Gynecologic Cancer InterGroup (GCIG) Consensus Review for Uterine and Ovarian Carcinosarcoma

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Abstract: Carcinosarcomas (also known as malignant mixed müllerian tumors) are rare and highly aggressive epithelial malignancies that contain both malignant sarcomatous and carcinomatous elements. Uterine carcinosarcomas (UCs) are uncommon with approximately more than 35% presenting with extra uterine disease at diagnosis. Up to 90% ovarian carcinosarcomas (OCs) will have disease that has spread beyond the ovary. Prognosis for localized stage disease is poor with a high risk of recurrences, both local and distant, occurring within 1 year. The survival of women with advanced UC or OC is worse than survival of endometrioid or high-grade serous histologies. No improvement in survival rates has been observed in the past few decades with an overall median survival of less than 2 years. Currently, there is no clear evidence to establish consensus guidelines for therapeutic management of carcinosarcomas. Until recently, gynecological carcinosarcomas were considered as a subtype of sarcoma and treated as such. However, carcinosarcomas are now known to be metaplastic carcinomas and so should be treated as endometrial or ovarian high-risk carcinomas, despite the lack of specific data. For UCs, a comprehensive approach to management is recommended with complete surgical staging followed by systemic chemotherapy in patients with both early and advanced stage disease. Active agents include paraplatin, cisplatin, ifosfamide, and paclitaxel. The combination of carboplatin-paclitaxel is the most commonly used regimen in the adjuvant and advanced setting. Adjuvant radiotherapy (external beam irradiation and/or vaginal brachytherapy) has not shown any overall survival benefit but has been reported to decrease local recurrences. For OCs and for other ovarian epithelial cancer, the mainstay of treatment remains cytoreductive surgical effort followed, even in early stage, by platinum-based chemotherapy, usually carboplatin-paclitaxel.

Key Words: Rare tumor, Gynecological carcinosarcomas, Molecular analysis, Primary treatment, Metastatic disease

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Carcinosarcoma is a rare gynecological neoplasm that belongs to the category of mixed müllerian tumors, with both components (epithelial and mesenchymal) being malignant, thus also called malignant mixed müllerian tumor. This tumor may occur in any part of the gynecological tract but it is most often seen in the uterine cavity where it accounts for less than 5% of malignancies, followed by the ovary (1% to 3% of ovarian tumors).

CLINICAL FEATURES

Carcinosarcoma is a highly aggressive tumor. Up to two thirds of patients present with advanced stage disease, with tumor extending outside the uterus or the ovary, and involving the peritoneum.

Uterine carcinosarcoma (UC) and ovarian carcinosarcoma (OC) typically occur in postmenopausal women at a median age of 65 years. Although a higher incidence has been reported in Afro-Americans, risk factors associated with the development of UCs are identical to other endometrial carcinomas, such as obesity, nulliparity, exogenous estrogen use, or tamoxifen therapy. Prior pelvic irradiation has been implicated as a risk factor in 5% to 30% of patients.[1]

Clinical symptoms are those typically found in classical uterine endometrial carcinomas, with vaginal bleeding, pelvic mass, lower abdominal pain, or abnormal Papanicolaou test. In the ovary, the tumor is often diagnosed at the time of peritoneal spread and presents as a pelvic mass with peritoneal carcinomatosis.

Clinical and radiological staging tend to underestimate the extent of disease, since up to 60% of clinical stage I uterine tumors are found to have lymph node metastases. The staging system for carcinosarcomas is the same as that applied to endometrial and ovarian carcinomas [International Federation of Gynecology and Obstetrics (FIGO 2014)].[2]

MORPHOLOGICAL FEATURES

Uterine carcinosarcoma is typically a polypoid, bulky mass filling the entire uterine cavity, and with a hemorrhagic and necrotic component. Myometrial invasion is frequent as well as extension beyond the uterus. Ovarian carcinosarcoma is also typically a very large tumor with massive areas of hemorrhage and necrosis. The morphological features and the biology of this tumor seem identical regardless of its site of origin in the female genital tract.[3]

Histologically, the tumor is biphasic, with both malignant epithelial and mesenchymal elements. The carcinomatous component is composed of an admixture of high-grade carcinomas of endometrioid grade 3, serous, clear cell, or undifferentiated features. The sarcomatous component is either homologous or heterologous. Homologous sarcoma is composed of high-grade undifferentiated round cell or spindle cell sarcomatous proliferation, with some features similar to an endometrial stromal sarcoma or fibrosarcoma. Heterologous elements, which are seen in approximately 50% of cases, may show cartilaginous, osteosarcomatous, rhabdomyosarcomatous, or liposarcomatous differentiation. Neural or angiomatoid differentiation may also be seen. Myxoid change with hyaline globules is a prominent feature. The proportion of each carcinoma or sarcoma component may vary from one tumor to another.[3]

The histology of the metastatic component is more in keeping with an epithelial origin, because myometrial and lymphovascular invasion often display an epithelial morphology. The metastatic tumors show, in approximately 69% of cases, an epithelial component, whereas both carcinomatous and sarcomatous elements are found in 25% of cases and sarcoma in only 6% of metastatic tumors.[4]

MOLECULAR GENETICS

The histogenesis of female genital tract carcinosarcomas has been a subject of debate and several theories have been proposed, including the collision between a carcinoma and an adenosarcoma, and the combination theory, in which both components arise from a single stem cell clone. However, the conversion theory postulating that sarcoma derives from carcinoma is actually favored.[4] Indeed, recent immunohistochemical and molecular findings support the hypothesis that gynecological carcinosarcomas represent metaplastic carcinomas. Cell lines established from carcinosarcomas are able to differentiate into either epithelial, mesenchymal components, or both.[5] Immunohistochemistry demonstrates the expression of epithelial markers in the sarcomatous component of carcinosarcoma. Moreover, clonality studies patterns, genomic analysis, and loss of heterozygosity studies have shown that carcinomatous and sarcomatous components of these tumors share common genetic alterations and are monoclonal.[6] The transformation of a carcinoma to a sarcoma in these tumors may represent a transdifferentiation as seen in epithelial-to-mesenchymal transition phenomena.[7]

The molecular alterations seen in UCs are more akin to type II non-endometrioid than type I endometrioid uterine carcinomas. Data concerning molecular alterations in OC and UC are scarce and based on the analysis of relatively small number of samples.[8] TP53 mutations and/or protein overexpression are considered to be the most frequent events with a p53 positivity observed in up to 60% of tumors and TP53 mutations in 23% of cases.[9] *PI3KCA* mutations were also reported in 19% of UC cases and *KRAS* mutations in 24%.[10] Contradictory results were found with *PTEN* mutations: 0% to 14%. In rare cases, mutations affecting β-*catenin* (7%), *NRAS* (2%) were identified. Studies have demonstrated that up to 45% of UCs express Abl, 19% HER-2/neu, 100% PDGF-R β, 32% ER-β, 23% EP-B. Overexpressions of Cox2 (33%), EGFR (30%), Trop-2 (35%–57%), c-KIT (16%–25%), and PARP have also been reported. VEGF is strongly expressed in UCs.[11] Consistent with the high frequency of P53 alterations, most UCs exhibit high chromosomal instability. Cytogenetic studies of UCs have revealed extremely complex karyotypes with gross chromosomal anomalies, such as polysomy 8. Comparative genomic hybridization studies have demonstrated gains and losses at multiple chromosomal loci.[6]

PROGNOSIS

Female genital tract carcinosarcomas have a very poor prognosis with an overall 5-year survival of less than 30%.

Although stage I UC has a better prognosis (50% of 5-year overall survival), it is still significantly worse than stage I high-grade endometrial carcinoma (80% of 5-year overall survival).[1] Median overall survival varies from 8 to 26 months.[12] Most patients experience a relapse within 1 year after completion of treatment. The FIGO stage, the patient's age (>55 years), the depth of myometrial invasion, and the patient's race are the most frequently reported prognosis factors in UC. Lymph node dissection, tumor size, lymphovascular space invasion, parity, and grade of the sarcomatous compound have a less certain prognostic value, whereas data about the presence of heterologous elements or pelvic radiotherapy are contradictory.[11–13]

Overall, the prognosis for OCs is worse than UCs[12] and high-grade ovarian carcinomas of a similar FIGO stage.[14] Most (90%) present as advanced disease and the median overall survival ranges from 7 to 27 months. For OCs, the FIGO stage is the strongest prognostic factor. Some reports indicate that complete cytoreduction, advanced age, grade (of the sarcomatous component), and the use of adjuvant chemotherapy are prognostic factors.[14] It should be noted that the limited number of patients in the retrospective studies does not allow definitive conclusions to be drawn.

INITIAL TREATMENT

Optimal treatment remains uncertain. Ovarian and uterine carcinosarcomas are routinely excluded from upfront clinical trials. Treatment recommendations are mainly based upon retrospective studies with small patient populations especially for OCs.

Surgery

Uterine Carcinosarcoma

Primary treatment includes peritoneal lavage for cytology, total abdominal hysterectomy, bilateral salpingo-oophorectomy with dissection of pelvic and para-aortic lymph nodes, and maximal tumor debulking. Surgical staging for these tumors should follow the procedures performed for ovarian carcinoma including detailed examination of the entire abdominal cavity and retroperitoneal spaces and appropriate biopsies. The role of lymphadenectomy is unclear and a subject of current debate. However, given the relatively high incidence of lymph node involvement (14% to 38% in early stage), regarding impact on survival, most of the retrospective studies suggest a significant survival benefit of the lymph node dissection in UCs.[15,16] So, adequate lymphadenectomy seems needed for both staging and therapeutic reasons. In advanced disease, primary cytoreductive surgery is generally performed, despite no clear evidence.

Ovarian Carcinosarcoma

Cumulative retrospective data support the benefit of an optimal surgical cytoreduction with total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, aspiration of abdominal fluid, pelvic and para-aortic lymph node dissection, and tumor debulking. Given the rarity of OCs, the role of cytoreductive surgery has not been prospectively evaluated. Several small retrospective studies of less than 50 patients have reported an improved outcome for patients undergoing an optimal debulking surgery, without residual disease. One of the largest studies, including 50 patients, reported DFS for patients with only microscopic disease of 19 months, compared to 10 months for those with less than 1 cm residual disease and 5 months for those with more than 1 cm ($P = 0.01$). Overall survival is 47, 18, and 8 months, respectively ($P = 0.02$).[14] The SEER database from Garg et al[12] reported an improved survival for patients with lymphadenectomy, suggesting the utility of lymph node dissection, although this may reflect stage migration. Conservative surgery is never indicated for OC even in adequately staged stage IA.

Adjuvant Treatment for Early Stage

Due to the high rate of local and distant recurrences, even for the early-stage disease, adjuvant systemic treatment is generally considered. There is still no clear consensus on the best adjuvant therapy for patients with OC as most studies are retrospective and describe the outcome in a small number of patients who were given a variety of treatment regimens.

Adjuvant Radiotherapy

Uterine carcinosarcomas

Pelvic recurrence is common, even for patients with an early-stage disease; thus, radiotherapy (pelvic with or without brachytherapy) has been commonly used and reduces the incidence of local pelvic recurrence.[17] However, its impact on patient survival is not proven and remains a subject of controversy. The only phase III study comparing pelvic radiotherapy and observation is the EORTC study from Reed.

Two hundred twenty-four FIGO stage I to II uterine sarcomas, including 91 carcinosarcomas, were randomized between observation and RT. Analysis of all patients revealed a reduction in local relapse ($P = 0.004$) but no effect in either overall or disease-free survival. The local recurrences rate was 18 (8%) for patients treated with radiotherapy and 35 (9%) in the observation arm. The same results were observed among the patients with carcinosarcomas. However, most patients relapsed simultaneously at distant sites and therefore radiotherapy seems to be only of limited value.[17]

The SEER database from Wright registered 1819 patients with stage I to II UCs and reported, in a multivariate model, a 21% reduction of death for women who underwent radiotherapy. The benefit was only observed for women who did not undergo lymph node dissection.[18] The second study using also SEER data (n = 2461) from Clayton Smith et al reported an improvement in overall survival for women with UCs treated with postoperative radiotherapy compared to surveillance. The overall 5-year survival was 41 (5%), using adjuvant radiotherapy compared to 33 (2%) ($P < 0.001$).[19] However, a third SEER analysis (n = 1855) did not show any impact of radiotherapy on further prognosis (also in the group of patients without lymphadenectomy).[15] Large databases reviews have limitations because of the lack of standardization of surgery, radiotherapy, and chemotherapy, the absence of centralized pathological review and the potential impact of patient's and physician's preference on adjuvant treatment.

The Gynecologic Oncology Group (GOG) has performed one of the few prospective randomized trials in UCs. Whole abdominal radiotherapy (WART) was compared

to 3 cycles of ifosfamide-cisplatin in 206 patients with stage I to IV after complete resection. The local and distance recurrence rates were 44 (7%) and 25 (7%), respectively, with WART and 42 (5%) and 23 (3%) with chemotherapy. Although there was no statistically significant survival benefit, an improved recurrence rate and survival was noted in the chemotherapy group (21% lower recurrence and 29% lower death, but this was not statistically significant). Toxicity was lower with chemotherapy compared to WART and this is no longer performed, due to its toxicity.[20]

In conclusion, external pelvic radiotherapy does not improve overall survival but decreases local recurrence rates, which could, in theory, impact favorably on quality of life.

Ovarian carcinosarcomas

There is little rationale for using radiotherapy in OCs as most are advanced at presentation. In patients with early OCs, the role of radiotherapy remains unknown.

Adjuvant Chemotherapy

The role of adjuvant chemotherapy in carcinosarcomas is still uncertain.

Uterine carcinosarcoma

Only 1 trial has prospectively addressed the question of adjuvant chemotherapy (3 cycles of ifosfamide-cisplatin) for UCs in comparison with radiotherapy (WART). This study was not able to demonstrate a significant difference in relapse rate or overall survival (OS), but a slight advantage favoring the use of chemotherapy.[20] Another trial, including also gynecologic sarcomas, failed to show a significant advantage with adjuvant chemotherapy on progression free survival (PFS) and OS.[21] A small study of 81 patients with a variety of uterine sarcoma histologies and FIGO stages, chemotherapy, using adriamycin, ifosfamide, and cisplatin, followed by radiation was superior to radiation alone at 3 years for disease-free survival (55% vs 41%) but not for overall survival. These data cannot be used to support a recommendation for adjuvant chemotherapy as standard treatment given the heterogeneity of the tumor types and stages and the very small sample size and no overall survival benefit.[22] In the prospective phase II GOG 232B study, 65 stages I to II completely resected UCs received 3 cycles of ifosfamide-cisplatin chemotherapy; PFS and OS at 7 years were 54% and 52%.[23] Due to its activity and favorable toxicity profile shown in advanced carcinosarcomas, the combination of carboplatin-paclitaxel is commonly used in the adjuvant setting.[24]

Ovarian carcinosarcomas

The recommendations, based on retrospective data, are to use platinum-based chemotherapy, either carboplatin-paclitaxel or ifosfamide-cisplatin.[25] The largest study of patients treated postoperatively with carboplatin-paclitaxel comprised only 50 patients.[14] A recent Cochrane review found no evidence to inform decisions about adjuvant or neoadjuvant chemotherapy.[26]

Multimodal Therapy in UCs

Several retrospective studies have shown a favorable survival outcome with sequential multimodality therapy including pelvic radiotherapy and chemotherapy with cisplatin-ifosfamide, paclitaxel-ifosfamide, or paclitaxel-carboplatin. Some studies suggest a better outcome with combined treatment versus radiotherapy alone. A retrospective study reported by Makker et al, included 49 stage I to IV patients receiving platinum-based chemotherapy after surgery (mainly carboplatin-paclitaxel), with or without radiation therapy or radiotherapy alone; the 3-year PFS for chemotherapy group was 35% compared to 9% for radiotherapy group and 3-year OS rates were 66% and 34%, respectively (NS).[27] In contrast, other publications did not report an effect of combination therapy (CT + RT) versus chemotherapy alone in patients with UCs.

The 2010 National Comprehensive Cancer Network guidelines recommend adjuvant treatment for all stage of UC, similar to type 2 carcinomas.[28]

ADVANCED/METASTATIC DISEASE AND RELAPSE

Uterine Carcinosarcomas

The main cytotoxic agents studied in UCs are ifosfamide [32% response rate (RR)], cisplatin (RR, 19%), and paclitaxel (RR, 18% as first- or second-line therapy).[29] In contrast to other gynecologic sarcomas, doxorubicin is only minimally active (10% RR)[30] but data are limited. Some responses have been reported with pegylated liposomal doxorubicin.[31] Responses are usually partial and of short duration.

Two prospective randomized trials had compared monochemotherapy and polychemotherapy with ifosfamide. Sutton et al reported 194 patients who received ifosfamide with or without cisplatin. Although RRs were higher with the combination (54% vs 36%) and PFS significantly higher (6 vs 4 months), no overall survival improvement was observed and the toxicity of the combination was notably increased.[29] The GOG 161 study included 179 patients treated with ifosfamide with or without paclitaxel and reported a significant difference in the objective RR (45% vs 29%), PFS (5, 8 vs 3, 6 months), and overall survival (13, 5 vs 8, 4 months) in favor of combination.[32] Finally, the Cochrane database including 579 women, concluded that, in advanced stage UC as well as in recurrent disease, combination chemotherapy with ifosfamide and paclitaxel is reported to be associated with lower risk of death compared with ifosfamide alone.[33] Thus, the ifosfamide-paclitaxel combination is currently considered as standard arm treatment in most countries.

The combination of paclitaxel-carboplatin is another option as it is a well-tolerated outpatient regimen. Several phase II trials reported high RRs (ranging from 54% to 69%), including a number of patients achieving a complete response. The median PFS was 7 (6 months) and the OS 14 (7 months).[24,34] The GOG 261 study is testing this regimen in an ongoing phase III noninferiority trial comparing ifosfamide-paclitaxel and carboplatin-paclitaxel.

As a result, paclitaxel-carboplatin is commonly used as routine therapy.

Many biological anticancer treatments have been evaluated (sorafenib, imatinib, thalidomide, VEGF-Trap, and iniparib plus paclitaxel and carboplatin). Response rates to targeted agents are poor in unselected populations (0%–5%).[35]

Ovarian Carcinosarcomas

Some data have led to the conclusion that the chemosensitivity of OCs is similar to that of UCs, but less than that of serous epithelial ovarian cancer. As a consequence, the conclusions drawn from the effects of chemotherapy in UCs are applied to the less common OCs.[12]

Published data evaluating benefit of the chemotherapy are based on a few nonrandomized prospective studies and some retrospective analysis. Common treatment combinations include platinum-paclitaxel and platinum-ifosfamide.

PERSPECTIVES

Further research on genetic and molecular signaling pathways is needed to improve the understanding of these tumor subtypes, including descriptive and functional analyses. Further prospective trials are clearly warranted in a larger group of patients. Ideally, these should be randomized trials or well-designed nonrandomized studies that use multivariate analysis to adjust for baseline imbalances.

Studies should incorporate molecular-targeted therapies alone or in combination with cytotoxic drugs, for example, paraplatin-paclitaxel. Although both UC and OC are rare, care should be taken to stratify patients based on a molecular profile. Such studies can only be done through international collaboration.

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