

Effect of tumor morcellation in patients with early uterine sarcoma: a multicenter study in Germany

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Abstract

Objective: The use of power morcellation at laparoscopy may worsen survival rates for patients with malignancy. The aim of the present study was to report the outcome of patients with early-stage uterine sarcoma after morcellation or total en-bloc resection, and evaluate potential signs of sarcoma preoperatively.

Material and Methods: This multicenter retrospective study consisted of patients, who underwent surgery for FIGO-stage-1 uterine sarcoma. Twenty-four patients were divided into a non-morcellation group and a morcellation group. Clinical records and the outcomes of patients, including one-, three- and five-year survival rates were reviewed. Preoperative characteristics of patients with sarcoma were compared to those of a control group with uterine myoma (1:4 ratio), matched by age and type of operation.

Results: Obesity was an independent risk factor for uterine myoma. Tumor growth, solitary growth, largest-diameter lesion >8.0 cm, and anechoic areas suggesting necrosis and increased vascularization were significantly more common in the sarcoma group. A large tumor diameter was significantly associated with mortality. Patients in the non-morcellation group had a slightly lower disease-free survival, but poorer overall survival (OS) rates compared to patients in the morcellation group, but neither difference was statistically significant. Patients in the non-morcellation group, who had undergone a re-exploration experienced late recurrence, but no upstaging was evident after the operation.

Conclusion: Preoperative ultrasound characteristics could be useful to distinguish sarcoma from leiomyoma of uterus. Morcellation of a sarcoma may increase abdominal and pelvic recurrence rates, but may not be associated with OS in patients with FIGO-stage-1 disease. (J Turk Ger Gynecol Assoc 2022; 23: 75-82)

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Introduction

Uterine sarcomas are rare malignancies that arise from the connective tissue or smooth muscle of the uterus, accounting for 1-2% of all malignancies of the uterus and less than 1% of all genital malignancies (1).

The prognosis or diagnosis of uterine sarcomas are rendered difficult by their rarity. Existing imaging techniques do not permit the differentiation of leiomyosarcoma (LMS) from myoma, preoperatively (2). A preoperative biopsy is obsolete because of the risk of tumor dissemination. Moreover, a sarcoma is not diagnosed easily during surgery because a frozen-section analysis or cytological investigation does not permit the differentiation of sarcoma from myoma (2). Thus, sarcomas tend to remain underdiagnosed and are usually treated by myomectomy or hysterectomy using morcellation techniques.

Minimally invasive surgery (MIS) is associated with lower surgical morbidity than laparotomy, but both methods have similar disease-related outcomes in patients with endometrial cancer (3-6). Despite the established advantages of MIS and the use of electromechanical morcellators (EMM), the morcellation of unexpected sarcomas during surgery has been known to cause the dissemination of tumor tissue, resulting in poor survival outcomes (7).

For patients undergoing myomectomy or hysterectomy, there was a warning, in April 2014, against the use of laparoscopic power morcellation by the FDA (8). Unexpected malignancy was estimated to occur in 1 out of 350 women (8-11). After this warning, several renowned hospitals across the world stopped using EMM.

The purpose of this multicenter analysis was to estimate the influence of morcellation on clinical outcomes in patients with early-stage uterine sarcomas (FIGO-stage-1) in Germany. Furthermore, we estimated risk factors for the presence of uterine sarcoma and analyzed preoperative ultrasound characteristics in order to determine signs of sarcoma preoperatively.

Material and Methods

A retrospective multicenter study was performed at four departments of obstetrics and gynecology in Germany from June 2007 to May 2019. The study was approved by the Ethical Committee of the Medical Faculty of the University of Luebeck (approval number: 18-115). The information system of the academic teaching hospitals of Klinikum Leverkusen, Vivantes Humboldt, the University Hospital of Luebeck, and the University Hospital of Kiel were used by the authors to identify women who had undergone surgery for FIGO-stage-1A or 1B uterine sarcoma (12). Patients with carcinosarcoma

and those who had been treated with endoscopic retrieval bags were also excluded.

The data of 24 patients were collected. Indications for the intervention, medical history, body mass index (BMI) and preoperative symptoms, histological results, and postoperative data were analyzed. Pathological slides were reviewed by two experienced pathologists. A clinical follow-up examination was performed every three months for all patients.

Tumor recurrence, disease-free survival (DFS), anatomical location of tumor recurrence and overall survival (OS) were recorded during follow-up examinations. Patients were divided into the following two groups: those who underwent total laparoscopic, abdominal or vaginal hysterectomy without morcellation (non-morcellation group), and those who underwent hysterectomy or myomectomy including vaginal, laparoscopic or abdominal, morcellation (morcellation group).

A group of patients with uterine myoma selected from all of those who underwent hysterectomy or myomectomy were matched by age and type of operation (4:1 ratio) during the same period. Patient characteristics and the indication for surgery were analyzed. Preoperatively, all patients were examined by experienced gynecologists on the basis of German guidelines (13). Preoperative ultrasound parameters (14), such as size of the tumor, anechoic areas suggesting necrosis (Figure 1), solitary growth, increased vascularization (Figure 2), an irregular lining, and endometrial thickness >5 mm in postmenopausal patients were taken into account. Ultrasound was performed within four weeks before surgery, and ultrasound characteristics of patients with uterine sarcoma were compared with those of controls with uterine myoma.



Figure 1. Transvaginal ultrasound showing the sagittal diameter of the fundus of the uterus and the size of the tumor. Inhomogeneous appearance, central hypoechoic area, degenerative cystic changes atypical for myoma suggesting necrosis

Statistical analysis

Data were collected in an Excel 2010 table (Microsoft Corporation, Redmond, WA, USA) and evaluated using SPSS software, Version 26 (IBM Inc., Armonk, NY, USA). To compare absolute and relative frequencies of clinical parameters, either a chi-square-test or a Fisher's exact test was performed, depending on scaling and distribution of the variables. A p-value <0.05 was considered statistically significant.

Results

The patients' characteristics were summarized in Table 1. The youngest woman was 40 years old and the oldest one was 84 years old. The mean weight of the uterus was 324.1 grams.

The most common indication for surgery was bleeding disorders (62.5%); the percentages of indications for surgical procedures are shown in Table 2. The types of operation in each department are summarized in Table 3. The majority of unexpected sarcomas (7/10) were diagnosed after performing laparoscopic supracervical hysterectomy (LASH).

One patient had used tamoxifen and another patient had undergone irradiation of the pelvis. Seven patients had a family history of cancer (29.1%), and one patient had a family history of sarcoma (4.2%). The principal characteristics of patients with sarcoma are summarized in Table 1. Seven patients underwent dilatation and curettage preoperatively. The diagnostic success rate was 71.4%; the outcome of the histological investigation was false negative in two cases.

Manual morcellation was applied in two patients who underwent laparoscopic hysterectomy as the initial procedure, while power morcellation was performed in eight patients who underwent laparoscopic myomectomy or subtotal hysterectomy as the initial procedure. In the morcellation

group, five patients underwent a staging laparotomy and two a staging laparoscopy with cytological examination of fluid from the pouch of Douglas, bilateral ovariectomy, removal of the cervical stump, omentectomy, and multiple peritoneal biopsies two to four weeks after the first procedure. In the non-morcellation group, only two patients underwent a staging operation. Two patients underwent a pelvic and para-aortic lymphadenectomy; no lymph node metastasis was found. A computed tomography scan of the pelvis and the chest was performed in all patients, either preoperatively or postoperatively. The staging operations and examinations did not reveal upstaging of the tumor. Subsequent treatment, the results of follow-up, and the relapse of sarcoma are shown in Table 1 and Figure 3. Four patients (16.7%) underwent a third operation at which a complete resection was performed. Four out of six patients with distant recurrence developed a metastasis in the lung.

The mean age (\pm standard deviation) of controls (55.3 ± 10.51 years) and the types of operations were similar (Table 4). Twelve women in the sarcoma group (50.0%) were postmenopausal, and 47 (49%) of the uterine myoma group. The average BMI of controls was 29.8 kg/m^2 . In contrast to women with sarcoma, a BMI of 25 kg/m^2 was an independent risk factor for uterine myoma ($p < 0.05$). The most common indications for surgery and potential ultrasound characteristics are shown in Table 4. The median diameter of the tumors was 5.6 cm. A large tumor diameter ($p < 0.05$) and higher tumor stage (FIGO-1B) were significantly associated with mortality rates ($p < 0.05$).

Discussion

We compared the outcomes of FIGO-stage-1 uterine sarcoma after morcellation versus hysterectomy without morcellation. Our results revealed a slightly better DFS for the non-morcellation group compared to the morcellation group, but with no benefit in OS. However, neither difference was statistically significant. Obesity (BMI $> 25 \text{ kg/m}^2$) was not significantly predictive of uterine sarcoma, which is in contrast to the general view of obesity as a risk factor for malignancies, and was also in contrast to the opposite trend for patients with uterine myoma. In a study comprising 31 patients with uterine sarcoma, Cho et al. (15) found a BMI $\leq 20 \text{ kg/m}^2$ to be an independent risk factor for disease. Obesity is known to be a major risk factor for breast cancer (hormone receptor positive) and endometrial cancer (type 1 endometrioid tumor) (16). Moreover, obesity is also a major risk factor for uterine myoma, which is typically an estrogen-dependent tumor (17). Pathophysiological differences between endometrial cancer, uterine myoma, and uterine sarcoma may explain the lower BMI in women with uterine sarcoma.



Figure 2. Transvaginal color Doppler ultrasound shows increased central vascularization in the heterogeneous tumor (transverse orientation of the ultrasound probe)

In accordance with published data (18), uterine bleeding and abdominal pain were almost equally common in patients with uterine sarcoma and those with uterine myoma in our study. However, tumor growth as an indication for surgery was significantly more common in the sarcoma group, which might explain the largest diameter of tumor in sarcomas group. Radiation exposure and a history of radiation therapy of the pelvis have all been reported to increase the likelihood of developing sarcoma; the same has been noted in breast cancer

patients treated with tamoxifen (19). However, in the present study only one patient had a history of radiotherapy and, also, one patient had undergone treatment with tamoxifen.

In our analysis 13 of 24 cases had abnormal uterine bleeding, however we performed dilatation and curettage preoperatively only in seven of them. The diagnostic success rate was 71.4%; false-negative results of histology were noted in two cases. Similar data were reported in a large review of 302 sarcomas by Wais et al. (20) in which uterine sarcoma was diagnosed

Table 1. Patient characteristics, adjuvant management and survival outcome

	n	Non-morcellation group	Morcellation group	Total	p
Age (years)	24	52.8±15.48	62.7±12.48	58.6±14.89	0.074
BMI (kg/m ²)	22	29.12±7.81	24.17±2.51	26.87±6.40	0.159
Menopause status					
Premenopausal	24	3 (21.4%)	6 (60.0 %)	9 (37.5%)	0.092
Perimenopausal	24	2 (14.3%)	1 (10.0 %)	3 (12.5%)	0.629
Postmenopausal	24	9 (64.3%)	3 (30.0 %)	12 (50.0%)	0.098
Tumor size >8 cm	22	8 (61.5%)	4 (44.4%)	12 (54.5%)	0.666
Abnormal bleeding	24	8 (57.1%)	7 (70.0%)	13 (54.2%)	0.697
High vascularisation	23	5 (35.7%)	3 (33.3%)	8 (34.8%)	0.633
LMS	24	8 (57.1%)	8 (80.0%)	16 (66.7%)	0.388
ESS	22	6 (50.0%)	2 (20.0%)	8 (36.4%)	0.204
Grading	19	-	-	-	0.524
1	-	7 (50.0%)	3 (60.0%)	10 (52.6%)	-
2	-	3 (21.4%)	0	3 (15.8%)	-
3	-	4 (28.6%)	2 (40.0%)	6 (31.6%)	-
FIGO	20	-	-	-	0.639
IA	-	4 (40.0%)	3 (30.0%)	7 (35.0%)	-
IB	-	6 (60.0%)	7 (70.0%)	13 (65.0%)	-
Upstaging	20	0	0	0	-
Chemotherapy	23	1 (7.1%)	1 (11.1%)	2 (8.7%)	0.640
Therapy with gestagene	24	0	2 (20.0%)	2 (8.3%)	0.163
Recurrence	24	5 (35.7%)	5 (50.0%)	10 (41.7%)	0.678
Location of recurrence					
- Abdomen/pelvis	-	3	1	3	-
- Distant (bone, lungs, liver, kidney)	-	1	3	4	-
- Both	-	1	1	2	-
DFS 1 year	23	70%	78.6%	75.5%	0.537
DFS 3 years	21	56%	61.5%	59.0%	0.623
DFS 5 years	15	29%	37.5%	33.3%	0.573
OS 1 year	23	100%	92.9%	95.8%	0.565
OS 3 years	18	87.5%	80%	85.7%	0.588
OS 5 years	12	80%	71.4%	72.7%	0.636
DFS 1 year					
- After reoperation	-	0%	-	-	-
- Without reoperation	-	100%	-	-	-

BMI: Body mass index, LMS: Leiomyosarcoma, ESS: endometrial stromal sarcoma, DFS: Disease free survival, OS: Overall survival, ESS: Endometrial stromal sarcoma

in 65% of patients, who underwent endometrial sampling preoperatively. Another analysis demonstrated a misdiagnosis rate of 19% for endometrial cancer and 36% for sarcoma (21). However, abnormal uterine bleeding remains a significant clinical sign and should not be underestimated. We encourage the use of endometrial sampling in patients with suspicious

myoma, especially in the presence of abnormal uterine bleeding.

Solitary tumors larger than 8 cm in size with intensified peripheral and central vascularization were the most common features of uterine sarcoma on ultrasound (14,22). According to Exacoustos et al. (14) ultrasound features, such as single lesions, increased central and peripheral vascularity, large-diameter lesions (≥ 8 cm), and cystic degeneration, were significantly associated with uterine sarcoma. Viewing these features together, the authors registered a sensitivity of 100% and a specificity of 86%. However, the small sample size of the study (8 patients with sarcoma compared with 225 patients with leiomyoma) was a limitation to come to a robust conclusion. We compared ultrasound features between 24 uterine sarcomas and 96 uterine myomas, and observed the following ultrasound features predictive of uterine sarcoma: solitary growth, largest-diameter lesion >8.0 cm, anechoic areas suggesting necrosis, and increased vascularization. However, we observed anechoic areas suggestive of necrosis in a mere 20.8% of our cases, and high vascularization in 34.8%.

Table 2. Indications for surgery

Indications for abdominal-vaginal hysterectomy, TLH, LASH, and myomectomy	Patients who underwent surgery n (%)
Bleeding disorders	13 (54.1)
Uterine growth	10 (41.6)
Histological diagnosis of sarcoma with D&C	5 (20.8)
Abdominal pain	5 (20.8)
Urinary disorders (incontinence or obstruction)	3 (12.5)

TLH: Total laparoscopic hysterectomy, LASH: Laparoscopic supracervical hysterectomy D&C: Dilatation and curettage

Table 3. Type of operations and their percentages

Type of operation	LASH	TLH	LM	VH	TAH	AM
Patients with sarcoma (n, %)						
Leverkusen Municipal Hospital	3	1	0	2	3	0
University Hospital of Luebeck	2	1	1	0	2	1
University Hospital of Kiel	2	1	0	0	2	0
Vivantes Humboldt, Berlin	0	2	0	0	1	0
Multicenter analysis	7	5	1	2	8	1
Preoperatively known sarcoma	0	2	0	0	3	0
Unexpected sarcoma without morcellation	0	2	0	2	5	0
Morcellated sarcoma	7	1	1	0	0	1

LASH: Laparoscopic supracervical hysterectomy, TLH: Total laparoscopic hysterectomy, LM: Laparoscopic myomectomy, VH: Vaginal hysterectomy, TAH: Total abdominal hysterectomy, AM: Abdominal myomectomy

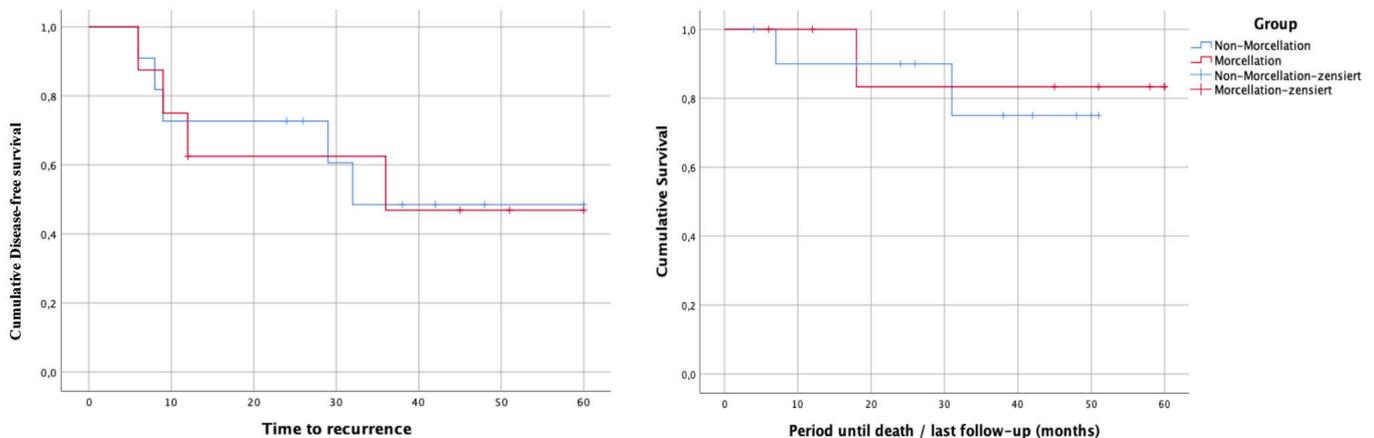


Figure 3. Oncologic outcome of 24 patients with apparently early uterine sarcoma in relation with tumor morcellation (overall survival at the right and disease-free survival at the left)

A greater frequency of sarcomas was noted in the presence of characteristics such as a solitary tumor (73.9%) and tumor size larger than 8 cm (54.5%). Uterine sarcomas are not easily identified.

Tumor size is known to be a prognostic factor for early LMS (23). In the present study, the tumor size was significantly associated with mortality rates. A higher tumor stage (FIGO-1B) was also significantly associated with the outcome. In a study comprising 34 patients with early LMS, Lin et al. (24) evaluated the effect of morcellation on the outcome and concluded that the size of tumor outweighed morcellation; the former was more significant than morcellation in predicting a poor outcome. However, it should be noted that, in small studies, a slight difference in tumor size might cause a large difference in the combined statistical analysis of survival outcome.

In unexpected uterine sarcomas the use of morcellators has been reported to result in cancer upstaging and worsen survival rates (25). However, we reported no upstaging of the tumor in 10 patients who underwent staging operations at two to four weeks after the initial procedure. Our results concur with the data reported by Park et al. (26), who performed complete staging surgery in 23.9% of their patients and observed no upstaging in any patient. In contrast, Einstein et al. (27) mention that approximately 15% of patients were upstaged by re-exploration, particularly those with LMS who underwent EMM. Even in a large systematic review (28), the authors were unable to conclude whether morcellation of sarcomas causes upstaging of cancer compared to *en bloc* removal. Different morcellation techniques could be the reason for the varying incidence of intra-abdominal spread.

Published data concerning the outcome of uterine sarcoma after morcellation are not homogeneous. In a large study including 58 patients, the authors (29) found that the median recurrence-free survival of patients with uterine LMS who

underwent EMM was significantly shorter than that of patients who underwent total abdominal hysterectomy (10.8 vs 39.6 months). However, the study was not limited to early-stage uterine sarcoma. In contrast, Wais et al. (20) reported no significant difference in survival for patients with FIGO-stages-1 and 2 disease with disruption (n=32) of uterine sarcoma compared to those without tumor disruption (n=143) over a median follow-up period of 2.9 years. The above mentioned reports highlight the need for further investigations focusing on patients with FIGO-stage-1 disease who have undergone surgery, with or without morcellation. Moreover, studies analyzing the outcome of patients with sarcoma after morcellation must be interpreted with caution.

Our homogenous data revealed a slightly better DFS for the non-morcellation group with FIGO-stage-1 uterine sarcoma compared to the morcellation group, but slightly worse OS. However, these differences were not statistically significant. Patients who underwent morcellation were slightly younger than the others (52.8 vs 62.7 years, $p=0.074$), and younger age is known to be associated with a better outcome (30). Furthermore, the morcellation group had slightly higher rate of LMSs than the non-morcellation group (80 vs 57.1%, $p=0.388$). However, the proportion of high grade sarcomas (Grading G3), which are associated with poor prognosis, were similar in both groups (20 vs 28%).

Raine-Bennett et al. (31) reported no significant difference in the unadjusted three-year DFS between patients with FIGO-stage-1 uterine sarcoma who did or did not undergo morcellation. In our study, patients who underwent morcellation experienced an intra-abdominal recurrence more often (80%) than did patients in the non-morcellation group (40%). Notably, in two cases, we observed dissemination of sarcoma after morcellation on both sides of the abdominal wall, in the area of trocar placement at the first operation. In contrast, Lin et al.

Table 4. Ultrasound characteristics of patients and survival outcome

Characteristics of the patients	n	Myomas group	Sarcomas group	Total	p
Ultrasound					
Tumor size >8 cm	118	19 (19.8%)	12 (54.5%)	31 (26.3%)	0.001
Solitary tumor	119	34 (35.4%)	17 (73.9%)	51 (42.5%)	0.001
Irregular lining	120	18 (18.7%)	5 (20.8%)	23 (19.2%)	0.770
High vascularization	119	9 (9.4%)	9 (39.1%)	18 (15.1%)	0.001
Anechogenic areas with suspicion for necrosis	120	7 (7.3%)	8 (33.3%)	15 (12.5%)	0.002
Indications for operation					
Bleeding disorders	120	37 (38.5%)	15 (62.5%)	52 (43.3%)	0.045
Uterine growth	120	21 (21.8%)	12 (50.0%)	32 (27.5%)	0.006
Type of operation					
Hysterectomy	119	84 (88.4%)	23 (95.8%)	107 (89.9%)	0.455
Myomectomy	120	4 (4.2%)	1 (4.2%)	5 (4.2%)	0.739

(24) reported that morcellation of sarcoma did not increase the abdominal pelvic recurrence rate, but may be associated with poorer survival in unexpected FIGO-stage-1 disease. Besides tumor morcellation, any type of tumor injury may aggravate hematogenous spread of tumor cells. The most common site of extra-pelvic recurrence in our patients was the lungs (67%), which is in accordance with the published literature (32). Factors that primarily affect the outcome of disease in patients with uterine sarcoma remain unclear. Notwithstanding the above mentioned negative outcome (33), the rarity of uterine sarcoma and its inherent poor prognosis should not affect the use of MIS for this condition.

We assumed a favorable prognosis for patients who had undergone a second operation with longitudinal laparotomy due to an unexpected morcellated sarcoma. Three patients who did not undergo re-exploration after morcellation of sarcoma experienced recurrent disease within 12 months. Of the remaining seven patients with morcellated sarcoma who underwent a re-exploration, only two experienced a recurrence after 12 months. In a review comprising 47 published studies, Tantitamit et al. (34) reported that early re-exploration (within 30 days) led to lower mortality rates and a better prognosis compared to late re-exploration (>30 days). Based on our data, we conclude that LASH or myomectomy as the first operation was no significant predictor of a poor prognosis when a re-exploration was performed. Our short re-operation interval (2 to 4 weeks) might have contributed to this result. However, the small number of patients does not permit definite conclusions.

Study Limitation

As mentioned, the main limitation of the present study is the small number of patients, which reduced the statistical power of the analysis. Although patients with sarcomas and those with uterine myoma were matched by age and type of operation, factors such as the gynecologists performing the ultrasound examination and the ultrasound device were not matched. On the other hand, detailed preoperative and postoperative information were available for all patients, and both groups of patients were followed up for a relatively long period of time. To our knowledge, published data concerning predictions and the outcome of FIGO-stage-1 uterine sarcoma are limited and inconsistent. Our data contribute significantly to the published literature on the subject.

Conclusion

We were not able to determine patient characteristics that could be clinically useful in the preoperative diagnosis of early-stage uterine sarcoma. Obese women are at no greater risk of developing uterine sarcoma. Ultrasound characteristics,

such as solitary and large tumors measuring more than 8 cm in size, with anechoic areas indicative of necrosis and high vascularization, might serve as signs of uterine sarcomas. In addition, a combination of BMI, age, and ultrasound characteristics may enhance the accuracy of preoperative diagnosis of uterine sarcoma. Sarcoma morcellation may increase abdominal pelvic recurrence rates, but may not be associated with OS in patients with FIGO-stage-1 disease. The effects of surgical techniques involving tumor disruption on survival remain controversial. Further studies should be designed to assess the positive effects of re-exploration after morcellation of occult sarcomas. The limited number of cases investigated in the present study, the low incidence of the disease, the level of evidence for risk factor, and the outcome of morcellated uterine sarcoma does not permit any specific recommendations about the treatment of uterine sarcomas. Future studies should be focused on the preoperative diagnosis and outcome of early-stage uterine sarcoma, while the rarity of the disease does not permit prospective investigations.

Ethical Committee Approval: *The study was approved by the Ethical Committee of the Medical Faculty of the University of Luebeck (approval number: 18-115).*

Informed Consent: *It was obtained.*

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