Abstract. Background: Ovarian sarcomas are poorly-studied rare tumors. Aim: To compare evolutions of sarcomas and epithelial ovarian carcinomas treated similarly. Patients and Methods: Eleven patients with ovarian sarcomas were retrospectively identified over 12 years at a single tertiary center, the Fundeni Clinical Institute, Bucharest. They were matched to similar patients with epithelial ovarian cancer treated in the same center, by the same surgical teams and according to the same principles in an attempt to clarify the survival difference according to histopathological type with interference given by the above-mentioned variables (surgeon, center, management strategies) eliminated. Results: For International Federation of Gynecology and Obstetrics (FIGO) stage II, overall survival for patients with sarcoma was 90.5 months while for those with epithelial carcinoma it was 113 months (p=0.048). For stage IIIB, overall survival for those with sarcomas was 62 months, while for those with epithelial carcinoma it was 81 months. For stage IIIC, overall survival for those with sarcoma was 14.5 months while it was 55 months for patients with epithelial ovarian cancer (p=0.007). For stage IV overall survival for sarcomas is 2 months while for epithelial cancer is 6 months (p=0.09). Conclusion: Survival and disease-free interval for patients with ovarian sarcoma are lower than those for patients with epithelial ovarian carcinoma. Re-laparotomy for ovarian sarcoma relapse does not seem to bring any survival benefit.

Ovarian sarcomas are rare malignancies; they mostly comprise of carcinosarcomas, formerly known as mixed malignant Mullerian tumors, and occasional cases of leiomyosarcoma, rhabdomyosarcomas, fibromyxosarcomas and angiosarcomas. (1). Ovarian carcinosarcomas are the most frequent sub-group, with a frequency under 2-4% of ovarian tumors and thus have been better studied than their non-carcinosarcoma counterparts (2-5).

The treatment principles of ovarian carcinosarcomas (OCS) are the same as those for epithelial ovarian cancer (EOC) but evidence for doing so is lacking due to a small number of cases and lack of randomized studies. This is also valid as far as adjuvant chemotherapy is concerned, where current practice varies from treating as EOC with a platinum/taxane regimen including ifosphamide or anthracycline (2). Rhabdomyosarcomas are extremely rare and generally described in case reports or small series. They are considered extremely aggressive and lethal (6-8); they are most frequently reported as embryonal rhabdomyosarcomas in children (9). Ovarian leiomyosarcomas are extremely rare and more often described in case reports (10-16). Primary ovarian angiosarcomas are also extremely rare and case reports are occasional; even though long survival for patients with early-stage disease has been described, most patients with advanced stages died in the first year following diagnosis (17-21).

Our study attempted to observe and objectify the difference in treatment results and survival between ovarian sarcoma and epithelial ovarian tumors in a single-center experience; the rationale was that in similar conditions (center, surgeons, principles of practice) the outcome difference would reflect solely the tumor behavior according to its’ histopathological type.
Patients and Methods

Between January 2002 and December 2013, 11 patients were retrospectively identified from the database of the Dan Setlacec Center of Gastrointestinal Diseases and Liver Transplantation of Fundeni Clinical Institute with histopathological findings of ovarian sarcoma. We attempted a case–control matched study by finding for each patient a counterpart patient with EOC similar in terms of age, FIGO stage, intraoperative findings and procedures performed. Age was matched using a similar period ±10 years. All patients underwent surgery at the same center, according to the same principles of practice regarding ovarian malignancies, by the same surgical teams and benefited from the same postoperative management.

After approval by the Fundeni Clinical Institute Ethics Comity the files of the patients diagnosed with ovarian sarcoma and epithelial ovarian cancer between January 2002 and December 2013 were retrieved. The diagnosis of ovarian sarcoma was confirmed by the histopathological examination. Date of death was confirmed with the National Register of Population. Statistical analysis was performed using SigmaPlot version 12.1.

Results

The mean age at initial diagnosis in the ovarian sarcoma group was 63 years (range=45-77 years). The FIGO stages were IIA in two cases, IIB in two, IIIB in one, IIC in four and FIGO stage IV in two cases. Both cases staged as IV presented with disseminated liver metastases. At the time of diagnosis, ascites was present in six cases, and the mean value of cancer antigen 125 (CA 125) was 458 U/ml (range=150-1000 U/ml). Peritoneal dissemination was found on preoperative computed tomography scan in six patients. A single patient was laparotomised at another center, IIC ovarian cancer being revealed intraoperatively, for which she underwent four cycles of chemotherapy, then complete R0 cytoreduction. None of the other 10 patients underwent neo-adjuvant chemotherapy (Table I).

The mean diameter of the tumoral ovaries was 10.05 cm (range=4.15 cm); four cases presented bilateral synchronous ovarian tumors.

Histopathological examination revealed nine carcinosarcomas, one fibrosarcoma, and one leiomyosarcoma. One of the cases of OCS was found to have associated elements of rhabdomyosarcoma. Interestingly, one case of OCS was diagnosed at relapse, initially being considered a poorly-differentiated EOC; the patient had undergone surgery 11 months before, followed by adjuvant chemotherapy with platinum/taxanes. It might be that the tumor was initially a carcinosarcoma and under adjuvant chemotherapy, the epithelial component was inhibited while the sarcomatous one continued to develop. The early postoperative course was uneventful for nine patients, while two presented complications: bronchopneumonia in one case and wound infection in the second. The mean hospitalization stay was 13.8 days (range=3.30 days).

The overall survival was 51 months (range=2-147 months). Five patients were still alive at the time of this study, so survival was censored.

Three out of the 11 patients were re-addressed to our service with bowel obstruction due to peritoneal sarcomatosis. The mean period between primary cytoreduction and recurrence was 4.3 months (range=2-7 months). Surgery was attempted in two cases, while in the third, the general biological status was considered too poor, and palliative care was initiated (the patient died seven days later). In the two cases which underwent laparotomy, an R1 resection was performed in one case (tumor resection en bloc with rectosigmoidal resection with remnant tumoral tissue at the level of the urinary bladder); in the other case, biopsy-alone was performed. The overall survival after secondary surgery was 3.3 months (range=2-5 months). The mean characteristics of the patients in whom secondary cytoreduction was attempted are shown in Table II.

One patient had a particularly good evolution: the patient underwent left adnexectomy en bloc with segmentary enterectomy for a moderately-differentiated fibrosarcoma; 12 years later, she is alive with no signs of recurrent disease. The patient also underwent a non-planned second look for an acute cholecystitis five years after initial surgery, no signs of recurrent disease were found.

Case–control matched study. FIGO stage II: Four patients with stage II ovarian tumors (two stage IIA and two stage IIB) were diagnosed with ovarian sarcomas on the basis of histopathological studies. One patient, 71 years old, underwent unilateral adnexectomy for a stage IIA tumor; the second one, 45 years old, with the same stage underwent total hysterectomy with bilateral adnexectomy; two cases with a mean age of 73 years, classified with stage IIB tumor underwent unilateral adnexectomy. In 2 cases segmentary enterectomy was also carried out. In all the cases, the postoperative evolution was uneventful.

These four cases were matched with similar patients diagnosed with EOC but all such cases were almost three decades younger. All patients with EOC experienced recurrences at an interval between 40 and 132 months, the median time to recurrence being 101.2 months. The overall survival for patients with EOC was 113 months (range=42-196 months), while that for those with ovarian sarcomas was 90.5 months ($p=0.048$).

Stage III B: One patient with stage III B ovarian cancer, 70 years old at diagnosis, in whom total hysterectomy with bilateral adnexectomy, omentectomy, pelvic peritonectomy and appendectomy were performed, was matched to a 63-year-old patient with III B EOC in whom the same procedure was performed. The survival for the patient with EOC was 81 months and the disease-free survival period was 75 months; the ovarian sarcoma counterpart had a survival of 62 months with disease-free survival of 38 months.
Stage IIIC: Four patients were diagnosed preoperatively with stage IIIC ovarian cancer. In two cases, total hysterectomy with bilateral adnexectomy and total omentectomy was performed, while in the other two cases, extended resections were performed: total peritonectomy, rectosigmoidial resections, segmentary enterectomy, and cholecystectomy. In all four cases, ovarian sarcomas were diagnosed on the basis of histopathological results. The mean

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**Table I. Characteristics of patients with ovarian sarcoma**

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age at diagnosis (years)</th>
<th>Intraoperative findings</th>
<th>Surgery</th>
<th>Type of resection</th>
<th>Histopathological type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>77</td>
<td>Right ovarian tumor invading the small bowel</td>
<td>Right adnexectomy en bloc with segmentary enterectomy</td>
<td></td>
<td>Carcinosarcoma</td>
</tr>
<tr>
<td>2</td>
<td>74</td>
<td>Left ovarian tumor invading the small bowel</td>
<td>Left adnexectomy en bloc with segmentary enterectomy</td>
<td></td>
<td>Fibrosarcoma</td>
</tr>
<tr>
<td>3</td>
<td>47</td>
<td>Stage IV ovarian cancer (liver metastases)</td>
<td>Total hysterectomy with bilateral adnexectomy and omentectomy</td>
<td>R2</td>
<td>Carcinosarcoma</td>
</tr>
<tr>
<td>4</td>
<td>70</td>
<td>Stage IIIB ovarian cancer</td>
<td>Total hysterectomy with bilateral adnexectomy and omentectomy, peritonectomy, appendectomy</td>
<td>R0</td>
<td>Carcinosarcoma</td>
</tr>
<tr>
<td>5</td>
<td>76</td>
<td>Stage IV ovarian cancer (liver metastases)</td>
<td>Total hysterectomy with bilateral adnexectomy and omentectomy and peritonectomy, appendectomy</td>
<td>R2</td>
<td>Carcinosarcoma</td>
</tr>
<tr>
<td>6</td>
<td>49</td>
<td>Stage III ovarian cancer</td>
<td>Total hysterectomy with bilateral adnexectomy and omentectomy</td>
<td>R1</td>
<td>Carcinosarcoma*</td>
</tr>
<tr>
<td>7</td>
<td>45</td>
<td>Left ovarian tumor</td>
<td>Total hysterectomy with bilateral adnexectomy</td>
<td></td>
<td>Carcinosarcoma</td>
</tr>
<tr>
<td>8</td>
<td>58</td>
<td>Stage III ovarian cancer</td>
<td>Total hysterectomy with bilateral adnexectomy and omentectomy</td>
<td>R1</td>
<td>Carcinosarcoma with areas of rhabdomyosarcoma</td>
</tr>
<tr>
<td>9</td>
<td>71</td>
<td>Right ovarian tumor</td>
<td>Right adnexectomy</td>
<td></td>
<td>Leiomyosarcoma</td>
</tr>
<tr>
<td>10</td>
<td>57</td>
<td>Stage III ovarian cancer</td>
<td>Total hysterectomy with bilateral adnexectomy and omentectomy, rectosigmoidectomy, cholecystectomy, peritonectomy</td>
<td>R0</td>
<td>Carcinosarcoma</td>
</tr>
<tr>
<td>11</td>
<td>67</td>
<td>Stage III ovarian cancer</td>
<td>Total hysterectomy with bilateral adnexectomy and omentectomy, rectosigmoidectomy, cholecystectomy, enterectomy</td>
<td>R0</td>
<td>Carcinosarcoma</td>
</tr>
</tbody>
</table>

*The tumor was first diagnosed as poorly differentiated epithelial cancer and as carcinosarcoma at relapse.

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**Table II. Characteristics of the patients in whom secondary cytoreduction was attempted.**

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Stage at initial laparotomy</th>
<th>Initial surgery performed</th>
<th>Time between primary and secondary surgery</th>
<th>Surgical procedures at the time secondary cytoreduction was attempted</th>
<th>Time from secondary surgery to death</th>
<th>Histopathological type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Stage IV</td>
<td>Total hysterectomy with bilateral adnexectomy and omentectomy and peritonectomy, appendectomy</td>
<td>3 Weeks</td>
<td>Biopsy</td>
<td>1 Week</td>
<td>Carcinosarcoma</td>
</tr>
<tr>
<td>2</td>
<td>Stage IIIC</td>
<td>Total hysterectomy with bilateral adnexectomy and omentectomy</td>
<td>7 Months</td>
<td>Biopsy</td>
<td>3 Months</td>
<td>Carcinosarcoma</td>
</tr>
<tr>
<td>3</td>
<td>Stage IIIC</td>
<td>Total hysterectomy with bilateral adnexectomy and omentectomy</td>
<td>2 Months</td>
<td>Rectosigmoidial resection</td>
<td>4.5 Months</td>
<td>Carcinosarcoma with areas of rhabdomyosarcoma</td>
</tr>
</tbody>
</table>

Stage IIIC: Four patients were diagnosed preoperatively with stage IIIC ovarian cancer. In two cases, total hysterectomy with bilateral adnexectomy and total omentectomy was performed, while in the other two cases, extended resections were performed: total peritonectomy, rectosigmoidial resections, segmentary enterectomy, and cholecystectomy. In all four cases, ovarian sarcomas were diagnosed on the basis of histopathological results. The mean
age for the sub-group in which extended resections were performed was 62 years, while that for the sub-group in which only omentectomy was added to total hysterectomy and bilateral adnexectomy was 54 years. Each sub-group of two patients was compared to a corresponding group of patients with stage IIC epithelial cancer.

The multivisceral resection sub-group was compared to an equivalent one formed by six patients with a median age of 63 years. The overall survival for patients with sarcoma was 20 months, while that for those with EOC was 51 months.

The sub-group which did not require associated resections was compared to an equivalent one composed of four patients with a median age of 54 years. The overall survival for patients with sarcoma was 4.5 months, while it was considerably longer for those with EOC: 23.6 months (range=18-31 months). At the time of recurrence in the sarcoma group, only one patient underwent secondary cytoreduction (an R2 resection was performed, while in the EOC group, all four patients underwent secondary cytoreductions (R0 resection was obtained in all cases, with a 31-month overall survival from secondary cytoreduction) \( p=0.007 \).

Stage IV: Two patients with a median age of 62 years were diagnosed with stage IV ovarian cancer (multiple liver metastases), with histopathological results of ovarian sarcoma. In both cases, total hysterectomy with bilateral adnexectomy and omentectomy were performed. In one case, peritoneal resection and appendectomy was associated. In none of the cases were liver metastases resected. The overall survival was 2 months. One of the patients was readmitted three weeks after initial surgery for intestinal obstruction through peritoneal sarcomatosis. Re-laparotomy was performed but was only of exploratory character; the patient died one week later. This group was compared to a similar one formed by two patients with stage IV EOC in whom the same surgical procedures were performed, the overall survival was 6 months \( p=0.09 \).

Survival differences between patients with ovarian sarcoma and those with EOC by FIGO stage are shown in Figure 1.

In the group with ovarian sarcomas, histopathological findings revealed eight carcinosarcomas, and three other cases with very rare histopathologies: fibrosarcoma, rhabdomyosarcoma associated with carcinosarcoma, and leiomyosarcoma.

Fibrosarcoma was diagnosed in a 74-year-old patient in whom adnexectomy with segmentary enterectomy was performed for a left adnexal mass invading the small bowel. Five years after the initial surgery, an incidental second look was performed for acute cholecystitis and no signs of recurrence were found. Twelve years after initial surgery the patient remains alive with no signs of recurrence.

Rhabdmyosarcoma was found in a 58-year-old patient with stage IIC ovarian neoplasia; the specimen revealed bilateral ovarian tumors, in association with carcinosarcoma. The first cytoreduction was an R1 resection, when total hysterectomy with bilateral adnexectomy and total omentectomy was performed. The patient started adjuvant chemotherapy and 2 months after surgery she presented with intestinal obstruction through diffuse peritoneal sarcomatosis invading the rectal wall and the urinary bladder. A R2 cytoreduction was performed: tumor cytoreduction en bloc with rectosigmoidal resection; remnant macroscopic tumor was still present on the surface of the urinary bladder. She continued chemotherapy but died of her disease 4.5 months later.

Leimyosarcoma was found in a 71-year-old patient who was diagnosed intraoperatively with a stage IIA ovarian tumor. The histopathological result confirmed the stage and classified the tumor as leiomyosarcoma. The postoperative evolution was uneventful, the patient being free of disease four years after.

Particular attention must be attributed to one patient diagnosed initially with stage IIIC EOC who underwent resection and adjuvant taxane-platinum chemotherapy. Disease recurred 7 months later when pathology showed carcinosarcoma; the patient died 3 months later although she had continued chemotherapy.

Discussion

Ovarian sarcomas are rare tumors and a greater understanding of better principles of treatment is crucial. OCS, the better-studied sub-groups of sarcomas, are clearly a different entity from EOC. A SEER (Surveillance, Epidemiology and End Results) analysis by Rauh-Hain et al. using registries from 1998 to 2009 compared 13,419 women with high-grade
Papillary serous carcinoma of the ovary with 1,334 women with OCS; women with OCS had poorer survival compared to those with papillary serous carcinoma, a difference that persisted throughout all FIGO stages (22). Similar features were highlighted by a SEER analysis from 1998 to 2007; women with OCS were 72% more likely to die from their disease than women with serous carcinomas (23).

The management of OCS is similar to that of EOC, consisting of cytoreductive surgery followed by adjuvant chemotherapy; in chemotherapy, platinum and taxane are more frequently used, but the efficacy of ifosphamide in uterine carcinosarcoma raises questions about the benefit of its incorporation in regimens for OCS. Basically OCS is a mixture of two different malignancies, epithelial and sarcomatous, which behave in independent manners; this is especially obvious in their patterns of metastasis: transperitoneal spread being almost exclusively accomplished by malignant epithelial deposits and with great difficulty by the sarcomatous component (2). One of the cases we reported may reflect this independent components theory, that of a 49-year-old patient who underwent laparotomy for ovarian peritoneal carcinomatosis and a total hysterectomy with bilateral adnexectomy, peritoneectomy and omentectomy, followed by taxane/platinum adjuvant chemotherapy that was diagnosed with OCS at relapse. We hypothesize that the sarcomatous component was present all along but became obvious after inhibition of the epithelial component with taxane/platinum chemotherapy.

The few case series present in literature tend to agree that maximal cytoreduction appears to correlate with better progression-free survival and overall survival and that complete cytoreduction should be the goal of surgical treatment (24-26). As far as adjuvant chemotherapy is concerned, a study by Rutledge et al. concluded that ifosphamide/cisplatin combination is associated with improved progression-free survival and overall survival compared to carboplatin/taxol (27).

Our study design ensured proper comparison between sarcomas of the ovary and EOC considering that all cases were treated in the same high-volume tertiary center by the same surgical teams, according to the same treatment principles, with the same intensive care unit and with similar adjuvant chemotherapy regimens. All sarcoma cases were matched to similar EOC counterparts in terms of FIGO stage, age (whenever possible), intraoperative description of the extent of disease, surgical procedures (classical total hysterectomy with bilateral adnexectomy, omentectomy and parietal peritoneal resection but also associated surgical procedures such as enterectomy or rectosigmoidal resection) and adjuvant chemotherapy. Its flaws are the small number of patients and the inclusion of different types of sarcomas (although 8 out of 11 cases were OCS). Our results were similar to those already present in literature, confirming poorer disease-free survival and overall survival of patients with ovarian sarcomas compared to those with EOC throughout all FIGO stages. Our only case of rhabdomyosarcoma had an extremely poor prognosis with 7 months survival following surgery. The unique case of fibrosarcoma diagnosed in FIGO stage II had a twelve years survival without recurrent disease. Secondary cytoreduction in EOC is already a standard proven to extend survival whenever R0 resection is achieved. Ovarian sarcoma does not seem to follow this principle; in the three attempts of secondary cytoreduction, resection proved impossible in two, and in the third, an R1 resection was achieved with only 4.5 months postoperative survival.

Conclusion

Ovarian sarcomas carry a poorer prognosis than epithelial ovarian malignancies and this difference is traceable throughout all FIGO stages. Secondary cytoreduction for ovarian sarcoma radically treated initially seems hardly feasible and ineffective. Further study is required in order to identify the best principles of treatment and ideal chemotherapy regimens for ovarian sarcomas.

References


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