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# Carcinosarcoma of the Ovary
## A Review

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**Carcinosarcoma of the ovary, also referred to as mixed mullerian tumor of the ovary, is a rare and aggressive tumor. This tumor type is unique in that it contains malignant epithelial and stromal elements. The average survival for a woman diagnosed with carcinosarcoma of the ovary is less than 2 years. Due to the rarity of this tumor, the optimal treatment for carcinosarcoma of the ovary has not been determined. We review the pathology, risk factors, and current treatment recommendations for carcinosarcoma of the ovary.**

**Target Audience:** Obstetricians & Gynecologists, Family Physicians

**Learning Objectives:** After completion of this educational activity, the participant should be better able to recall the existence of carcinosarcoma of the ovary, demonstrate that with rare tumors, analogous treatment regimens are used, and plan to refer patients with carcinosarcoma of the ovary to gynecologic oncologist for treatment.

There were an estimated 25,000 cases of epithelial ovarian cancer in 2008, which pales in number when compared to the incidence of breast, colon, and lung cancers in the same year. Ovarian carcinosarcomas occur even less frequently, and are considered to be rare cancers, representing 1% to 5% of all ovarian cancers. Eighty percent of carcinosarcomas occur in postmenopausal women of low parity. Most carcinosarcomas of the ovary present in women who are 50 to 70 years. The International Federation of Gynecology and Obstetrics surgical staging system for epithelial ovarian cancers is utilized to stage ovarian carcinosarcomas. Given the infrequent occurrence of these tumors, most studies evaluating prognostic factors and clinical management are small and retrospective.

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## PATHOLOGY

Carcinosarcoma tumors of the ovary contain both malignant epithelial and sarcomatous (mesenchymal) elements. The epithelial component is often serous, endometrioid, or undifferentiated adenocarcinoma but may also be clear cell adenocarcinoma or squamous cell carcinoma. The sarcomatous element may be homologous tissue native to the ovary or heterologous tissue not native to the ovary. Examples of homologous sarcomatous components include endometrial stromal sarcoma, fibrosarcoma, and leiomyosarcoma. Examples of heterologous sarcomatous elements include chondrosarcoma, rhabdomyosarcoma, and, less frequently, osteosarcoma or liposar-

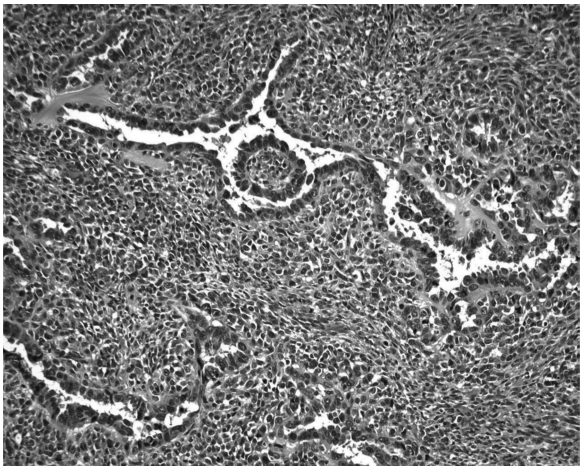

Fig. 1. Histology of carcinosarcoma of the ovary illustrating both epithelial and sarcomatous components. Courtesy of Dr. Chad Livasy, UNC Hospital Department of Pathology.

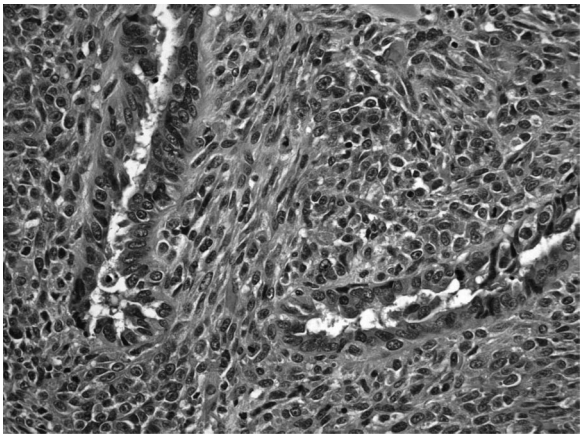

Fig. 2. Epithelial and sarcomatous components of carcinosarcoma of the ovary at higher magnification (600X). Courtesy of Dr. Chad Livasy, UNC Hospital Department of Pathology.

coma. Figures 1 and 2 illustrate 2 cell types seen in carcinosarcoma of the ovary.

Poorly differentiated carcinomas may be confused with carcinosarcomas; however, the different tumor types can be distinguished through immunohistochemical staining with a panel of cytokeratins. Hyaline bodies that are periodic acid-Schiff positive and diastase resistant are used to identify the sarcomatous component. Grossly, these tumors appear similar to epithelial ovarian cancer (1). They commonly present as friable complex adnexal masses with intra-abdominal metastases often accompanied by ascites. Retroperitoneal lymph node metastases and pleural effusions may occur.

## GENETICS

Tumors composed of 2 malignant components are genetic enigmas. The genetic origin of these tumors has led to the proposal of several hypotheses. The following theories have been proposed:

1. Collision Theory: The 2 tumors (epithelial and sarcomatous) evolve separately and merge. In this scenario, the tumors are considered to be biclonal in origin, that is, each neoplastic component originates from a different stem cell.
2. Combination Theory: A common stem cell precursor gives rise to a carcinoma and sarcoma. These tumors are considered to be monoclonal.
3. Conversion Theory: An original stem cell precursor differentiates into 1 cell type which in turn differentiates into the second cell type.

Jin et al reported a comprehensive genetic analysis of 12 uterine and 3 ovarian carcinosarcomas. Their study addressed X-chromosome inactivation, identification of p53 mutations, and microsatellite analysis. Results showed that all ovarian carcinosarcomas were monoclonal in origin supporting the combination theory. Interestingly, while their results also supported a monoclonal etiology for uterine carcinosarcoma, 2 uterine cancers appeared to have a biclonal origin supporting the collision theory of carcinogenesis. There is increasing support for the combination or monoclonal theory that ovarian carcinosarcoma develops from 1 stem cell (2).

But the evidence for the origin of carcinosarcomas is still confusing. Schipf et al in his study of 30 ovarian carcinosarcoma performed comparative genomic hybridization and fluorescence in situ hybridization. Chromosomal amplification of the c-*myc* proto-oncogene on chromosomes 8q and 20q was observed, and also suggested a monoclonal origin for these tumors. However, they also noted that genetic aberrations were similar to serous carcinomas in that these tumors could also be metaplastic consistent with the conversion theory (3). Sonoda et al reported a case of carcinosarcoma where clonal loss of *BRCA2* allele and a somatic mutation in p53 were found in both carcinoma and sarcomatous components. These results lend further support to the combination theory (4). In contrast, Gallardo et al evaluated 2 ovarian serous epithelial carcinomas which recurred as carcinosarcomas. An evaluation of loss of heterozygosity, p53 mutation, and microsatellite analysis showed identical findings in the primary tumor and recurrent carcinosarcoma, thus lending support to the conversion theory (5).

## CARCINOSARCOMA OF OTHER FEMALE GENITAL TRACT ORGANS

### Uterus

Overall carcinosarcoma are rare tumors of the reproductive tract. Although carcinosarcoma of the uterus accounts for less than 5% of uterine corpus cancers, it is the most common gynecologic site for carcinosarcoma. Postmenopausal (mean age: 65–67) women are generally affected and the incidence rises with age (6,7). A higher percentage of patients with carcinosarcoma are African-American as compared to endometrioid endometrial cancer (28% as compared to 8%) (8).

Most cases of uterine carcinosarcoma are diagnosed by endometrial biopsy when the patient presents complaining of abnormal vaginal bleeding (often with a polyploid fleshy mass protruding through the cervix) (9). Compared to ovarian carcinosarcoma, a higher percentage of uterine carcinosarcoma patients are diagnosed at earlier stages (43% vs. 28%). This discrepancy is likely due to symptoms of uterine bleeding allowing for earlier diagnosis of uterine carcinosarcoma. Despite the earlier stage at diagnosis, the 5-year survival rate is no more than 35% (10). The appropriate adjuvant therapy for uterine carcinosarcoma is also controversial. Radiotherapy has historically been the mainstay of adjuvant therapy for uterine carcinosarcoma. Radiotherapy may provide local disease control, but has not lengthened the progression-free or overall survival rate. Current interest lies in chemotherapy. Table 1 illustrates the risk factors for uterine carcinosarcoma.

### Vagina

Carcinosarcoma of the vagina is uncommon. Prior pelvic radiotherapy is a risk factor for carcinosarcoma of the vagina, and about half of the women with this disease have a history of radiotherapy (11–13). Carcinosarcoma of the vagina has a poor prognosis with a 5-year survival of 17% (14). Pure sarcomas represent about 3% of primary vaginal cancers, and the most common histologic type is leiomyosarcoma.

TABLE 1
Risk factors for uterine carcinosarcoma

| |
|---|
| Obesity |
| Low parity |
| Anovulation |
| Prior pelvic radiation |

### Cervix

About 30 cases of carcinosarcoma of the cervix have been reported in the literature. The mean age of patients is 65 years (23–87 years) (15).

## CLINICAL MANAGEMENT OF OVARIAN CARCINOSARCOMA

Patients typically present with symptoms similar to advanced ovarian cancer with abdominal symptoms, distension, and bloating. On exam, patients will often have a palpable pelvic mass. Most women (75%) will have widespread metastasis (stage III or IV) at initial surgery; at diagnosis, the majority of carcinosarcoma (>90%) have spread beyond the ovary. One-third of cases involves bilateral ovaries. A high percentage of women will have ascites at presentation (67%–100%) (16,17). More than half of patients will have metastatic nodal disease at the time of diagnosis (16,18,19). Unlike uterine carcinosarcoma, metastases (5%) are rarely found in the lungs or brain (18,19).

Metastatic disease commonly contains both epithelial and sarcoma cell types. Carcinosarcoma of the ovary has a worse survival rate when compared to epithelial ovarian cancers with median survival of less than 18 months; reports in the literature estimate median survivals of 7 to 27 months.

### Radiologic Diagnosis

There are few preoperative diagnostic tests for ovarian carcinosarcomas. Cho et al described the preoperative imaging findings of 13 occurrences, 8 patients were found to have carcinosarcoma of the ovary on final pathology. Unilateral lesions were found in 3 patients and bilateral in 5. Eleven of the lesions were mixed solid and cystic, while 2 were multiseptated cystic masses with irregular, thick walls, and septa. The cystic fluid in 2 of the cases proved to be hemorrhage on final pathologic review. In the majority of cases, the largest diameter of the tumor was greater than 10 cm. All patients had ascites. Ovarian carcinosarcomas may have a more aggressive and larger appearance on preoperative imaging than epithelial ovarian cancers. However, the nonspecific imaging findings will only suggest this diagnosis (20).

### Prognostic Factors

While the overall clinical prognosis of ovarian carcinosarcoma appears dismal, some efforts have been made to identify prognostic factors (5). Initially,

it was proposed that the type of sarcomatous (heterologous vs. homologous) tumor present was prognostically significant. In an early study, Sood et al found that cancers with homologous sarcomatous elements demonstrated significantly better survival compared to those cancers containing heterologous elements (21). However, recent studies suggest that there is no correlation; currently, it is not felt that the origin of the sarcomatous element is a prognostic factor (22). Histologic factors (grade, mitotic index) have not been correlated with outcome or the ability to predict development of distant metastases. Rather, histologic characteristics of the epithelial component of the tumor have been shown to be more predictive of distant disease. Selective grade and myometrial vascular invasion have been shown to correlate with metastatic disease (23). Serous epithelial components are associated with worse survival than nonserous epithelial components (24). The presence of more than 25% sarcomatous component in the primary tumor adversely affects outcome. Tumors with predominately sarcomatous characteristics and a high number of small vessels have poor survival (25).

In a study of 25 patients with uterine and ovarian carcinosarcomas, increased vessel number and increased VEGF and VEGFR-3 expression were correlated with poor survival (25). Immunohistochemical study of a panel of markers and receptors in 9 patients with ovarian carcinosarcoma indicated that only p53 overexpression correlated with improved overall survival (26). Liu et al showed that ovarian carcinosarcoma overexpresses *p53* protein, and expression was noted in a higher proportion than any other gynecologic malignancy. *P53* overexpression has been associated with advanced stage, poor prognosis epithelial ovarian cancers, and some posit that the high p53 expression in ovarian carcinosarcoma might explain their poor prognosis (27).

Clinical prognostic factors associated with poor survival include advanced stage at presentation, suboptimal debulking, and older age. Recurrence rates of 50% were noted for stage I, 100% for stage II, 90% for stage III, and 100% for stage IV disease (16,20,28,29). Table 2 shows the median survival and recurrence rate averaged from 4 studies (16,20,28,29).

TABLE 2
Average median survival and recurrence rate by stage at diagnosis of ovarian carcinosarcoma

| Stage | Median Survival (mo) | Recurrence Rates % |
|---|---|---|
| I | 75.5 | 50 |
| II–IV | <10 | 90 |

### Tumor Markers

Approximately 74% to 90% of patients with ovarian carcinosarcoma will have an elevated CA-125 (16,21). Sood et al found that greater than 90% of patients manifested an elevated CA-125. Furthermore, a preoperative CA-125 level >75 portended a poor outcome. CA-125 provided prognostic information and correlated well with disease status (21). Some investigators presumed CA-125 was a useful marker and integrated this parameter into their studies without question (22,30). Other investigators did not consider the use of CA-125 in their patients (18,29).

Case reports have suggested that alpha-fetoprotein may serve as a marker for patients with carcinosarcoma of the ovary; however, it was noted that serum levels did correlate with response to chemotherapy (31).

## TREATMENT

### Surgery

Optimal surgical cytoreduction followed by platinum-based chemotherapy results in improved progression-free survival according to large retrospective series (21,32). The benefit of optimal debulking for epithelial ovarian cancers is well known. However, given the rarity of ovarian carcinosarcoma, there have been no prospective studies evaluating the role of debulking and its relationship to outcome; thus, we rely on collective evaluation of retrospective studies to show the benefit of optimal debulking. Table 3 summarizes the data available on surgical debulking of ovarian carcinosarcoma.

Early studies were not convincing of the role of debulking, however, retrospective reviews from the last 10 years generally find that patients fare better after optimal debulking (33,34). In a series of 28 patients, Duska et al showed that optimal cytoreduction was correlated with improved time to recurrence in 14 patients (38). Silasi et al also found a trend toward improved survival after optimal debulking with a median survival of 46 months in patients who were optimally debulked compared to a median survival of 27 months in patients who were suboptimally debulked (39). Similarly, Rutledge et al observed improved survival in optimally debulked patients (25 vs. 16 months) (29). Multiple investigators retrospectively have noted improved outcomes after optimal debunking (16,21,28,40). Cumulative retrospective data supports an effort to optimally debulk ovarian carcinosarcomas. Table 3 summarizes the results of optimal surgical cytoreduction and its impact on outcome.

TABLE 3
Published data regarding the effect of optimal cytoreductive surgical debulking on survival in ovarian carcinosarcoma

| Reference | No. Patients | Definition of Optimal Cytoreduction | Effect on Survival |
|---|---|---|---|
| Barakat et al, 1990 (33) | 24 | <2 cm | No improvement |
| Plaxe et al, 1990 (34) | 15 | <2 cm | No improvement |
| Terada et al, 1989 (35) | 15 | <1.5 cm | No improvement |
| Harris et al, 2003 (19) | 40 | <2 cm | Improved |
| Muntz et al, 1994 (32) | 23 | <2 cm | Improved |
| Sood et al, 1998 (21) | 41 | <1 cm | Improved |
| Morrow et al, 1986 (36) | 30 | NR | Improved |
| Anderson et al, 1987 (37) | 14 | NR | Improved |
| Duska et al, 2002 (38) | 14 | <2 cm | Associated with improved time to recurrence, not death |
| Rutledge et al, 2006 (29) | 19 | <1 cm | Associated with survival |
| Brown et al, 2004 (16) | 41 | <2 cm | Associated with survival |

## Radiation Therapy

Radiotherapy has been utilized in the treatment of uterine carcinosarcoma, however, in ovarian carcinosarcoma where widespread intra-abdominal disease is common, there has been little use or rationale for radiation. There may be utility for recurrences located in a single area, but this has not been studied.

## Chemotherapy

After primary cytoreductive surgery, the consensus recommendation for treatment of carcinosarcoma of the ovary is a platinum-based chemotherapy combination. This consensus is based on the data available from heterogeneous trials of patients of various stages and combinations of chemotherapy within the same study. Whether platinum agents should be administered alone or in combination is undetermined. Common treatment combinations utilized to date include platinum and/or paclitaxel and platinum and/or ifosfamide. Other combinations of platinum with adriamycin and dacarbazine have been utilized. Table 4 outlines the retrospective studies of chemotherapy in carcinosarcoma of the ovary.

Prospective studies by the GOG have shown that adriamycin is not sufficient for treatment of carcinosarcoma of the ovary, and that platinum and ifosfamide in combination are active against carcinosarcoma of the ovary (36,48,49). These prospective trials were difficult due to the rarity of disease and accrual took many years. Table 5 outlines the prospective GOG studies of chemotherapy treatment of ovarian carcinosarcoma.

The combination of paclitaxel and carboplatin has been an effective regimen for epithelial ovarian cancers; physicians have hypothesized that this regimen would also be effective for treatment of ovarian carcinosarcomas. Duska et al reported 26 patients who were treated with first-line paclitaxel and/or carboplatin. Sixteen (55%) achieved a complete response, and 6 patients had a partial response for a total response rate of 72%. Overall median survival for the group was 27 months (38). However, when compared to a group of patients with serous adenocarcinoma of the ovary, Brown et al demonstrated that women with carcinosarcoma have a significantly lower response rate ($P = 0.02$) (16).

Ifosfamide and cisplatin has been effective therapy for uterine carcinosarcoma, and this has led clinicians to treat ovarian carcinosarcoma with the same regimen (48,44). The median survival of patients receiving ifosfamide was 23 months on the GOG prospective study (48). In one study, when compared to paclitaxel/carboplatin, the ifosfamide/cisplatin regimen resulted in a better overall survival rate. Notably 15% to 20% of patients developed a grade 3 or 4 neutropenia, and it was felt that this regimen was more toxic than paclitaxel/carboplatin (29). The GOG is currently conducting a phase II study of paclitaxel/carboplatin for the treatment of uterine carcinosarcoma. Results of this study may influence selection of treatment choices for ovarian carcinosarcoma.

Platinum-based chemotherapy regimens appear to be the best treatment for carcinosarcoma of the ovary. While there are significant selection biases in retrospective studies, platinum-based chemotherapy combinations are the most efficacious in multiple small studies. The selection of ifosfamide or paclitaxel as the compliment to platinum must be made based on patient factors and tolerability.

Despite the fact that ovarian carcinosarcoma responds to chemotherapy, the prognosis and median survival still lags behind that of ovarian epithelial

TABLE 4
Published data regarding response to chemotherapy in women with ovarian carcinosarcoma

| Reference | No. Patients | Chemotherapy Regimen | Response | Type of Study | Median PFS/OS (mo) |
|---|---|---|---|---|---|
| Anderson et al, 1989 (37) | 10 | Platinum based | 4 CR<br>2 PR | Retrospective | NR/16 |
| Piver et al, 1982 (41) | 11 | CYVADIC | 1 CR<br>2 PR<br>RR 27% | Retrospective | NR |
| Morrow et al, 1984 (42) | 13 | VAC + RT | 3 CR<br>1 PR<br>RR 31% | Retrospective | NR |
| Moore et al, 1986 (43) | 15 | CYVADIC or CAP | 6 CR<br>3 PR<br>RR 60% | Retrospective | NR |
| Plaxe et al, 1990 (34) | 13 | Cisplatin/doxorubicin | 10 CR<br>1 PR<br>RR 85% | Retrospective | 17/NR |
| Sood et al, 1998 (21) | 10 | Platinum based | 3 CR, 5 PR, 80% RR | Retrospective | NR/15 |
| | 8 | Non-platinum | 1 CR, 0 PR, 12% RR | | NR/6.6 |
| Sit et al, 2000 (44) | 14 | 8 Platinum/ifosfamide<br>6 Platinum/taxane | NR | Retrospective | NR/23<br>NR/19 |
| Duska et al, 2002 (38) | 28 | Carboplatin/paclitaxel | 16 CR, 6 PR; RR 72% | Retrospective | NR/27.1 |
| Harris et al, 2003 (19) | 26<br>6 | Platinum based<br>Non-platinum based | RR 40% | Retrospective | NR/8.7 |
| Brown et al, 2004 (16) | 12 | Platinum based | 1 CR, 2 PR 25% RR | Retrospective | 6.4/8.2 |
| | 2 | Non-platinum based | 0 | | |
| | 17 | | 41% RR | | |
| Rutledge et al, 2006 (29) | 11 | Ifosfamide /CDDP | Better PFI | Retrospective, $P = 0.03$ for improvement in overall survival with Ifosfamide/ CDDP, except in advanced disease | NR/81% at 2 yrs |
| | 16 | Carboplatin/paclitaxel | | | 12/55% at 2 yr |
| Prendiville et al, 1994 (45) | 15 | Mixed, mostly cyclophosphamide | 2 CR, 5 PR | Retrospective | NR |
| Chang et al, 1995 (46) | 24 | Most platinum based | 1 CR, 7 PR 33% | Retrospective | NR |
| Inthasorn et al, 2003 (28) | 6 | Platinum based | 2 CR (33%) | Retrospective | NR/23 |
| Mok et al, 2006 (22) | 10 | Platinum based | NR | Retrospective | NR/46 |
| Crotzer et al, 2007 (47) | 9 | Ifosfamide/cisplatin | 7 CR<br>1 PR<br>RR 78% | Prospective | 10/17.1 |
| Leiser et al, 2007(30) | 28 | Platinum based | 12 CR<br>7 PR | Retrospective | 12/43 |
| Cicin et al, 2008 (40) | 22 | Platinum based | NR | Retrospective | NR/26 |

NR indicates not reported.

cancers. Novel chemotherapies are being developed and are much needed for this disease. Biological targets specific to tumors will likely predominate future chemotherapy. Currently trabectedin (Yondelis) is undergoing study in Europe in patients with advanced soft tissue sarcomas after failure of standard chemotherapy. This may prove a useful adjuvant to initial chemotherapy in ovarian carcinosarcoma. The vascularity of carcinosarcomas has led others to advocate treatment with VEGF inhibitors.

## CONCLUSIONS

Carcinosarcoma of the ovary is a rare and aggressive gynecologic malignancy. Patients present with symptoms similar to women with epithelial ovarian

TABLE 5
Three GOG prospective studies have been conducted on ovarian carcinosarcoma

| Reference | No. Patients | Chemotherapy Regimen | Response | Median PFS/OS (mo) |
|---|---|---|---|---|
| Morrow, 1986 (36) | 31 | Adriamycin | 1 PR<br>RR 10% | NR |
| Sutton, 1994 (48) | 28 | Ifosfamide/mesna | 1 CR<br>4 PR<br>RR 17.9% | |
| Thigpen, 2004 (49) | 44* | Cisplatin | 1 CR<br>8 PR<br>RR 20% | 5.2/11.7* of 130 patients |

*Evaluable of 130 on study.

cancers, but stage for stage, outcomes are worse. The rarity of the disease has limited our ability to study treatments in a timely prospective fashion. Therefore, treatment recommendations are based upon retrospective studies with small patient populations.

Patients with carcinosarcoma of the ovary appear to have a higher survival rate if they undergo optimal tumor debulking followed by a platinum-based chemotherapy regimen. Combination chemotherapy with ifosfamide and cisplatin or taxol and carboplatin is favored at the moment. There is not likely to be a randomized trial comparing these 2 regimens. Treatment decisions are thus based on the preference of the physician and patient, and usually rely on the patient's functional status. Unfortunately, even with the best treatment, women with this diagnosis face a dismal long-term survival outcome.

Future study to improve the treatment of carcinosarcoma of the ovary will likely involve better understanding of the molecular basis of disease and the risk factors for disease development. Targeted therapies may ultimately become an intimate part of therapy.

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