ORIGINAL RESEARCH

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# Optimal Cytoreduction is an Independent Prognostic Factor in Ovarian Carcinosarcoma: A Turkish Gynecologic Oncology Group Study

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**ABSTRACT Objective:** To determine prognostic factors for women with ovarian carcinosarcoma (OCS). **Material and Methods:** A multicenter, retrospective department database review was performed to identify patients with OCS at eight gynecologic oncology centers in Turkey. Demographic, clinicopathological, and survival data were collected. **Results:** We identified 94 patients with OCS. The median age was 60.0 years (range, 31-78), and the median follow-up duration was 36.0 months (range, 4-188). After primary cytoreductive surgery, 61 (64.9%) patients had ≤1 cm of residual disease (optimal debulking), whereas 33 (35.1%) had >1 cm of residual disease (suboptimal debulking). For the entire cohort, the 5-year progression free survival (PFS) rate was 25.2%, whereas the 5-year overall survival (OS) rate was 49.4%. Women with optimal cytoreduction had a median PFS of 41.0 months (95% Confidence Interval [CI]: 19.71-62.28, Standard Error [SE]: 10.86) compared with women with suboptimal cytoreduction who had a median PFS of 15.0 months (95% CI: 8.79-21.21, SE: 3.16; p=0.011). The 5 year OS rate for women with optimal cytoreduction was significantly higher than that of women with suboptimal debulking (57.6% vs. 33.9%; p=0.005). Positive peritoneal cytology (hazard ratio [H]: 2.35, 95% CI: 1.19-4.63; p=0.013) and suboptimal cytoreduction (H: 2.61, 95% CI: 1.32-4.99; p=0.004) were independent risk factors for decreased OS. **Conclusion:** Suboptimal cytoreduction seems to be an independent prognostic factor for decreased OS in women with OCS.

**Keywords:** Cytoreductive surgery; ovarian carcinosarcoma; overall survival

Ovarian carcinosarcoma (OCS), accounting for only 1-4% of all ovarian malignancies, is a rare neoplasm characterized by sarcomatous and epithelial elements.[1-3] Some authors have proposed that OCSs originate from the müllerian epithelium and then differentiation/metaplasia to a sarcomatous structure, supporting the hypothesis that OCS is a metaplastic epithelial carcinoma.[4-6] OCS is highly aggressive and has a poor prognosis, presenting with a disease that has spread beyond the ovary in up to 90% of cases at

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the time of diagnosis.[7,8] It is currently being treated similarly to epithelial ovarian cancer (EOC) despite a lack of good evidence.[9]

The disease's rarity seems to be the major barrier for designing proper clinical studies providing evidence for improved treatment options.[9] A Gynecologic Oncology Group (GOG) study could only accrue 136 patients with OCS over a span of 20 years.[10] Because of the rarity, the management of OCS has frequently been similar to that of EOC. Anecdotal experience or retrospective studies with small patient populations are thus important.[11]

Several factors associated with poor prognosis have been described, such as older age, advanced stage at presentation, suboptimal surgical resection and non-paclitaxel/platinum chemotherapy.[2,12-15] Most of the retrospective studies have supported the role of cytoreductive surgery (CRS) in these tumors, with optimal debulking improving survival.[13-19] However, no improvement in survival rates has been observed during the past few decades despite integrating aggressive CRS and platinum-based chemotherapy into the treatment.

Because of the rare occurrence of OCS, the sample size is often a limitation for studies investigating outcomes in OCS.[20] It is often impossible to present a large series of patients with OCS; therefore, our knowledge on how to treat this disease is inadequate.[21] In addition, the prognostic factors associated with OCS remain debatable.[22] Prospective clinical studies are very difficult in this disease, and the lack of a large data collection is another problem.[23] Therefore, we focused on combining multi-institutional datasets of women with OCS. In this retrospective study, we determined the prognostic factors in OCS using a multicenter database.

## MATERIAL AND METHODS

Patients with a postoperative pathological diagnosis of OCS who had been treated with upfront surgery between 1 January 2000 and 31 December 2017 were identified in the institutional databases of eight gynecologic oncology departments in Turkey. The Institutional Review Board of Zekai Tahir Burak Women's Health Training and Research Hospital, Faculty of Medicine, University of Health Sciences, Ankara, Turkey, (IRB Approval Number: 15, Date: 1 March 2017) approved the study. Informed consent regarding the research use of patient medical information was obtained from each patient at admission.

The inclusion criterion was postoperative pathology-proven carcinosarcoma of the ovary. Patients who received neoadjuvant chemotherapy, women with incomplete medical records, and those with synchronous malignancies were excluded. We also excluded patients who died within 30 days of surgery due to operative complications or nondisease-related causes.

For each case, the diagnosis of OCS was established via conventional microscopy by an experienced gynecologic pathologist at each participating institution. Central pathology review was not available. However, particularly, in the case of poorly differentiated tumors with indeterminate morphology, the diagnosis was confirmed by immunohistochemistry (IHC) with the help of cytokeratin and vimentin staining. IHC staining for cytokeratin typically demonstrated diffuse strong staining of the epithelial component, and staining with vimentin demonstrated rare staining of the epithelial component and diffuse strong staining of the mesenchymal component.[24] Classification based on the origin of the mesenchymal tissue (homologous vs. heterologous) was not used.

All clinicopathologic data, i.e., demographic characteristics, preoperative serum cancer antigen 125 (CA 125) level, the date and type of surgical procedure, tumor size, presence or absence of ascites, tumor bilaterality, the size of residual tumor (RD) after surgery, disease stage, type of first-line chemotherapy, the date, and site of recurrence, treatment after recurrence, the date of last medical examination and the date of death were collected from the medical, surgical, pathology, and chemotherapy reports of the patients. The 1988 International Federation of Gynecology and Obstetrics classification system was used for staging purposes.[25] Some of the patients in this study were within the context of one of our previous studies.[26]

Gynecologic oncologists performed all operations for achieving optimal cytoreduction. RD status after primary CRS was defined as optimal (no gross residual disease or maximal diameter of the largest residual tumor nodule ≤1 cm at the completion of the primary operation) and suboptimal (>1 cm of RD) for statistical purposes. Retroperitoneal lymph node (LN) dissection was performed after the completion of intraperitoneal debulking procedures.

All patients received adjuvant chemotherapy regardless of the disease stage. Patients were followed-up every three months for the first two years, biannually for the next three years, and annually thereafter. All patients had computed tomography or magnetic resonance imaging annually. The survival status was determined as alive or dead at the time of the final follow-up. For all nonsurvivors, the event of death was confirmed through a social security death index search.

After initial diagnosis, progressive disease was defined in cases of >25% increase of measurable lesions or occurrence of new lesions. Progression-free survival (PFS) was defined as the duration in months between the date of surgery and the date of first recurrence or progression by imaging or the date of death from any cause, whichever occurred first, or the date of the last visit for patients alive without recurrence. Overall survival (OS) was defined as the duration in months between the initial diagnosis of OCS and the date of death from any cause or the date of last contact. Surviving patients were censored at their last known follow-up.

Survival curves were generated using Kaplan-Meier plots, and the log-rank test was used for survival comparisons. The chi-squared test was used for nominal variables. Student's *t*-test and the Mann-Whitney U test were used for continuous variables with and without normal distribution, respectively. Cox logistic regression models were used to determine co-variates affecting survival, and presented as hazard ratios (HRs) and 95% confidence interval (CI), unadjusted or adjusted, for all factors. All variables with a *p*-value of <0.05 in the univariate analysis were included in the multivariate analysis. SPSS software (version 23.0, IBM Corp., Armonk, NY, USA) was used for performing all statistical analyses. A *p*-value of <0.05 was considered statistically significant.

## RESULTS

One hundred eleven women underwent primary surgical treatment for OCS at eight gynecologic cancer centers during the study period. We excluded six patients who received neoadjuvant chemotherapy, eight who died within 30 days of surgery because of operative complications or nondisease-related causes, one with synchronous colon cancer, and two with incomplete medical records. Therefore, the present analysis addresses the remaining 94 women with OCS. The patient includes tumor characteristics and is shown in Table 1.

The median age was 60.0 years (range, 31-78 years), and the median follow-up duration was 36.0 months (range, 4-188 months). All patients underwent a hysterectomy and bilateral salphingo-oophorectomy. Sixty-two women (65.9%) underwent omentectomy, 49 (52.1%) appendectomy, 9 (9.5%) bowel resection, and 5 (5.3%) colostomy. Fifteen women (22.7%) underwent an upper abdominal surgery, with 9 (60%) having diaphragm stripping and 6 (40%) having a splenectomy.

After primary CRS, 53 (56.4%) had only a microscopic disease, whereas 8 (8.5%) had RD ≤1 cm but with the residual macroscopic disease. However, 33 patients (35.1%) received suboptimal debulking (RD >1 cm). For statistical purposes, we divided the patients into two groups: optimal debulking (RD ≤1 cm) (n=61) and suboptimal debulking (RD >1 cm) (n=33). Clinicopathologic characteristics were not significantly different among the patients receiving optimal or suboptimal CRS (Table 2).

For 61 patients (64.9%) undergoing lymphadenectomy, the median number of total LNs harvested was 48.0 (range, 9-97). The median number of pelvic and para-aortic LNs removed was 30.0 (range, 5-59) and 18.0 (range, 2-58), respectively. Retroperitoneal LN metastases were detected in 32 patients (52.4%). Twenty-two patients had pelvic LN involvement (36.1%), and 20 had para-aortic

**TABLE 1:** Baseline characteristics of the patients.

| Characteristic | Values |
|---|---|
| Age, years (median) | 60 (31-78) |
| Menopausal status, N | |
| Postmenopausal | 75 (79.8%) |
| Premenopausal | 19 (20.2%) |
| Serum CA 125 (median, IU/mL) | 253 (8-2327) |
| Bilaterality | |
| Present | 37 (39.4%) |
| Absent | 57 (60.6%) |
| Tumor size (mean, cm) | 12.1±4.6 |
| <15 cm | 61 (64.9%) |
| ≥15 cm | 33 (35.1%) |
| Ascites, N | |
| Present | 55 (58.5%) |
| Absent | 39 (41.5%) |
| Peritoneal cytology, N | |
| Positive | 52 (55.3%) |
| Negative | 42 (44.7%) |
| Cytoreduction | |
| Maximal | 53 (56.4%) |
| Optimal | 8 (8.5%) |
| Suboptimal | 33 (35.1%) |
| LND status, N | |
| Performed | 61 (64.9%) |
| Not performed | 33 (35.1%) |
| Number of LNs removed (median) | 48.0 (9-97) |
| Number of pelvic LNs removed (median) | 30.0 (5-59) |
| Number of para-aortic LNs removed (median) | 18.0 (2-58) |
| Retroperitoneal LN metastases, N | |
| Present | 32 (52.4%) |
| Absent | 29 (47.6%) |
| Stage, n | |
| IA | 5 (5.3%) |
| IC | 6 (6.4%) |
| IIIA | 2 (2.1%) |
| IIIB | 1 (1.1%) |
| IIIC | 65 (69.1%) |
| IV | 3 (3.2%) |
| Not properly staged | 12 (12.8%) |

N: Number; LND: Lymph node dissection; LN: Lymph node.

LN involvement (32.8%). Isolated pelvic LN metastasis was detected in 12 women (19.7%). Interestingly, ten patients had isolated para-aortic LN metastasis (16.4%). Ten patients had pelvic and para-aortic LN metastases at the same time (16.4%).

All patients received adjuvant chemotherapy. Sixty-six patients (70.2%) received paclitaxel plus carboplatin. Twelve patients (12.7%) received ifosfamide with cisplatin, 10 (10.6%) received PAC regimen (cisplatin, doxorubicin, cyclophosphamide), and 6 (6.4%) received carboplatin plus doxorubicin.

In the entire cohort, the number of total recurrences was 44 (46.8%). The median time to recurrence was 17.0 months (95% CI: 15.37-18.62, standard error [SE]: 0.82). We observed 10 (22.7%) pelvic recurrences, 21 (47.7%) abdominal failures, and 13 (29.6%) systemic recurrences. Of the 44 patients with recurrence, 25 (56.8%) had secondary cytoreduction followed by systemic chemotherapy. The remaining 19 women were treated only with salvage chemotherapy.

For the entire cohort, the 5-year PFS rate was 25.2%, whereas the 5-year OS rate was 49.4%. The median PFS varied significantly among patients who received optimal and suboptimal CRS. Women with optimal cytoreduction had a median PFS of 41.0 months (95% CI 19.71-62.28, SE: 10.86) compared with women with suboptimal cytoreduction who had a median PFS of 15.0 months of (95% CI: 8.79-21.21, SE: 3.16; p=0.011) (Figure 1). The 5-year OS rate for women with optimal cytoreduction was significantly greater than that for women with suboptimal debulking (57.6% vs. 33.9%; p=0.005) (Figure 2).

Univariate analysis revealed postmenopausal status (p=0.02), positive peritoneal cytology (p=0.007), bilaterality (p=0.001), and suboptimal debulking (p=0.01) as significant factors for decreased PFS (Table 3). In multivariate analysis, bilaterality (H: 2.07, 95% CI: 1.22-3.52; p=0.007) and suboptimal debulking (H: 1.8, 95% CI: 1.07-3.02; p=0.027) remained as independent prognostic factors for decreased PFS (Table 3).

Univariate analysis revealed positive peritoneal cytology (p=0.02) and suboptimal debulking (p=0.005) as significant factors for decreased OS (Table 4). Positive peritoneal cytology (H: 2.35, 95% CI: 1.19-4.63; p=0.013) and suboptimal cytoreduction (H: 2.61, 95% CI: 1.32-4.99; p=0.004) were independent prognostic factors for decreased OS in

**TABLE 2:** Baseline characteristics of the patients with respect to cytoreduction status.

| Characteristics | Optimal CRS (n=61) | Suboptimal CRS (n=33) | p value |
|---|---|---|---|
| Age, years (median) | 59 (31-77) | 63.0 (33-78) | 0.17 |
| <60 | 32/61 (52.5%) | 13/33 (39.4%) | 0.22 |
| ≥60 | 29/61 (47.5%) | 20/33 (60.4%) | |
| Menopausal status, N | | | 0.36 |
| Postmenopausal | 47/61 (77.0 %) | 28/33 (84.8%) | |
| Premenopausal | 14/61 (23.0%) | 5/33 (15.2%) | |
| Serum CA 125 (median, IU/mL) | 257 (9-2322) | 250 (8-2327) | 0.58 |
| ≥250 IU/mL | 32/61 (52.5%) | 18/33 (54.5%) | 0.84 |
| <250 IU/mL | 29/61 (47.5%) | 15/33 (45.5%) | |
| Bilaterality | | | 0.66 |
| Present | 25/61 (41.0%) | 12/33 (36.4%) | |
| Absent | 36/61 (59.0%) | 21/33 (63.6%) | |
| Tumor size (median, cm) | 12 (2.5-24) | 11 (3.5-20) | 0.37 |
| <15 cm | 39/61 (63.9%) | 22/33 (66.7%) | 0.79 |
| ≥15 cm | 22/61 (36.1%) | 11/33 (33.3%) | |
| Ascites, n | | | 0.89 |
| Present | 36/61 (59.0%) | 19/33 (57.6%) | |
| Absent | 25/61 (41.0%) | 14/33 (42.4%) | |
| Peritoneal cytology, n | | | 0.74 |
| Positive | 33/61 (54.1%) | 19/33 (57.6%) | |
| Negative | 28/61 (45.9%) | 14/33 (42.4%) | |
| Stage, n | | | 0.16 |
| IA | 5 (8.2%) | - | |
| IC | 6 (9.8%) | - | |
| IIIA | 2 (3.3%) | - | |
| IIIB | 1 (1.6%) | - | |
| IIIC | 46 (75.4%) | 19 (57.6%) | |
| IV | 1 (1.6%) | 2 (6.1%) | |
| Not properly staged | - | 12 (36.4%) | |

N: Number; LND: Lymph node dissection; LN: Lymph node.

multivariate analysis (Table 4). At the time of reporting, of the 94 patients with OCS, 37 (39.4%) were alive with no evidence of OCS, 18 (19.1%) were alive with OCS, and 39 (41.5%) died because of OCS.

## DISCUSSION

Our results indicate that women with OCS undergoing optimal CRS had a median PFS of 41.0 months compared with women with OCS receiving suboptimal debulking who had a median PFS of 15.0 months (p=0.01). Tumor bilaterality (H: 2.07, 95% CI: 1.22-3.52; p=0.007) and suboptimal debulking (H: 1.8, 95% CI: 1.07-3.02; p=0.027) were independent prognostic factors for decreased PFS, whereas positive peritoneal cytology (H: 2.35, 95% CI: 1.19-4.63; p=0.013) and suboptimal debulking (H: 2.61, 95% CI: 1.32-4.99; p=0.004) independently increased the risk of death.

Surgery for OCS is difficult and associated with high morbidity.[21,27] OCS is typically a very large tumor with massive areas of hemorrhage and necrosis in addition to hemorrhagic ascites in some cases.[8,23] Tumors tend to be fleshy and hemorrhagic, with heavy blood loss happening commonly.[1] Thus, the achievement of optimal CRS is often troublesome because of widespread metastases at the time of surgery and aggressive tumor growth.[21] In this study, the

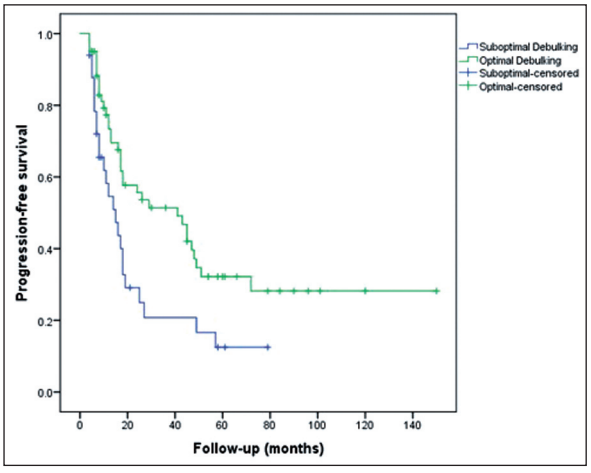


**FIGURE 1:** Kaplan-Meier plots of ovarian carcinosarcoma patients receiving optimal (n=61) versus suboptimal (n=33) cytoreduction with regard to progression-free survival.

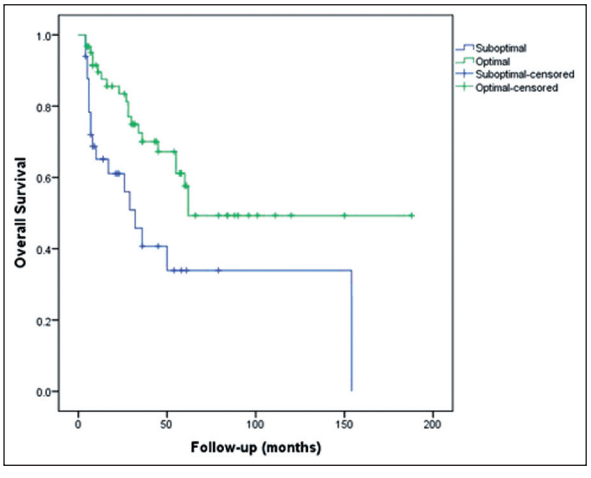


**FIGURE 2:** Kaplan-Meier plots of ovarian carcinosarcoma patients receiving optimal (n=61) versus suboptimal (n=33) cytoreduction with regard to overall survival.

rate of achieving optimal cytoreduction was 64.9%. Two previous studies including <50 patients have reported the rate to be 57.0% and 78.7%.[13,28] Women with OCS should undergo CRS by experienced gynecologic oncologists in highly specialized centers since the risk of complications may be higher in OCS than in EOC.[29]

Although recent studies have repeatedly identified a benefit for aggressive cytoreduction, Jernigan et al. emphasized that a cause and effect relationship between cytoreduction and survival cannot be shown on the basis of data from small, retrospective studies.[13,15,18,19] Garg et al. reported that retrospective studies where a large proportion of patients did not undergo a complete staging procedure should be interpreted cautiously because up to 30% of patients with apparently early OCS would be upstaged to regional or distant disease after a complete surgical procedure.[20] Thus, evaluating OCS in patients who have been surgically staged becomes important.[20] In this study, the rate of surgical staging was 64.9% (61/94) with all patients receiving LN dissection in the optimal debulking group. Among patients receiving comprehensive surgical staging, 53% had a positive nodal status with 16.7% of isolated para-aortic LN involvement. Cumulative retrospective data support the benefit of an optimal surgical cytoreduction with total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, abdominal fluid aspiration, pelvic and para-aortic lymphadenectomy, and tumor debulking.[8]

Using the Surveillance, Epidemiology and End Results database, Garg et al. reported on 924 women with OCS defined during a period of 18 years. Age, disease stage, and lymphadenectomy were significant predictors of survival.[20] Chun et al. reported that suboptimal debulking and non-paclitaxel/platinum chemotherapy were independent prognostic factors for decreased OS.[15] Jernigan et al. reported that age, stage, and cytoreduction to no gross RD were associated with improved survival in a series of 47 women with OCS.[18] Complete cytoreduction, advanced age, and the use of adjuvant chemotherapy have been reported as prognostic factors in OCS in another previous study including 50 patients.[13]

Compared with previous studies, our study confirmed the importance of optimal CRS for improving PFS and OS with a larger sample size (n=94). The findings of our study seem to define bilaterality as an independent prognostic factor for decreased PFS and positive peritoneal cytology as an independent prognostic factor for decreased OS. However, survival data from previous studies and this study must be carefully interpreted as surgical approach and available chemotherapeutic regimens dramatically change over the span of study inclusion dates, including several decades.[30]

There is no current evidence to guide clinical practice with regard to various adjuvant treatment regimens in OCS.[9] Platinum-based chemotherapy is the mainstay of adjuvant systemic treatment.[31] All

**TABLE 3:** Univariate and multivariate analyses for progression-free survival in women with ovarian carcinosarcoma.

| | Univariate Analysis | Multivariate Analysis | | |
|---|---|---|---|---|
| **Variable** | **P** | **H** | **95% CI** | **p** |
| Age (<60 vs. ≥60) | 0.22 | | | |
| Menopausal Status (pre. vs. post.) | 0.021 | | | |
| CA 125 (<250 vs ≥250) | 0.91 | | | |
| Tumor Size (<15 cm vs. ≥15 cm) | 0.35 | | | |
| Positive peritoneal cytology | 0.007 | | | |
| Ascites (Absent vs. Present) | 0.083 | | | |
| Bilaterality | 0.001 | 2.07 | 1.224-3.528 | 0.007 |
| Cytoreduction (optimal vs. suboptimal) | 0.011 | 1.8 | 1.071-3.028 | 0.027 |

Pre: Premenopausal; Post: Postmenopausal; CI: Confidence Interval; H: Hazard ratio.

**TABLE 4:** Univariate and multivariate analyses for overall survival in women with ovarian carcinosarcoma.

| | Univariate Analysis | Multivariate Analysis | | |
|---|---|---|---|---|
| **Variable** | **P** | **H** | **95% CI** | **p** |
| Age (<60 vs. ≥ 60) | 0.57 | | | |
| Menopausal Status (pre. vs. post.) | 0.33 | | | |
| CA 125 (<250 vs. ≥250) | 0.87 | | | |
| Tumor Size (<15 cm vs. ≥15 cm) | 0.69 | | | |
| Positive peritoneal cytology | 0.02 | | | |
| Ascites (absent vs. present) | 0.25 | | | |
| Bilaterality | 0.75 | 2.35 | 1.194-4.639 | 0.013 |
| Cytoreduction (optimal vs. suboptimal) | 0.005 | 2.61 | 1.321-4.946 | 0.004 |

Pre: Premenopausal; Post: Postmenopausal; CI: Confidence Interval; H: Hazard ratio.

women included in the current study received platinum-based chemotherapy as the first-line treatment postoperatively. Although the carboplatin-paclitaxel combination is often used as a standard first-line treatment for OCS, the largest study of patients treated postoperatively with carboplatin-paclitaxel included only 54 patients.[26,32] Paclitaxel or ifosfamide should be added to platinum in first-line treatment according to patient factors and associated toxicities.[31] However, the GOG has recently stopped enrolling patients with uterine and ovarian carcinosarcoma in a phase III trial (GOG 261) to compare the paclitaxel+carboplatin regimen with the ifosfamide+paclitaxel regimen.[33] The results of this trial should be awaited to reach a conclusion about an adjuvant chemotherapy regimen in OCS.

Limitations of our study include the retrospective study design and the inherent drawbacks common to all retrospective reviews. The data were gathered from eight centers using different chemotherapy protocols. The various chemotherapy regimens were not evaluated and their effects might have contributed to the observed differences in survival. The lack of a central pathology review is another limitation. A centralized pathology review is important in rare tumors and would definitely improve the impact of our findings. However, the major strength of our study is its multicenter nature with a large number of patients with OCS.

## CONCLUSION

Positive peritoneal cytology and suboptimal debulking are independent prognostic factors for decreased OS in women with OCS. The cytoreductive surgical effort seems to be the only modifiable feature for improving survival in those women.

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*During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.*

### *Conflict of Interest*

*No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.*

### *Authorship Contributions*

***Idea/Concept:*** *Ali Ayhan, İrfan Çiçin;* ***Design:*** *Ali Ayhan, İrfan Çiçin;* ***Control/Supervision:*** *İrfan Çiçin, Ali Gökyer;* ***Data Collection and/or Processing:*** *Ali Ayhan, İrfan Çiçin, Mustafa Erkan Sarı, Ahmet Taner Turan, Salih Taşkın, Kemal Güngördük, Özgur Akbayır, Pınar Saip, Hanifi Şahin, Gonca Çoban, İlker Selçuk, Gökhan Tulunay, Mehmet Mutlu Meydanlı,* ***Analysis and/or Interpretation:*** *Ali Ayhan, İrfan Çiçin;* ***Literature Review:*** *Ali Ayhan, İrfan Çiçin;* ***Writing the Article:*** *Ali Ayhan, İrfan Çiçin, Ali Gökyer;* ***Critical Review:*** *Ali Ayhan, İrfan Çiçin, Ali Gökyer;****References and Fundings:*** *Ali Ayhan, İrfan Çiçin, Ali Gökyer;****Materials:*** *İrfan Çiçin, Ali Gökyer, Mustafa Erkan Sarı.*

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