival outcomes. Our study was also restricted by a lack of central pathology review. Despite the above limitations, we think that our study contributes to the limited body of knowledge on this topic.

Several authors reported that OCS histology per se is an independent prognostic factor associated with decreased OS [8, 9, 14]. Rauh-Hain et al. [8] identified OCS histology (HR

Table 2 Univariate and multivariate analyses for prognostic factors for disease-free survival in the entire cohort

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*	HR	95% CI	*p*
Age (<60 vs ≥60 years)			0.28			
Histology (OCS vs HGSC)			0.76			
CA125 (<250 vs ≥250 IU/ml)	**1.98**	**1.25–3.14**	**0.003**	1.47	0.81–2.66	0.2
Cytology (positive vs negative)	**1.64**	**1.07–2.52**	**0.02**	1.35	0.70–2.57	0.36
Ascites (present vs absent)	**2.17**	**1.28–3.68**	**0.004**	1.16	0.58–2.33	0.67
Bilaterality (bilateral vs unilateral)	**2.59**	**1.61–4.17**	**< 0.001**	**2.7**	**1.53–4.74**	**< 0.001**
Tumor size (<15 vs ≥15 cm)			0.62			
Retroperitoneal LN metastases (present vs absent)	**1.64**	**1.06–2.53**	**0.02**	1.05	0.59–1.87	0.84
Platinum status (resistant vs sensitive)	**7.11**	**3.93–12.85**	**< 0.001**	**29.33**	**10.9–78.94**	**< 0.001**

Bold values indicate statistically significant correlation

HR hazard ratio, *CI* confidence interval, *OCS* ovarian carcinosarcoma, *HGSC* high-grade serous ovarian carcinoma, *LN* lymph node

Table 3 Univariate and multivariate analyses for prognostic factors for overall survival in the entire cohort

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*	HR	95% CI	*p*
Age (<60 vs ≥60 years)			0.34			
Histology (OCS vs HGSC)			0.53			
CA125 (<250 vs ≥250 IU/ml)	1.7	0.95–3.04	0.07	1.01	0.49–2.07	0.97
Cytology (positive vs negative)			0.10			
Ascites (present vs absent)	**2.4**	**1.20–5.11**	**0.01**	**2.32**	**1.02–5.25**	**0.04**
Bilaterality (bilateral vs unilateral)			0.12			
Tumor size (<15 vs ≥15 cm)			0.42			
Retroperitoneal LN metastases (present vs absent)	1.7	0.95–3.05	0.07	1.47	0.73–2.97	0.27
Platinum status (resistant vs sensitive)	**8.2**	**3.19–21.3**	**< 0.001**	**5.05**	**2.32–11.00**	**< 0.001**

Bold values indicate statistically significant correlation

HR hazard ratio, *CI* confidence interval, *OCS* ovarian carcinosarcoma, *HGSC* high-grade serous ovarian carcinoma, *LN* lymph node

1.7; 95% CI 1.1–2.8, $p = 0.01$) as an independent predictor of decreased OS. George et al. [9] analyzed women diagnosed with OCS between 1988 and 2007 and after adjusting for other prognostic factors, women with OCS were 72% more likely to die from their cancer (HR 1.72; 95% CI 1.52–1.96) when compared to women with HGSC. A study which included a large cohort of women with OCS treated from 1988−1997 aimed to compare the survival of women with OCS to that of women with ovarian serous tumors and noted inferior survival rates for OCS patients with advanced-stage disease but found no significant difference in survival between the two histologic subtypes for early stage tumors [7]. In contrast to the previously published studies, we found that histopathologic type does not affect survival outcomes when patients were treated with optimal cytoreductive surgery followed by platinum plus taxane combination chemotherapy. We found that only platinum resistance (HR 66.86; 95% CI 7.36–606.73, $p < 0.001$) was an independent predictor of decreased OS in women with OCS.

It is well known that optimal cytoreduction is associated with improved outcomes in ovarian HGSC [15, 16]. Survival is significantly better for women who have no visible residual disease after primary surgery when compared to women with any visible residual disease. Therefore, achievement of complete surgical resection should be the goal of primary surgery whenever possible [17]. Despite the proven benefit of optimal cytoreductive surgery in ovarian HGSC, its role in the management of OCS has not been prospectively evaluated. Although some authors have reported that there is no impact of optimal cytoreductive surgery on survival in OCS [18, 19], recent studies with relatively larger numbers of cases have repeatedly identified a benefit for aggressive surgical cytoreduction in OCS [20–23].

Because of the rarity of disease, there are only four published studies that assessed the survival of women with OCS compared to that of HGSC [8–10, 14]. The largest case–control study by Rauh-Hain et al. [8] indicated that the median DFS was 11 months for women with OCS compared to

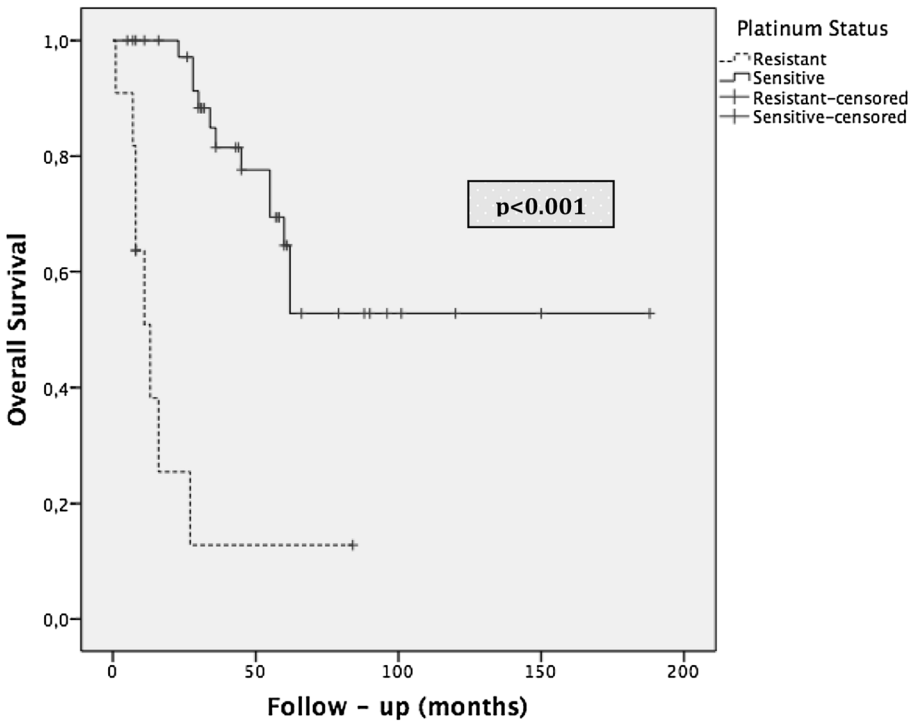

Fig. 3 Overall survival curve of women with platinum-sensitive disease ($n = 38$) compared to that of women with platinum-resistant disease ($n = 11$) diagnosed with ovarian carcinosarcoma

16 months among controls with HGSC. Median OS was also significantly decreased for women with OCS when compared to that of HGSC (24 vs 41 months) [8]. The SEER database from George et al. [9] analyzed 27,737 women (1763 with OCS vs 25,974 with HGSC). The authors reported that OCS was associated with decreased survival compared to HGSC for both early and advanced-stage disease. In another SEER analysis of 1334 women with OCS, Rauh-Hain et al. [10] also documented worsened cancer-specific survival for patients with OCS compared to HGSC for stages I–IV disease. In a recent National Cancer Database analysis by the same author, median OS was 21.6 versus 50.6 months for women with OCS and HGSC, respectively [14]. However, the treatment policies for patients with OCS and HGSC were not standardized in the above-mentioned studies. Based on standard treatment policies in both groups, we demonstrated similar median OS in women with OCS and ovarian HGSC (62 vs 82 months, respectively). Therefore, we suggest that a more aggressive initial surgical attempt as well as adjuvant platinum plus taxane combination chemotherapy might have led to better survival outcomes for OCS in the current study when compared with previous reports.

There is currently no evidence to determine whether any form of chemotherapy is better or worse for prolonging survival in OCS. A clinical practice guideline in 2010 by the European Society of Medical Oncology (ESMO) expressed that there is still a dilemma about chemotherapy regimens used to treat OCS [24]. Although platinum plus taxane combination protocol is the most preferred chemotherapy regimen [20], there is no randomized controlled trial to recommend this treatment as a routine practice [4]. Therefore the treatment of OCS is still primarily based on reported experience from retrospective studies [20].

One of the largest retrospective series published by Rauh-Hain et al. [8] reported a 62% overall response rate to carboplatin and paclitaxel combination chemotherapy among 50 patients with OCS. The rate of achieving optimal cytoreduction was 78.7% in that study. Duska et al. [25] reported a response rate of 72% in 28 patients with OCS. Studies have shown that the overall response rate to platinum-based chemotherapy for patients with OCS varies between 25 and 70% [8, 26, 27]. Additionally, a prospective Gynecologic Oncology Group (GOG) study analyzed cisplatin as an active agent in OCS [28]. Tate Thigpen et al. [28] concluded that platinum response in OCS is lower than for epithelial ovarian tumors, but it can be considered as an active initial therapy for OCS. Furthermore, there is still an on-going GOG phase 3 (GOG 261) trial comparing carboplatin plus paclitaxel regimen with ifosfamide plus paclitaxel [29]. Even though the GOG 261 study has recently stopped enrolling patients, the results of this trial are still expected to reach a conclusion about the standard adjuvant chemotherapy regimen in OCS.

The strengths of the current study lie in its multicentric nature with a large number of patients with OCS. Our study has the advantage that its time period encompasses the past 17 years, during which all patients were treated with the platinum plus taxane combination regimen. In addition, most

of the patients in the current study underwent systematic LND whereas all patients had optimal cytoreductive surgery. These factors seem to reduce the possibility of confounding, and enhance the reliability of the prognostic effects that have been estimated.

The current study is one of the largest retrospective series of patients with OCS histology that addresses the clinical outcome of patients. Our findings have some important clinical implications. First, our data indicated that the DFS and OS rates of women with OCS and HGSC seem to be similar when the patients are treated with optimal cytoreductive surgery followed by platinum plus taxane combination chemotherapy. Second, platinum resistance seems to be an independent prognostic factor for decreased OS in women with OCS. This case–control study indicated that OCS when optimally debulked is almost as responsive as HGSC to platinum plus taxane combination chemotherapy. Therefore, we suggest that the principal treatment guidelines be identical for patients with either diagnosis.

In conclusion, the DFS and OS rates of patients with OCS and ovarian HGSC seem to be similar whenever optimal cytoreduction is achieved and is followed by platinum plus taxane combination chemotherapy. Clinicians should try to perform optimal cytoreductive surgery and prescribe adjuvant platinum plus taxane combination chemotherapy in OCS in order to achieve similar oncologic outcomes with ovarian HGSC. However, we should emphasize that our findings should be validated in further studies involving a larger number of patients.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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