Endometrial Stromal Sarcomas – a Retrospective Analysis of 11 Patients

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Abstract. *Background: Endometrial stromal sarcoma (ESS) is a malignant tumour with its origin in the endometrial stroma. Little is known about the pathogenesis, risk factors, optimal therapy or outcome of this disease. Patients and Methods: Eleven patients with ESS, treated between 1972 and 1996, are reported on. The hospital records of all the patients, including pathology and operative reports, were reviewed and information on treatment, recurrence and survival was obtained. Results: The mean age of our patients was 56.6 years. The main symptom was abnormal vaginal bleeding. Most patients were diagnosed at FIGO stage I. Treatment modalities were surgery, radiation and, in one patient, chemotherapy. The median follow-up time was 42.1 months; 27.3% of the patients had local recurrence. The 1-year, 2-year and 5-year survival rates were 36.3%, 18.1% and 9.1%, respectively. Conclusion: ESS is a uterine sarcoma with a difficult differential diagnosis. Patients are frequently diagnosed in an early tumour stage but still experience local or distant recurrence. The prognosis is poor, with early recurrence and low long-time survival rates. The treatment includes surgery and adjuvant radiation, with endocrine therapy being a promising new approach. In order to obtain more information about the pathogenesis of the tumour and to find the optimal therapy, it is necessary that studies, even with small numbers of patients, are undertaken.*

Sarcomas of the female genital organs are rare, with only around 2-3% of all malignant tumours of the genital tract being sarcomas (1-3). They comprise 3 main tumours: leiomyosarcoma, carcinosarcoma and endometrial stromal sarcoma (ESS). ESS (or endolymphatic malignant stromatosis, stromamyosis) has its origin in the endometrial stroma. Due to the low number of cases, it is very difficult to obtain complete information about this disease and little is known about its pathogenesis, risk factors, optimal therapy or outcome. Few observations in large numbers of patients exist. Here, 11 patients with ESS, who were treated at the University of Saarland, Germany, are presented and an overview of the current literature concerning ESS is given.

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Patients and Methods

During the 24-year period from 1972-1996, 11 patients were diagnosed with ESS in the Department of Gynaecology and Obstetrics of the University Hospital of Saarland, Germany. The hospital records of all the patients, including pathology and operative reports, were reviewed and any information on treatment, recurrence and survival was obtained.

Results

Age and parity. The age range of the 11 patients was 36 - 74 years, with a mean age of 56.6 years (SD±14.1 years). Six patients were postmenopausal (54.4%) and 5 premenopausal (45.5%). The mean age at menarche was 13.7 years (SD±1.3; minimum 11 years, maximum 15 years) and at menopause 49 years (SD±5.1; minimum 40 years, maximum 52 years). The mean birth rate per patient was 2.4, while the mean pregnancy rate was 2.6.

Symptoms and diagnosis. Postmenopausal bleeding (36.4%) and atypical premenopausal bleeding (18.2%) were the main symptoms of these patients. In 3 cases (27.3%), the diagnosis was found accidentially.

Table I. *Cytological findings.*

	No. of patients	Percentage
Pre-operative swab		
PAP I	3	60
PAP II	1	20
PAP III	1	20
PAP IV	0	0
PAP V	0	0
Intra-operative peritoneal washing		
PAP I	0	0
PAP II	2	40
PAP III	0	0
PAP IV	1	20
PAP V	2	40

Table II. *Localisation of metastases.*

Tumour	pT	pN	Grade	Localisation of metastases
Corpus	3	0	no data	mesenterium, parametrium
Corpus	4	1	III	retroperitoneal
Corpus	2b	x	III	small intestine
Corpus	4	x	no data	peritoneum, liver

pTNM-staging: postoperative histopathological classification of malignant tumours according to the recommendations of the Union Internationale Contre le Cancer (UICC).
pT: extension of the primary tumour.
pN: involvement of regionary lymph nodes.

Table III. *Lymph node metastases.*

Tumour	pT	M	Grading	Lymph nodes
Retroperitoneal	3a	0	no data	interiliacal
Corpus	4	0	III	iliacal, paraaortal

pTNM-staging: postoperative histopathological classification of malignant tumours according to the recommendations of the Union Internationale Contre le Cancer (UICC).
pT: extension of the primary tumour.
M: clinical proof of the (non-) existence of distant metastases.

In 3 cases (27.3%), a diagnostic curettage was performed and led to the diagnosis of an ESS in 2 patients (66.7%). In 5 patients (45.5%), a smear was taken pre-operatively. The cytological results were PAP I in 3 patients (60%) and PAP II and PAP III in 1 patient each (20%). Cytological examinations of intra-operatively-assessed peritoneal washings were performed in 5 patients. The results results are shown in Table I. No patient had pre-operatively elevated tumour markers. Three patients (27.8%) suffered from thyroid disease, 3 (27.8%) from obesity and 2 from diabetes mellitus (18.2%). Leiomyomas were found in 2 patients (18.2%).

FIGO-classification and tumour grading. Five patients (45.5%) had a primary tumour FIGO Stage I, 1 patient (9.1%) had FIGO II, 1 patient had FIGO III (9.1%), 3 patients had FIGO IV (27.3%), and in 1 patient the tumour stage was not assessed. Four patients (36.4%) had metastatic disease at the time of the first diagnosis. The localisation of the metastases is shown in Tables II and III. A highly-differentiated tumour (GI) was found in 1 case, undifferentiated tumors (GIII) in 4 cases, while in the other patients there was no information about the grading.

Treatment. Hysterectomy with bilateral salpingo-oophorectomy was performed in 7 patients (63.6%) and 1 patient had an additional omentectomy. Due to poor health status, 2 patients had a simple abdominal hysterectomy and 1 patient had a supracervical amputation of the uterus. Five patients (45.5%) had operative therapy alone. Five patients (45.5%) received adjuvant percutaneous pelvic radiation and 2 of them an additional afterloading radiation. One patient (9.1%) had adjuvant chemotherapy (vincristine, etofurane, methotrexate).

Survival rates and rate of recurrence. The median follow-up time was 42.1 months (minimum 4, maximum 228). Three patients (27.3%) had local recurrence and 3 patients died of the sarcoma. The 1-year survival rate was 36.3% (n=4), the 2-year survival rate was 18.1% (n=2) and the 5-year survival rate was 9.1% (n=1). The survival rate of premenopausal patients (n=5) was 33.3% and of postmenopausal patients (n=6) was 75%. The survival rate of patients with a FIGO Stage I (n=4) was 66.6%, of those with FIGO Stage II (n=1) 100%, of those with FIGO Stage III (n=2) 100%, and of those with FIGO Stage IV (n=3) 66.6%. The survival rate of patients with tumour grade I (n=1) was 100% and with tumour grade III (n=3) was 33.3%. The survival rate of patients with adjuvant therapy was 83.3% (Table IV).

Discussion

ESS are very rare tumours, with the estimated annual incidence being 1.7 per 100, 000 females (4). Only 0.2% of all uterine neoplasms and 6-20% of all uterine sarcomas are ESS (5-11). Due to the low number of patients with a proper follow-up, it is difficult to find statistically reliable information on the disease.

Macroscopically there is often a polypous, powerful tumour which sometimes grows into the cervix. In 75% of all cases, there is an early infiltration of the myometrium.

Table IV. *Mean survival times of patients with endometrial stromal sarcoma.*

Criteria	Mean survival time [months]	Minimum [months]	Maximum [months]
All patients	42.14	4	228
Menopausal status			
premenopausal	80	10	228
postmenopausal	13.75	7	24
Parity			
nullipara	–	–	–
para >1	42.14	4	228
Pre-operative smear			
PAP I	228	–	–
PAP II	7	–	–
PAP III	12	–	–
Peritoneal washing			
PAP II	–	–	–
PAP III	9.50	7	12
PAP V	–	–	–
Grading			
I	8.00	–	–
II	–	–	–
III	24	–	–
Hemangiosis			
Yes	86.33	7.00	228.00
No	9.00	4.00	12.00
Lymphangiosis			
Yes	228.00	–	–
No	11.16	**4.00**	**24.00**
Localisation			
Corpus uteri	42.14	4.00	228.00
Cervix uteri	–	–	–
FIGO-stage			
I	8.00	4.00	12.00
II	24.00	–	–
III	118.00	8.00	228.00
IV	7.00	–	–
Adjuvant therapy			
Yes	55.00	4.00	228.00
No	10.00	8.00	12.00
Percutan radiotherapy			
Yes	67.75	7.00	228.00
No	8.00	4.00	12.00
Afterloading			
Yes	12.00	–	–
No	11.00	4.00	24.00
Chemotherapy			
Yes	4.00	–	–
No	12.60	7.00	24.00
Recurrence			
Yes	86.33	7.00	228.00
No	9.00	4.00	12.00

The tumour shows infiltrating growth into the myometrium and forms some macroscopically visible tumor cell strains in the lymphatic scissures. Microscopically, there is an oval- to spindle-shaped picture of cells, which resemble the stroma cells of a proliferating endometrium, and show more than 10 mitoses per 10 high-power fields (HPF, ten fields at a 400-fold enlargement in a microscope). Eighty per cent of ESS are mesenchymal malignomas of the corpus uteri (12). They are differentiated by their form of growth and by the rate of mitosis. Histologically, there is a monotonous picture of cells. The main criteria is the striking discrepancy of only a few glands to large areas of stroma. Due to the monotonous picture of the cells, it can be difficult to tell the difference between inconspicuous stromal structures. Polymorphy of the stromal tumor cells is not a reliable sign for diagnosis. Even if the stroma is rich in cells and is suspicious of being a sarcoma, it is not a sarcoma as long as there are equally-distributed glands. There is a limited tendency of metastasis, but local recurrence often occurs.

In the literature, two groups of ESS, low-grade (LGESS) and high-grade (HGESS), are mentioned. The terms "endometrial stromal sarcoma" for LGESS and "undifferentiated or poorly-differentiated uterine sarcoma" for HGESS are cited (13-16).

ESS often express both oestrogen and progesterone receptors (17-20). The amounts of these receptors are higher than in other uterine sarcomas, higher than the mean found in normal endometrium during the proliferative phase and much higher than during the secretory phase (17, 21). LGESS are richer in oestrogen and progesterone receptors than HGESS (17, 18). In contrast to oestrogen receptors, the content of progesterone receptors is higher in women under 50 years of age. These findings indicate a potential hormone-responsiveness of ESS. Hence, progesterone receptors are important for a potential therapy with gestagenes. The presence of oestrogen receptors may be related to a longer survival (17). The expression of the *Erb-B2* (*HER2/neu*) gene has been reported in subtypes of uterine sarcomas, but not in ESS (22).

In defining the diagnosis histopathologically, the distinction between smooth muscle and the endometrial stroma-derived neoplasms is often a problem. Smooth muscle neoplasms are thought to be distinguishable from endometrial stromal tumours by the expression of conventional muscle markers, such as smooth muscle actin or desmin (23). Other immunohistochemical studies, however, have revealed that ESS, like normal myometrium, may express both epithelial and/or muscle-related antigens (24, 25). These findings could reflect a common mesodermal-Mullerian derivation and demonstrate an intimate relationship between the endometrial stromal cells and the endometrial glands and myometrium. h-Caldesmon, an actin- and tropomyosin-binding protein, as well as staining of the smooth muscle myosin heavy chain and calponin has been shown to be helpful in distinguishing between benign cellular leiomyomata (CL) and ESS, but not between uterine leiomyosarcoma and ESS (23, 26, 27).

The CD10 antigen has been shown to be an immunohistochemical marker of normal endometrial stroma. Positivity was also found in endometrial stromal nodules and LG ESS (27, 28). Therefore, it has been suggested that it is used to distinguish these tumours from histological mimics, such as cellular leiomyoma or adult granulosa cell tumour, which are generally negative. Positive staining with CD10 in a high-grade uterine sarcoma, which is negative with muscle markers, might indicate endometrial stromal differentiation and can be helpful in identifying HGESS in a group of undifferentiated uterine sarcomas (28).

A study of 11 ESS revealed the expression of metalloproteinases (MMP), a group of proteolytic enzymes with a central role in extracellular matrix invasion and degradation. The authors of this study suggested that MMP-2 may contribute to differentiating HGESS from LGESS and that MMP-9 may contribute to differentiating normal endometrial stroma from LGESS and HGESS. However, MMP expression, was not found to predict the outcome of the disease (29).

The median age at primary diagnosis of uterine sarcomas is quoted to be between 39 and 65 years (2, 5, 30-39). In our patients, the median age was 56.6 years, with a range from 36 to 74 years. One study group reported 11 cases, with only one patient with ESS older than 50 years, but all 7 patients with a poorly-differentiated ESS were older than 50 years (13). The disease can occur both in premenopausal and postmenopausal women. ESS can also, rarely, be located in the ovaries (30, 40).

In most malignancies of the uterus, the first symptom is often abnormal vaginal bleeding. Hence, as in many other reports, most of our patients clinically presented with abnormal bleeding (5, 34, 35, 41). Therefore, a pre-operative curettage is a common step towards arriving at a diagnosis (41). However, the patients also suffer from abdominal swelling or pain, back pain or weight loss (30, 32, 35, 38).

Vaginal bleeding occurs after penetration of the tumour into the epithelial layer. Cytological examinations are, therefore, not helpful in offering an early diagnosis. In our patients, a normal pre-operative PAP smear was found in 4 patients and a PAP III in 1 patient.

As in our study, most patients with ESS are diagnosed in Figo Stage I, with fewer patients diagnosed in later stages (33, 38, 39, 41-46). Recurrence can occur locally or distantly or both (38). Pelvic or paraaortal lymph nodes are involved in 25% of cases (47), and the sites of metastasis are the abdomen, lungs or bones (38).

The treatment modalities for uterine sarcomas are surgery, radiation, chemotherapy and endocrine treatment. Most patients undergo hysterectomy and bilateral salpingo-oophorectomy, often accompanied by lymph node resection and, in advanced tumour stages, tumour debulking (5). Most of our patients underwent surgery and half received additional radiation. The rate of recurrence after surgery only is quoted as 56% (38). Riopel *et al.* found a high incidence of lymph node involvement in LGESS (48), however, whether this is of prognostic relevance is not clear. In a group of 28 patients, no significant difference in overall survival could be found in patients who underwent lymphadenectomy compared to those who did not (49).

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 contradictionary. In a group of 28 patients, postoperative radiation did not affect disease-free or overall survival (49). In the study by Jereczek *et al.*, 2 patients with radiotherapy alone progressed after 4 months and 10 months. However, 2 patients with G2 ESS were irradiated for vaginal recurrences; 1 patient died after 7.5 years with no evidence of recurrence and 1 after 11.5 years due to pelvic recurrence (38). An Italian study of 66 patients, all of whom underwent initial surgery, showed pelvic recurrence in 5 out of 20 patients with LGESS, with the disease confined to the uterus after a median of 36 months and only 1 out of 6 with disease outside the uterus with recurrence occuring after 93 months. In HGESS patients, 11 out of 20 with disease confined to the uterus developed recurrent disease after a median of 5 months and 9 out of 12 with extrauterine disease after a median of 12 months (6). Another study including 15 patients with surgery (abdominal or vaginal hysterectomy and bilateral salpingo-oophorectomy in 13 cases, abdominal hysterectomy in only 2 cases) and adjuvant radiotherapy reported an overall actuarial survival and a disease-specific survival rate of 72% and 79%, respectively, after 5 years and 60% and 79% after 10 years (50). Livi *et al.* found that adjuvant radiotherapy decreased the local recurrence rate in uterine sarcomas, but without significant impact on survival (31). Mansi *et al.* recommended adjuvant radiotherapy in patients with HGESS, but only after relapse in LGESS (51). In an older analysis of 25 cases, radiation therapy alone seemed to be inadequate treatment for patients in Stage I and II, but was an effective addition to surgery in terms of increasing survival and decreasing pelvic recurrences (53). In conclusion, several study groups recommend a combination of surgery and adjuvant radiation due to better locoregional tumour control (6, 31, 33, 38, 39, 45, 50-54).

The successful use of hormone therapy has been reported by several authors (18, 51, 55-57). Hormone therapy with progestogens is reported in the literature with a 46% response rate and a 46% rate of disease stabilization (58). Katz *et al.* and Scribner *et al.* reported the successful use of Megestrolacetate (18, 59). One group describes a case of LGESS of the ovary arising from foci of endometriosis where megestrol acetate was successfully used (40).

Aromatase inhibitors, such as aminogluthetimide and the third-generation aromatase inhibitor letrozole, have been applied to ESS patients with a good tumour response, however, these are case reports (55, 60, 61). Gonadotropin-releasing hormone receptors I and II have been stained in primary and recurrent ESS with a higher expression in recurrences (56), which might explain the successful use of the gonadotropin-releasing hormone analogue triptorelin in 1 case report in a patient with LGESS (57).

Chemotherapy is not a common choice in the treatment of ESS, since it does not seem to improve survival (33). Jereczek *et al.* reported the use of doxorubicin and dacarbazine in 1 patient. In this case, the patient had metastasis in the paraaortic lymph nodes 16 months after the initial surgery. Radiation was then applied and the patient died 10 years later due to another paraaortic recurrence (38). Furthermore, chemotherapy with oral etoposide was used with a median 20-month remission in 3 patients before progression (58).

The prognosis of ESS is poor. Again, the data regarding survival times and rates of recurrences vary. In our group, we found a 1-year survival rate of 36.3%, a 2-year survival rate of 18.1% and a 5-year survival rate of 9.1%, with a better survival rate of postmenopausal patients. The median survival time quoted in the literature is from 4.2 to 132 months (2, 5, 62), the reported 2-year survival rate is 75%, the 3-year survival rate is 63% and 51% and the data for the 5-year survival rates ranges from 39% to 70% (5, 31, 33, 38, 39, 45, 62-64). Jereczek *et al.* reported relapses in 5 out of 9 patients, 3 with local and 2 with distant recurrence. Distant recurrence occurred in 1 of 4 patients with radiation after radical surgery; the other 4 relapses occurred in patients not given adjuvant radiotherapy (38). Calais *et al.* reported 5 out of 22 patients with local recurrence and 6 out of 22 with distant metastasis (33). Some studies indicate a better survival and/or a better relapse-rate for LGESS than for HGESS (6, 34, 49, 51). Disease-free survival (DFS) is quoted as 11 months (63).

It is difficult to find accurate information about prognostic factors for ESS. Of all the histological subtypes of uterine sarcomas, ESS seems to have the most favourable prognosis (4). Tumour stage, tumour size, free resection margins at primary surgery and age and menopausal status of the patient as well as the depth of myometrial invasion, tumour grading, histological subtype (LGESS favourable to HGESS) and type of treatment, are all important prognostic factors (4, 13, 33, 34, 42, 52, 53, 63). The mitotic count was also considered to be an important prognostic factor in LGESS and in HGESS by several, but not all, study groups (6, 44, 51, 63). However, the mitotic index or cytological atypia were not considered predictive of tumour recurrence for patients with Stage I tumours (42). Brooks *et al.* determined the association of race with the incidence of uterine sarcoma in large group of 2677 cases. For ESS, however, they could not prove any differences of incidence between the races (16). Most interestingly, one study group could not find a difference in the overall survival for patients with local *versus* advanced disease (49). An observation of a high incidence of familial hormone-dependent cancers in patients with ESS led to the hypothesis that ESS patients are carriers of an unknown gene mutation which renders them susceptible to hormone-dependent growth promotion and/or to cellular damage from particular oestrogen metabolites (65).

Conclusion

ESS is a uterine sarcoma with a difficult differential diagnosis. Patients are frequently diagnosed in an early tumour stage but still experience local or distant recurrences. The prognosis is poor with early recurrence and low long-time survival rates. Treatment including surgery and adjuvant radiation should be considered. Whereas chemotherapy is uncommon, endocrine treatment might be a promising new approach in the therapy of ESS. In order to obtain more information about the pathogenesis of the tumour and to find the optimal therapy, we consider that even studies with small numbers of patients should be published.

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