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Radical surgical cytoreduction in the treatment of ovarian carcinosarcoma[★]

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Abstract

Objective.—Carcinosarcomas are rare and aggressive ovarian malignancies. Treatment recommendations, which include surgical cytoreduction followed by platinum based chemotherapy, have been based on small amounts of retrospective data or extrapolated from experience with high-grade epithelial ovarian adenocarcinoma. Our objective was to determine the effects of radical primary cytoreduction on progression-free survival (PFS) and overall survival (OS).

Methods.—Following IRB approval, records of women with ovarian carcinosarcomas diagnosed between 2000 and 2012 at our institution were reviewed. Demographics, tumor characteristics, treatments, PFS, and OS were collected. Patients were divided into three groups based on the amount of residual disease: N1 cm of disease, 1 cm of disease, or no visible disease. Chi-square and student's t-test were used to compare variables among groups. Kaplan–Meier survival curves were generated and compared with the log-rank test.

Results.—51 patients with ovarian carcinosarcoma were identified and all underwent primary cytoreductive surgery. Following surgical cytoreduction, 18 patients (35%) had no visible disease, 20 (39%) had 1 cm of disease, and 13 (25%) had >1 cm of residual disease. Median PFS varied significantly among groups: 29 vs. 21 vs. 2 months ($p = 0.036$) as did median OS: 57 vs. 32 vs. 11 months ($p = 0.015$). When patients with stage 3 disease were analyzed separately, median OS still varied significantly among groups: 57 versus 31 versus 3 months ($p = 0.009$).

Conclusion.—Degree of surgical cytoreduction appears to correlate with PFS and OS. Radical surgery resulting in no visible disease is recommended for the upfront surgical treatment of ovarian carcinosarcoma.

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Conflict of interest

The authors declare that there are no conflicts of interest.

Disclosures

None.

Keywords

Ovarian carcinosarcoma; Optimal cytoreduction

Introduction

Carcinosarcomas are rare and aggressive gynecologic malignancies. Also known as malignant mixed müllerian tumors, they can be found throughout the female reproductive tract including the uterus, cervix, and vagina. Ovarian carcinosarcomas (OCS) account for 1–4% of all ovarian malignancies, and median survival is reported to be less than 18 months [1–3]. Most patients are diagnosed between the ages of 50 and 70, and 75% present at stage 3 or 4 [4,5]. The most significant predictor of survival is the stage at diagnosis [1].

Carcinosarcomas are defined histologically as having a carcinomatous and a sarcomatous component. They are further classified as homologous or heterologous depending on whether or not the sarcomatous element is made up of tissues commonly found in the uterus or ovary. Though the homologous versus heterologous classification was once thought to be a significant prognostic factor, recent data have shown that this is not the case [2,3,5].

Due to the rarity of the tumor, there is limited data to guide treatment for OCS, and recommendations thus far have been largely based on retrospective reviews or extrapolated from experience with epithelial ovarian carcinoma. Therefore, primary treatment typically follows the paradigm of treatment for epithelial ovarian cancer, which includes cytoreductive surgery followed by chemotherapy [6]. It has been well established that survival in epithelial ovarian cancer is strongly correlated to the degree of surgical cytoreduction [7]. However, in order to remove as much tumor as possible, patients must undergo longer and more extensive procedures, and typically have higher postoperative morbidity [8,9]. For this reason it is important to establish whether or not a similar correlation exists between survival and cytoreductive status in OCS. Therefore, the objective of this study was to determine the impact of radical primary cytoreduction on progression-free survival (PFS) and overall survival (OS) in OCS.

Methods

Following approval from the Institutional Review Board, a cohort of women who were treated for OCS at the University of Alabama at Birmingham (UAB) between 2000 and 2012 were identified using the Institutional Tumor Registry. The diagnosis of OCS was confirmed by gynecologic pathologists, and all patients were treated by fellowship-trained gynecologic oncologists. For this retrospective cohort study, exposure was defined as extent of cytoreduction. Based on the paradigm used for treatment of epithelial ovarian cancer, patients were separated based on extent of surgical cytoreduction into three cohorts: no visible disease, less than or equal to 1 cm of residual disease, or greater than 1 cm of residual disease.

Extent of residual disease, demographic information, adjuvant treatment regimens, and survival data were extracted from patient charts. Date of death was confirmed with the

Social Security Death Index. Chi-square and student's t-test were used to compare variables among groups. Kaplan–Meier survival curves were generated and survival differences were quantified using the log-rank test. PFS was calculated as the time between the date of diagnosis and the date of recurrence, identified by either physical exam or imaging. OS was defined as the time between date of diagnosis and date of death. Surviving patients were censored at their last known followup at our institution. Statistical tests were considered significant at $p \leq 0.05$. All analyses were performed using SPSS statistical software version 21 (IBM, Armonk, NY).

Results

Fifty-one patients with OCS were identified. Following primary cytoreductive surgery, 18 had no visible disease, 20 had ≤ 1 cm of residual disease, and 13 had >1 cm of residual disease. Table 1 summarizes the demographic and clinical characteristics of the three groups. Age, BMI, and race were similar among the three groups. Not surprisingly, the extent of cytoreduction varied significantly by stage. Compared to patients with stage 3 or 4 disease, patients with stage 2 disease were more likely to be cytoreduced to no visible disease after primary surgery ($p = 0.002$).

In total, 48 patients (94%) underwent salpingo-oophorectomy, 41 (80%) underwent omentectomy, and 31 underwent hysterectomy (61%). Eighteen (35%) had a bowel resection, 5 (10%) had retroperitoneal lymph node dissection, 4 (8%) had peritoneal stripping, and 3 (6%) had a colostomy.

Thirty-seven patients (73%) received adjuvant chemotherapy. Thirty-two of these patients (63%) received platinum and taxane-based treatment (median 6 cycles, range 1–8). Three patients (6%) received ifosfamide with cisplatin (median 5 cycles, range 3–6), 1 patient (2%) received a single cycle of ifosfamide, and 1 (2%) received 11 doses of weekly avastin. Fourteen patients (27%) did not receive adjuvant chemotherapy due to either comorbidities or early death after primary surgery. Patients who were cytoreduced to >1 cm of disease were significantly less likely to receive adjuvant chemotherapy due to early postoperative death ($p = 0.03$). The median survival among those that did not receive adjuvant chemotherapy was 1.1 months.

Median PFS varied significantly among the groups. Those who were surgically cytoreduced to no visible disease had a median PFS of 29 months, versus 21 months in those who were cytoreduced to ≤ 1 cm, and 2 months in those who were cytoreduced to >1 cm ($p = 0.036$) (Fig. 1). Median OS varied significantly among the groups. Patients with no visible disease had an OS of 57 months versus 32 months in those with ≤ 1 cm of residual disease and 11 months in those with >1 cm of residual disease ($p = 0.015$) (Fig. 2).

Because stage 2 patients were significantly more likely to be surgically cytoreduced to no visible disease (which introduces bias into survival estimates), a separate analysis of stage 3 patients was performed. Thirty-three patients were diagnosed with stage 3 disease. Six were cytoreduced to no visible disease, 18 were cytoreduced to ≤ 1 cm of disease, and 9 were cytoreduced to >1 cm of disease. Once again, median OS varied significantly among groups;

those with no visible disease had a median OS of 57 months versus 31 months in the group with ≤ 1 cm of disease and 3 months in the group with >1 cm of disease ($p = 0.009$) (Fig. 3).

Discussion

Ovarian carcinosarcomas are very aggressive tumors and are associated with an extremely poor prognosis. Because these tumors are so uncommon, prospective trials have been difficult to conduct, and even retrospective reviews covering long periods of time have only identified small numbers of patients. As a result, the optimal treatment regimen for this disease has yet to be determined, and recommendations are made based on retrospective reviews, anecdotal data, and experience with other types of gynecologic malignancies, particularly epithelial ovarian cancer.

In this study, we found that the degree of surgical cytoreduction was associated with improved progression-free and overall survival. Patients who were cytoreduced to no visible disease had the most favorable outcomes and this survival advantage remained consistent in stage 3 patients.

Based on data from cooperative group trials, primary surgery with the intention of removing all visible disease is commonly accepted as the surgical goal in the treatment of epithelial ovarian cancer [7]. However, the radical surgeries that are necessary to achieve this goal are associated with higher postoperative morbidity [8]. Chi et al. compared postoperative complications between two groups of patients who underwent primary cytoreductive surgery for advanced stage epithelial ovarian cancer [9]. One group received extensive upper abdominal procedures to remove as much tumor as possible, and the other underwent conventional procedures involving just the pelvis and mid-abdomen. They found that although survival was improved, the group who had undergone upper abdominal procedures had a significantly larger amount of blood loss, higher transfusion requirements, longer operative times, a higher rate of infection, and higher rates of hematologic and gastrointestinal morbidity. In a follow-up study, they reported a major complication rate of 22% in patients who underwent extensive upper abdominal procedures [10]. Before subjecting women with OCS to surgeries with similarly high complication rates, it is important to understand the effect of radical surgical cytoreduction on survival in this disease.

Other single institutional reports have tried to address the potential impact of the degree of cytoreduction and survival in OCS [3,5,11–23]. Early reviews did not demonstrate a correlation between degree of cytoreduction and survival in OCS [11–14]. However, the preferred outcome of primary surgery, in terms of residual disease at surgical completion for epithelial ovarian cancer, has varied over time, and early reports in OCS reflect these variations. Historically, the definition of optimal cytoreduction in epithelial ovarian cancer has varied between less than 1 to less than 3 cm [24–26]. More recent data on epithelial ovarian cancer suggests that cytoreduction to no visible disease should be the goal of primary surgical treatment [7]. Studies that have included cytoreduction to no visible disease have shown similar results in OCS. Rauh-Hain et al. found that in a group of 47 OCS patients who were cytoreduced to no visible disease, ≤ 1 cm of disease, or >1 cm of disease,

there was a significant correlation between cytoreductive status and disease-free and overall survival [22]. Jernigan et al. found a similar correlation between cytoreductive status and overall survival in a group of 47 patients when separated into the same three cytoreductive categories [21]. Our results corroborate these reports and reinforce the notion that primary surgery resulting in no visible disease should be the goal of upfront surgical treatment of OCS.

Though the role of neoadjuvant chemotherapy was not evaluated in this study, there have been case reports indicating its utility in the treatment of OCS, especially in the presence of widespread metastatic disease. Takami et al. reported a case of stage IV OCS with lung and liver metastases that responded remarkably to treatment with irinotecan and cisplatin. After 7 rounds of treatment with this regimen, the extra-abdominal metastases disappeared and the patient was able to undergo cytoreductive surgery [27]. In another report, a patient with late-stage OCS had an extremely large intra-abdominal tumor and received neoadjuvant chemotherapy rather than primary surgery. The patient received five courses of paclitaxel and ifosfamide and experienced a significant reduction in the size of the tumor. This treatment was followed by successful cytoreductive surgery [28]. These reports and others have shown that neoadjuvant chemotherapy may be a successful strategy in the treatment of late stage OCS and its role warrants further investigation in the treatment of this disease [29,30].

Limitations to this study include the inherent drawbacks common to all retrospective reviews such as unmeasured confounding and other types of bias, as well as the small sample size. Though the differences in survival among groups were statistically significant, causation cannot be proven based on the data from this study. In addition, it is impossible to know from these data whether the observed improvement in survival is a result of more complete surgical cytoreduction or a function of the inherent aggressiveness of the tumor. Differences in chemotherapy regimens among patients included in this study were also not evaluated and their effects may contribute to the observed differences in survival. To our knowledge, this is the largest review comparing cytoreductive status to survival in OCS patients to date. Additionally, this is the first study to display a significant correlation between cytoreductive status and survival when just examining patients with stage 3 disease.

Similar to the recommendations from the NCCN and taking into account the results of our study, radical surgery resulting in no visible disease is associated with improved survival and is recommended for the upfront surgical treatment of OCS. In light of the paucity of prospective data regarding the treatment of OCS, guidelines will slowly evolve and will likely continue to rely heavily on small retrospective series. Results from an ongoing cooperative group trial (GOG 261; NCT 00954174) comparing paclitaxel plus carboplatin to paclitaxel plus ifosfamide in patients diagnosed with carcinosarcoma of the uterus, fallopian tube, peritoneum, or ovary may provide further insight into adjuvant treatment regimens and will potentially reveal more effective means with which to treat this devastating disease.

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Abbreviations:

OCS	ovarian carcinosarcoma
PFS	progression-free survival
OS	overall survival

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HIGHLIGHTS

- Extent of primary surgical cytoreduction correlates with progression-free and overall survival in ovarian carcinosarcoma.
- This correlation is still present when patients with stage 3 disease are analyzed independently.
- Cytoreduction resulting in no visible disease should be the goal of upfront surgical treatment of ovarian carcinosarcoma.

Fig. 1.
Progression-free survival by cytoreductive status.

Fig. 2.
Overall survival by cytoreductive status.

Fig. 3.
Overall survival of stage 3 patients by cytoreductive status.

Table 1

Comparison of clinical and demographic factors among study groups.

	NVD (N = 18)	1 cm (N = 20)	>1 cm (N = 13)	p-Value
Age (SD)	65.1 (9.5)	67.5 (8.2)	61.8 (6.3)	0.17
BMI (SD)	28.5 (4.9)	28.3 (6.3)	32.8 (7.9)	0.14
Race				0.85
African-American	6 (33%)	5 (25%)	4 (31%)	
Caucasian	12 (67%)	15 (75%)	9 (69%)	
Stage				0.002
2	9 (50%)	1 (5%)	1 (8%)	
3	6 (33%)	18 (90%)	10 (77%)	
4	3 (17%)	1 (5%)	2 (15%)	
Receipt of adjuvant chemotherapy	16(89%)	15 (75%)	6 (46%)	0.03