Abstract. Background: Carcinosarcomas (CS) are mixed epithelial and stromal tumours with both components being malignant. Twenty-one patients with carcinosarcomas who were treated at the University of Saarland, Germany, are presented. Patients and Methods: The hospital records of all patients were reviewed. Results: The mean age range for homologue CS (homCS) was 60.7 years and for heterologue CS (hetCS) 68.4 years. Post-menopausal bleeding and abdominal pain were the main symptoms. Treatment modalities included surgery, adjuvant radiation therapy and various chemotherapy regimens. The median follow-up time was 17.6 months (homCS) and 31.1 months (hetCS). The 1-year survival rate was 55.6% (hetCS 58.3%) and the 5-year survival rate was 11.1% (hetCS 8.3%). Conclusion: Carcinosarcoma is a uterine sarcoma with a poor prognosis. Treatment includes surgery and adjuvant chemotherapy, whereas radiotherapy does not necessarily lead to a benefit. Treatment with trastuzumab might be a new approach in the therapy of HER-2/neu-positive CS.

Sarcomas of the female genital organs are rare. Only about 2-3% of all malignant tumours of the genital tract are sarcomas and they comprise 3 main tumors: leiomyosarcoma, carcinosarcoma and endometrial stromal sarcoma. Carcinosarcomas (or malignant mixed mesodermal or müllerian tumour, CS) are mixed epithelial and stromal tumours with both components being malignant, the most common malignant uterine tumours after carcinomas. They present as polypoid masses filling the endometrial cavity. The epithelial component can be of endometrioid, serous, clear cell, mucinous, undifferentiated or squamous type. The stromal component can be of the pure endometrial stromal or fibrosarcomatous type in which case the tumours are called homologue carcinosarcomas (homCS). If the stromal component is non-uterine tissue such as in rhabdomyosarcomas, chondrosarcomas, osteosarcomas or liposarcomas they are called heterologous carcinosarcomas (hetCS) (1). Due to the low number of cases, it is very difficult to obtain satisfying information about this disease and little is known about its pathogenesis, risk factors, optimal therapy or outcome. Observations in large numbers of patients hardly exist. In this article, 21 patients with carcinosarcomas who were treated at the University of Saarland, Germany, are presented and an overview of the current literature concerning carcinosarcoma is provided.

Patients and Methods

During the 24-year period from 1972-1996, 21 patients were diagnosed with a homCS or hetCS in the Department of Gynaecology and Obstetrics of the University Hospital of Saarland, Germany. The hospital records of all patients including pathology and operative reports were reviewed and any information on treatment, recurrence and survival was obtained.

Age and parity. The age range of the 9 patients with homCS was 45 – 81 years, with a mean age of 60.7 years (SD±11.6 years). Six patients were post-menopausal (66.6%) and 3 patients were pre-menopausal (33.3%). The mean age at menarche was 14.5 years (SD±2.7; minimum 10 years, maximum 18 years) and at menopause 48 years (SD±4.9; minimum 41 years, maximum 53 years). The mean birth rate per patient was 2.8 births, the mean pregnancy rate was 2.6 per patient.

In the 12 patients with hetCS, the age range was 46 – 82 years, with a mean of 68.4 years (SD±10.8 years). Eleven patients (91.7%) were post-menopausal and one was pre-menopausal (8.3%). The mean age at menarche was 13.5 years (range 12-15 years, SD±1) and at menopause 47.8 years (range 42-53 years; SD+/−3.31). The mean birth rate was 2.4 births, the mean pregnancy rate was 2.6 per patient.
Medical history. In the group with homCS, one patient suffered from thyroid disease, three from obesity and three from diabetes mellitus. Leiomyomas were found in 1 patient. One patient had been diagnosed with homCS of the vagina (stage IV) 13 years after having had a combined Radium-Telekobalt-therapy because of a polymorph-cellular sarcoma of the cervix uteri. In the patients with hetCS, six had a struma nodosa, two had diabetes mellitus, two were obese and two had leiomyomas. One patient was diagnosed with ovarian sarcoma 16 years ago, one with Morbus Hodgkin 12 years ago and one with breast cancer seven years ago. The average time between radiation therapy and diagnosis of heterologous carcinosarcoma was 11.6 years. Another two patients were currently treated adjuvantly with Tamoxifen for breast cancer.

Results

Symptoms and diagnosis. Post-menopausal bleeding (55.5% in homCS, 58.3% in hetCS) and abdominal pain (16.6% in hetCS) were the main symptoms of these patients. In two cases of homCS (22.2%) and two cases of hetCS (16.6%), the diagnosis was found accidentally. In one patient, the homCS was found in the ovary. In five cases of homCS (55.5%) and six cases of hetCS (50%), a diagnostic curettage was performed and led to the diagnosis in four patients with homCS and all patients with hetCS. In five patients with homCS and eight with hetCS, a PAP smear was taken pre-operatively. A cytological examination of intra-operatively assessed peritoneal washings was performed in three patients with homCS and seven patients with hetCS. The cytological findings are shown in Table I. No homCS patient had pre-operatively elevated tumour markers, but in five hetCS patients CA12-5 was elevated.

FIGO-classification and tumour grading. In the homCS patients, four had a primary tumour FIGO Stage I, two had FIGO II, one had FIGO III and two patients had FIGO IV. In one case the tumour was grade II, in five cases grade III and in 3 cases the tumour grading was not assessed. Four patients had metastatic disease at the time of the first diagnosis. In the hetCS patients, five were FIGO I, two were FIGO II, four were FIGO III and one was FIGO IV. A grade II tumour was found in two cases, undifferentiated tumours (GIII) in 6 cases and in the other patients there was no information about the grading. Four patients had metastatic disease. The localisation of the metastases is shown in Tables II and III. The heterologue component was osteosarcomatous in 3 cases, rhabdomyosarcomatous in 4 cases and chondrosarcomatous in 3 cases. In 2 cases there was no further information available.

Therapy

a) Homogenous carcinosarcoma. Six patients with homCS of the corpus uteri had hysterectomy with bilateral salpingo-oophorectomy. One patient could not be operated on due to generally poor health condition. The patient with the previous cancer of the cervix had a biopsy of the vagina first.
and then underwent hysterectomy with bilateral salpingo-oophorectomy as well. The patient with the sarcoma of the ovary underwent a Wertheim-Meigs-Okabayashi operation. Three patients underwent adjuvant radiation of the pelvis and additional afterloading radiation, 1 had afterloading radiation only, 1 had percutaneous radiation plus chemotherapy with a combination of vincristin, doxorubicin and proresid (VAP), one had percutaneous radiation only and the patient with homCS of the ovary had chemotherapy only. Two patients underwent surgery only and died postoperatively of lung embolism and toxic shock, respectively.

**b) Heterologous carcinosarcoma.** Seven patients with hetCS underwent hysterectomy with bilateral salpingo-oophorectomy and three of these also underwent additional removal of the upper part of the vagina. One patient with a carcinosarcoma of the cervix uteri only had a biopsy. One patient with a carcinosarcoma of the breast had breast conserving therapy including axillary lymphadenectomy. There were three patients with carcinosarcoma of the ovary. One had a bilateral salpingo-oophorectomy, omentectomy and a partial resection of small intestines; one had a removal of metastases only and one underwent tumour debulking only. Six patients had adjuvant radiation of the pelvis and two of them had additional afterloading radiation. One patient received chemotherapy with carboplatin and cyclophosphamide, one with cisplatin and treosulfan and one with doxorubicin, methotrexate and cisplatin. Two patients died shortly after surgery and one patient with inoperable disease refused further therapy.

**Survival and recurrence rates.** In the patients with homCS, the median follow-up time was 17.6 months (range 2-72 months). Four patients had recurrence and the disease-free intervals were 2, 4, 6 and 52 months, respectively (Table IV). The 1-year survival rate was 55.6% and the 5-year survival rate was 11.1% (Table IV).

In the hetCS patients, the median follow-up time was 31.1 months (range 2-192 months). Six patients had recurrence and the disease-free intervals were 3, 4, 5, 5, 10 and 20 months, respectively (Table IV). The 1-year survival rate was 58.3% and the 5-year survival rate was 8.3% (Table IV).

**Discussion**

Carcinosarcomas are very rare tumours. They consist of an epithelial and a mesenchymal component, and both components are malignant. CS have been regarded as a subtype of uterine sarcoma. However, there is evidence that
most, but not all, of these tumours are rather monoclonal neoplasms deriving from a stem cell that undergoes divergent differentiation, and that they are metaplastic carcinomas. The epithelial component appears to be dominant (2-4).

The median age of manifestation of carcinosarcomas is given as 50 to 71 years, with a possibly lower age for homCS than for hetCS (5-11). In our patients, the average age for homCS was 60.7 years and in hetCS was 68.4 years. Both histological subtypes seem to occur predominantly in postmenopausal women as was demonstrated in our analysis and in previous studies (7, 12, 13).

To our knowledge, there are no well-established risk factors for the development of carcinosarcoma. Several studies suggest ethnic differences with a higher prevalence of CS in women of African origin than in Caucasians and also a worse survival for the former (14-17). One study describes a prevalence of the human papillomavirus in CS of the uterine cervix (18). Five of our patients with hetCS suffered from struma nodosa. Three out of all 21 patients were obese. Two of our patients had been previously treated with tamoxifen for breast cancer. There are data indicating that treatment with tamoxifen, short- and long-term, increased the risk of developing carcinosarcoma (19-24). A case of CS with overexpression of the HER-2/neu oncogene developing in a patient given tamoxifen therapy for breast cancer over a period of 2 years was reported (23).

In our study, four patients developed CS after previous radiation. The average time from radiation to diagnosis was 9.8 years. Also, in some studies and reports, previous radiation therapy was also discussed as a risk factor for uterine carcinomas or carcinosarcoma of ovary (7, 25, 26). George et al. correlated radiation therapy to the development of a uterine sarcoma after 4 to 21 years (7). Furthermore, patients with previous radiation therapy might have a worse prognosis (27, 28). However, two working groups could neither confirm the positive correlation of radiotherapy to the incidence of sarcomas nor the negative correlation to the prognosis (29, 30).

As in most malignancies of the uterus, the first symptom is often abnormal vaginal bleeding (10, 11, 14, 31). Hence, as in many other reports, most of our patients clinically presented with abnormal bleeding. Therefore, a pre-operative curettage is a common step in the arriving at the diagnosis (32). Vaginal bleeding occurs after penetration of the tumour into the epithelial layer. Cytological examinations are, therefore, not helpful in having an early diagnosis. In our patients, a normal pre-operative PAP smear was found in two patients with homCS and in four with hetCS, but a PAP III was found in four hetCS patients. Ito et al. retrospectively found a sarcomatous component in a pre-operatively assessed specimen from the endocervical canal and endometrial cells in 12 out of 14 cases of uterine and vaginal sarcoma. However, four cases of CS were overlooked in the first examination (33). Snyder et al. found 60% of conventional PAP smears abnormal in a group of 25 patients with carcinosarcoma and in this group four patients were also overlooked in the first examination. All malignant elements in the smears were epithelial. The abnormal PAP result was correlated with worse survival (34).

The tumour marker CA 12-5 was elevated in 41.7% of our patients with hetCS, which is in agreement of a report of Hackett et al. who found elevated CA 12-5 in 46% of patients with carcinosarcoma (35).

The treatment modalities for uterine sarcomas are surgery, radiation and chemotherapy. Total hysterectomy with bilateral salpingo-oophorectomy is the most common surgical approach. It may be completed by omentectomy and, due to the potential spread to pelvic and paraaortic lymph nodes, by lymphadenectomy (11, 16, 36-38). Radiation modalities include external beam irradiation, as well as intracavitary irradiation or a combination of both. The data regarding the positive effect of radiation therapy are not clear. Adjuvant pelvic radiotherapy, with or without brachytherapy, might improve the outcomes of defined patient groups concerning 5-year survival, rate of pelvic recurrence or distant failure and death (10, 17, 39-46). Other studies did not reveal any influence of post-operative radiation on local or distant recurrence or overall survival (45, 47, 48).

Data regarding the use of chemotherapy vary. Neither Nordal et al. could see any change in 5-year survival after the introduction of chemotherapy in a large number of patients with uterine sarcoma, nor could Sagae et al. prove a benefit of adjuvant chemotherapy (32, 49). However, Thigpen et al. used cisplatin with a relatively good tumour response rate of 18%. (50). The Gynecologic Oncology Group treated 65 patients in FIGO stage I or II adjuvantly with cisplatin/ifosfamid and reported progression-free survivals (PFS) and overall survivals (OS) of 69% and 82% at 24 months and 54% and 53% at 84 months with a 5-year survival of 62% (8). Another phase III trial of the same group including 194 patients suggested that the addition of cisplatin to ifosfamid improved PFS but not OS, with the price of a higher toxicity (51). Sartori et al. reported overlapping survival curves in patients with advanced disease treated with cisplatin-containing regimens or with doxorubicin (52). A French study group enrolled 39 women with uterine sarcomas and treated them with a combination of doxorubicin, dacarbazine, vindesine, cisplatin and either cyclophosphamide or ifosfamide. They demonstrated good response with an overall response rate of 54% and median OS of 14 months, however, they had very high toxicities (9).

In our patient group, cisplatin was used in combination with treosulfan in one patient, who survived 16 months. The combination of paclitaxel and carboplatin was reported to be successful and with tolerable toxicities (53). Menczer et
favoured a sequential adjuvant treatment with chemotherapy followed by whole pelvic irradiation according to their results of a retrospective analysis of 49 patient records (54). The Gynecologic Oncology Group treated 48 patients with topotecan and could not been prove success in advanced or recurrent disease; however, 92% of the patients enrolled in this study had received prior chemotherapy or radiation (55). The same group used paclitaxel in patients with persistent or recurrent disease with a response rate of 18.2% (56). A combination therapy with mesna, doxorubicin, ifosfamide and dacarbazine did not show any effect in CS patients (57).

An interesting new therapeutic approach could be the use of trastuzumab. The presence of the HER-2/neu receptor was demonstrated in primary and in recurrent CS (58-60). In receptor-positive CS, the receptor was mostly found in the epithelial but rarely in the sarcomatous component (58, 61). Expression of HER-2/neu was not correlated with the clinical outcome (59-61).

The prognosis of CS is poor. In our group, we found a mean survival of 17.6 months for homCS and 13.6 months for hetCS; the 1-year survival rate was 55.6% (homCS) and 58.3% (hetCS) and the 5-year survival rate was 11.1% (homCS) and 8.3% (hetCS). The median survival time quoted in the literature ranges from 11 months to 59 months and the data for 5-year survival rates range from 21% to 78.8% (8, 10, 15, 32, 41, 47, 62). In the study of Sutton et al., PFS and OS, respectively, were 69% and 82% at 24 months and 54% and 52% at 84 months (8). Both local and distant recurrence occurred, with the most common sites of distant metastases being lungs, bone, abdomen and brain (11).

It is difficult to find clear information about prognostic factors for carcinosarcomas. Some authors suggested poorer results for heterologous tumours, others did not (63-66). In our patients, the patients with a chondrosarcomatous component had the shortest survival (9.6 months) and the patients with an osteosarcomatous component had the longest survival (23 months). Nordal et al. described tumours with components of serous or clear cell carcinoma as a prognostic factor (49). Factors such as late onset of menopause, tumour stage, tumour diameter, depth of myometrial invasion, epithelial nuclear grade, the presence of extratumor extension, gross residual disease and distant metastasis were suggested to be important prognostic factors in uterine sarcoma (11, 16, 32, 38, 46, 47, 49, 59, 67). The data concerning age, vascular and lymphatic space invasion, stromal grade, type of stromal component and predominance of either the stromal or epithelial component as prognostic factors are not undisputed (38, 46, 47, 49, 67).

We conclude that carcinosarcoma is a uterine sarcoma with a poor prognosis. Patients are frequently diagnosed in an early tumour stage but still experience early local or distant recurrence. Treatment includes surgery and adjuvant chemotherapy should be considered, whereas radiotherapy does not necessarily lead to a benefit. Treatment with trastuzumab might be a new approach in the therapy of HER-2/neu-positive CS.

References


