Cancer Association of South Africa (CANSA)

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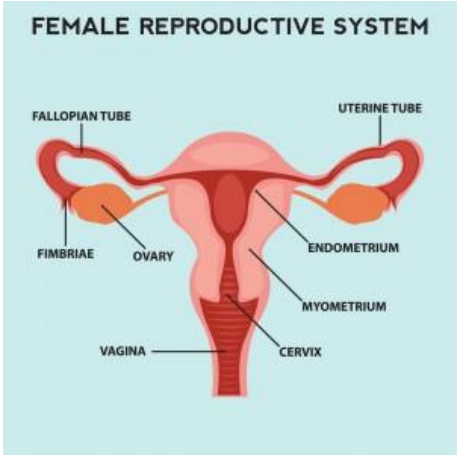
Fact Sheet on Gynaecological Sarcoma

Introduction

Gynaecological sarcomas, sometimes shortened to 'gynae sarcomas' occur in the female reproductive system: the uterus (womb), ovaries, vagina, vulva and fallopian tubes. The term 'uterine sarcoma' is also often used. These sarcomas can affect women of any age.



[Picture Credit: Female Reproductive System]

3-4% of all gynaecological cancers are sarcomas and they make up 13% of all sarcomas. Most gynaecological sarcomas (85%) occur in the uterus (womb) and 7% occur in the ovaries. The remainder occur less commonly in the vagina, vulva, fallopian tubes and other areas of the female reproductive system.

The main types of gynaecological sarcomas:

- 52% are leiomyosarcoma – a cancer of the smooth or involuntary muscle, mostly but not always occurring in the uterus
- 24% are endometrial stromal tumours – a cancer of the connective tissue in the uterus
- 16% are sarcoma not otherwise specified (NOS) and include undifferentiated endometrial sarcoma (UES)

The remaining 12% are mostly made up of:

- Rhabdomyosarcoma - a cancer of the skeletal muscle, mostly occurring in the uterus and vagina
- Fibrosarcoma – a cancer of the fibrous tissues, mostly occurring in the ovaries
- Liposarcoma – a cancer of the fatty tissues, mostly occurring in the ovaries, vulva and uterus

Nasioudis, D., Ko, E.M., Kolovos, G., Vagios, S., Kalliouris, D. & Giuntoli, R.L. 2019.
OBJECTIVE: To evaluate the effect of ovarian preservation on oncologic outcomes for women with low-grade endometrial stromal sarcoma of the uterus.
METHODS: A systematic search of the Medline, Embase, Cohrane, and Web of Science databases was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines. Studies including patients with low-grade endometrial stromal sarcoma who had hysterectomy were identified. Data on tumor recurrence and death rate were pooled using a random effects model.

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RESULTS: A total of 17 studies met the inclusion criteria and reported on 786 patients. Based on available information, ovarian preservation was noted in 190 patients while 501 had bilateral salpingo-oophorectomy. A significantly increased tumor recurrence rate was observed in the ovarian preservation group (89/190, 46.8%) compared with the bilateral salpingo-oophorectomy group (121/501, 24.2%) (OR 2.70, 95% CI 1.39 to 5.28). Based on data from 162 patients, no difference in death rate was noted between the ovarian preservation (2/34, 5.9%) and bilateral salpingo-oophorectomy (9/128, 7%) groups (OR 0.80, 95% CI 0.18 to 3.47).
CONCLUSIONS: Approximately one-quarter of patients with low-grade endometrial stromal sarcoma were managed with ovarian preservation. These women experienced a higher recurrence rate. Hormone exposure may be responsible for this elevated risk. Given the apparent high salvage rate, however, ovarian preservation may be an option only in a well-informed patient population.

Mbatani, N., Olawaiye, A.B. & Prat, J. 2018.
"Uterine sarcomas account for approximately 3%-7% of all uterine cancers. Since carcinosarcomas are currently classified as metaplastic carcinomas, leiomyosarcomas remain the most common subtype. Exclusion of several histologic variants of leiomyoma, as well as atypical smooth muscle tumors (so-called "smooth muscle tumors of uncertain malignant potential"), has highlighted that the vast majority of leiomyosarcomas are high-grade tumors associated with poor prognosis even when apparently confined to the uterus. Low-grade endometrial stromal sarcomas are indolent tumors associated with long-term survival. High-grade endometrial stromal sarcomas and undifferentiated endometrial sarcomas behave more aggressively than tumors showing nuclear uniformity. Adenosarcomas have a favorable prognosis except for tumors showing myometrial invasion or sarcomatous overgrowth. The prognosis for carcinosarcomas (which are considered here in a postscript fashion) is usually worse than that for grade 3 endometrial carcinomas. Tumor stage is the single most important prognostic factor for uterine sarcomas."

Incidence of Gynaecological Sarcomas
The National Cancer Registry (2016) does not provide any information regarding Gynaecological Sarcomas.

Multinu, F., Casarin, J., Tortorella, L., Huang, Y., Weaver, A., Angioni, S., Melis, G.B., Mariani, A., Stewart, E.A. & Laughlin-Tommaso, S.K. 2019.
BACKGROUND: Minimally invasive hysterectomy may require the use of morcellation to remove the uterus. In the presence of unexpected sarcoma, morcellation risks disseminating malignant cells and worsening survival outcomes. As a consequence, in 2014 the US Food and Drug Administration issued a black box warning against the use of power morcellator for the treatment of uterine fibroids. However, the proportion of unexpected sarcoma at the time of hysterectomy for presumed benign indication remains unclear.
OBJECTIVE: The objective of the study was to estimate the incidence of sarcoma among women undergoing hysterectomy for benign indication in Olmsted County, MN, between 1999 and 2013.
STUDY DESIGN: We conducted a population-based study including all hysterectomies performed for benign indication in Olmsted County women between Jan. 1, 1999, and Dec. 31, 2013. Cases were identified using the medical records-linkage system of the Rochester Epidemiology Project, and data were abstracted by a gynecologist who reviewed the complete medical records of each woman who underwent hysterectomy. An expert pathologist reviewed the pathologic slides of each sarcoma to ensure the accuracy of the diagnosis. Incidences of sarcoma (overall and by type of sarcoma) were estimated both overall and stratified by menopausal status, indication for surgery, and uterine weight as a rate per 100 persons.
RESULTS: A total of 4232 hysterectomies were performed during the study period. Among them, we identified 16 sarcomas, of which 11 (69%) were suspected preoperatively and 5 (31%) were unexpected. Of

the total number of hysterectomies, 3759 (88.8%) were performed for benign indication. Among those, the incidence of unexpected sarcoma was 0.13% (5 per 3759 [95% confidence interval, 0.04-0.31%]). Uterine fibroids comprised 27.3% of all hysterectomies for benign indication (n = 1025) and was the indication most commonly associated with diagnosis of unexpected sarcoma. The incidence of unexpected sarcoma among surgeries for uterine fibroids was 0.35% (3 of 851) for premenopausal women and 0.57% (1 of 174) for peri/postmenopausal, and all 4 unexpected sarcomas were leiomyosarcoma. The incidence of unexpected sarcomaprogressively increased with higher uterine weight with an incidence of 0.03% (1 of 2993) among women with a uterine weight <250 g vs 15.4% (2 of 13) with a uterine weight ≥2000 g.
CONCLUSION: Unexpected uterine sarcoma was low in all women undergoing hysterectomy for benign indication (0.13% or 1 in 752 surgeries) while it was increased in women with uterine fibroids (0.39% or 1 in 256 surgeries). Peri/postmenopausal women, women with large uteri, and age ≥45 years were risk factors for sarcoma.

Ghezelayagh, T., Raub-Hain, J.A., Brooks, R.A. & Growdon, W.B. 2016.
Objectives: Race has previously been shown to affect survival in soft tissue sarcoma and uterine sarcoma, but little is known about racial disparities in the survival of other gynecologic sarcomas. We explored the impact of race on gynecologic sarcoma incidence and survival in the United States.
Methods: Age-based incidence rates of gynecologic sarcoma were calculated for 2000 to 2012 from within the National Cancer Institute's Surveillance, Epidemiology, and End Results database catchment area. Primary and invasive cases diagnosed between 1973 and 2012 were then culled from the database. Demographic and clinicopathologic factors, including neighborhood socioeconomic status markers, were compared between white, black, and Asian/Pacific Islander (API) patients using parametric and nonparametric methods. Survival outcomes were compared with Kaplan-Meier methods and multivariable Cox proportional hazards modeling, with multiple sensitivity analyses.
Results: Compared with white women, black women demonstrated a 43% higher incidence rate of gynecologic sarcoma whereas API women demonstrated a 27% lower rate. In our final cohort, 15,061 women self-identified as white, 3,426 identified as black, and 1,310 as API. API women tended to be younger at diagnosis and had higher rates of grade I–II and lymph node–negative disease. Black women had greater uterine disease, higher lymph node positivity, and were less often treated surgically. They were also more likely to come from metropolitan areas with poor socioeconomic indicators. Black women had significantly worse 5-year cancer-specific survival compared with white and API women (46.0% vs 55.3% and 55.9%, respectively). After adjusting for clinicopathologic factors, black women still faced a 34% higher risk of cancer-specific death (95% CI 1.27–1.42) whereas API women had a 13% higher risk (95% CI 1.02–1.24). This disparity did not significantly change after adjusting for socioeconomic status, and persisted on multiple sensitivity analyses, including the exclusion of uterine cases.
Conclusions: Black and API patients diagnosed with gynecologic sarcoma have worse prognoses than white patients, with results suggesting minimal contribution of clinicopathologic and neighborhood socioeconomic factors. More research is needed on possible biologic etiologies of this disparity.

Signs and Symptoms of Gynaecological Sarcomas
Symptoms of gynaecological sarcomas can vary depending on the size and location of the tumour. They may include:

- Heavy periods or bleeding in between periods
- An enlarging fibroid
- Vaginal bleeding after the menopause
- Pelvic pain
- A feeling of fullness in the abdomen

- Blood in vaginal discharge
- Abdominal pain and bloating
- A noticeable lump on a section of the vulva
- A mass in the vagina
- Frequent urination

Symptoms can be confused with more common gynaecological conditions for example, problems with contraceptive devices such as the coil, menopause, post menopause symptoms, and fibroids. Most women with these symptoms will be referred to a gynaecologist by their General Practitioner.

Santos, P. & Cunha, T.M. 2015.
"Uterine sarcomas are a rare heterogeneous group of tumors of mesenchymal origin, accounting for approximately 8% of uterine malignancies. They comprise leiomyosarcoma, endometrial stromal sarcoma, undifferentiated endometrial sarcoma, and adenosarcoma. Compared with the more common endometrial carcinomas, uterine sarcomas behave more aggressively and are associated with a poorer prognosis. Due to their distinct clinical and biological behavior, the International Federation of Gynecology and Obstetrics introduced a new staging system for uterine sarcomas in 2009, categorizing uterine carcinosarcoma as a variant of endometrial carcinoma, rather than a pure sarcoma. Magnetic resonance imaging (MRI) has a developing role in the assessment of these malignancies. Features such as tumor localization, irregular or nodular margins, necrosis, rapid growth, intense contrast enhancement, and restriction at diffusion-weighted imaging can suggest the diagnosis and help differentiate from more common leiomyomas and endometrial carcinoma. MRI is therefore extremely useful in preoperative detection and staging and, consequently, in determination of appropriate management. This pictorial review aims to discuss the clinical features of uterine sarcomas, as well as their most common appearances and distinct characteristics in MRI."

Risk Factors for Gynaecological Sarcomas
Risk factors for uterine sarcomas are
- Prior pelvic radiation
- Tamoxifen use

Kurnit, K.C., Previs, R.A., Soliman, P.T., Westin, S.N., Klopp, A.H., Fellman, B.M., Lu, K.H., Ramondetta, L.M. & Fleming, N.D. 2019.
OBJECTIVE: Evaluate the impact of clinicopathologic characteristics and adjuvant treatment on survival outcomes in early stage uterine carcinosarcoma patients.
METHODS: We performed a retrospective cohort study of women with stage I or II uterine carcinosarcoma at our institution between March 1990 and June 2016. All pathology had been reviewed and confirmed by gynecologic pathologists. Data were extracted from the electronic medical record. Descriptive and comparative statistics were used to compare clinicopathologic characteristics. Univariable and multivariable analyses were performed for survival outcomes.
RESULTS: 140 patients were identified. Median age was 67 years (range: 36-91). Median follow-up was 39.1 months (2.9-297.4). The majority of patients had stage IA (67%) versus stage IB (21%) or stage II (11%) disease. The majority of patients (63%) received adjuvant treatment: vaginal brachytherapy only (14%); whole pelvic radiation therapy only (16%); chemotherapy only (n = 13, 9%); combination chemotherapy and vaginal brachytherapy (15%); combination chemotherapy and whole pelvic radiation (9%). 52 patients (37%) received no adjuvant therapy. Median overall survival (OS) was 48.0 months (95% CI 32.7-80.9). On multivariable analysis for OS, advancing age (HR 1.05, 95% CI 1.03-1.08, $p < 0.001$), higher stage (stage IB: HR 1.64, 95% CI 0.91-2.95, $p = 0.10$; stage II: HR 3.04, 95% CI 1.51-6.13, $p = 0.002$), and the presence of a

rhabdomyosarcoma component (HR 1.66, 95% CI 1.02-2.70, p = 0.04) were significantly associated with worse OS.
CONCLUSIONS: Advancing age, stage, and the presence of a rhabdomyosarcoma component were all associated with worse OS in patients with early stage uterine carcinosarcoma. New treatment algorithms should incorporate factors aside from stage alone.

Diagnosis of Gynaecological Sarcomas
If cancer is identified preoperatively, CT or MRI is typically done. If uterine sarcoma is diagnosed after surgical removal, imaging is recommended, and surgical re-exploration can be considered.

Ludovisi, M., Moro, F., Pasciuto, T., Di Noi, S., Giunchi, S., Savelli, L., Pascual, M.A., Sladkevicius, P., Alcazar, J.L., Franchi, D., Mancari, R., Moruzzi, M.C., Jurkovic, D., Chiappa, V., Guerriero, S., Exacoustos, C., Epstein, E., Frühauf, F., Fischerova, D., Fruscio, R., Ciccarone, F., Zannoni, G.F., Scambia, G., Valentin, L. &Testa, A.C. 2019.
Objective: To describe the clinical and ultrasound characteristics of uterine sarcomas.
Methods: This was a retrospective multicenter study. From the databases of 13 ultrasound centers, we identified patients with a histological diagnosis of uterine sarcoma with available ultrasound reports and ultrasound images who had undergone preoperative ultrasound examination between 1996 and 2016. As the first step, each author collected information from the original ultrasound reports from his/her own center on predefined ultrasound features of the tumors and by reviewing the ultrasound images to identify information on variables not described in the original report. As the second step, 16 ultrasound examiners reviewed the images electronically in a consensus meeting and described them using predetermined terminology.
Results: We identified 116 patients with leiomyosarcoma, 48 with endometrial stromal sarcoma and 31 with undifferentiated endometrial sarcoma. Median age of the patients was 56 years (range, 26-86 years). Most patients were symptomatic at diagnosis (164/183 (89.6%)), the most frequent presenting symptom being abnormal vaginal bleeding (91/183 (49.7%)). Patients with endometrial stromal sarcoma were younger than those with leiomyosarcoma and undifferentiated endometrial sarcoma (median age, 46 years vs 57 and 60 years, respectively). According to the assessment by the original ultrasound examiners, the median diameter of the largest tumor was 91 mm (range, 7-321 mm). Visible normal myometrium was reported in 149/195 (76.4%) cases, and 80.0% (156/195) of lesions were solitary. Most sarcomas (155/195 (79.5%)) were solid masses (> 80% solid tissue), and most manifested inhomogeneous echogenicity of the solid tissue (151/195 (77.4%)); one sarcoma was multilocular without solid components. Cystic areas were described in 87/195 (44.6%) tumors and most cyst cavities had irregular walls (67/87 (77.0%)). Internal shadowing was observed in 42/192 (21.9%) sarcomas and fan-shaped shadowing in 4/192 (2.1%). Moderate or rich vascularization was found on color-Doppler examination in 127/187 (67.9%) cases. In 153/195 (78.5%) sarcomas, the original ultrasound examiner suspected malignancy. Though there were some differences, the results of the first and second steps of the analysis were broadly similar.
Conclusions: Uterine sarcomas typically appear as solid masses with inhomogeneous echogenicity, sometimes with irregular cystic areas but only very occasionally with fan-shaped shadowing. Most are moderately or very well vascularized.

Treatment of Gynaecological Sarcomas
- Treatment of Gynaecological Sarcomas may include:
- Surgery

- Radiotherapy
- Chemotherapy Hormone Therapy

A gynaecological sarcoma can reappear in the same area after the treatment of a previous tumour; this is called a recurrence. A recurrence of sarcoma may be accompanied by cancer in other parts of the body; this is called metastasis or secondary cancer.

Secondary gynaecological sarcomas may also appear in the abdomen.

Meurer, M., Floquet, A., Ray-Coquard, I., Bertucci, F., Auriche, M., Cordoba, A., Piperno-Neumann, S., Salas, S., Delannes, M., Chevalier, T., Italiano, A., Blay, J.Y., Mancini, J., Pautier, P. & Duffaud. F. 2019.
OBJECTIVE: High grade endometrial stromal sarcoma and undifferentiated uterine sarcomas are associated with a very poor prognosis. Although large surgical resection is the standard of care, the optimal adjuvant strategy remains unclear.
METHODS: A retrospective analysis of patients with localized high grade endometrial stromal sarcoma and undifferentiated uterine sarcomas (stages I-III) treated in 10 French Sarcoma Group centers was conducted.
RESULTS: 39 patients with localized high grade endometrial stromal sarcoma and undifferentiated uterine sarcomas treated from 2008 to 2016 were included. 24/39 patients (61.5%) were stage I at diagnosis. 38/39 patients underwent surgical resection, with total hysterectomy and bilateral oophorectomy completed in 26/38 (68%). Surgeries were mostly resection complete (R0, 23/38, 60%) and microscopically incomplete resection (R1, 6/38, 16%). 22 patients (58%) underwent postoperative radiotherapy (including brachytherapy in 11 cases), and 11 (29%) underwent adjuvant chemotherapy. After a median follow-up of 33 months (range 2.6-112), 17/39 patients were alive and 21/39 (54%) had relapsed (9 local relapses and 16 metastases). The 3 year and 5 year overall survival rates were 49.8% and 31.1%, respectively, and 3 year and 5 year disease free survival rates were 42.7% and 16.0%, respectively. Median overall survival and disease free survival were 32.7 (95% CI 16.3-49.1) and 23 (4.4-41.6) months, respectively. Medians were, respectively, 46.7 months and 39.0 months among those who underwent adjuvant radiotherapy and 41.0 months and 10.3 months for those who underwent adjuvant chemotherapy. In multivariate analysis, adjuvant radiotherapy was an independent prognostic factor for overall survival (P=0.012) and disease free survival (P=0.036). Chemotherapy, International Federation of Gynecology and Obstetrics I-II stages, and Eastern Cooperative Oncology Group-performance status 0 correlated with improved overall survival (P=0.034, P=0.002, P=0.006), and absence of vascular invasion (P=0.014) was associated with better disease free survival.
CONCLUSIONS: The standard treatment of primary localized high grade endometrial stromal sarcoma and undifferentiated uterine sarcomas is total hysterectomy and bilateral oophorectomy. The current study shows that adjuvant radiotherapy and adjuvant chemotherapy appear to improve overall survival. A prospective large study is warranted to validate this therapeutic management.

Zhang, Y.Y., Li, Y., Qin, M., Cai, Y., Jin, Y. & Pan, L.Y. 2019.
OBJECTIVES: The aim of this study was to evaluate the factors associated with progress-free survival (PFS) and overall survival (OS) in patients with high-grade endometrial stromal sarcoma (HG-ESS).
PATIENTS AND METHODS: A total of 40 patients were enrolled in this study at the Peking Union Medical College Hospital, Beijing, China, from 2006 to 2016. The study retrospectively analyzed clinical and pathological data, and associations of these variables with PFS and OS were evaluated.
RESULTS: The age of the patients at the time of diagnosis ranged from 16 to 73 years. Abnormal vaginal bleeding was the most commonly observed symptom. The tumor size ranged from 2 to 19 cm. The tumor locations were as follows: vulva (1 case), ovary (2 cases), broad ligament (2 cases), cervix (7 cases), and uterus (28 cases). A total of 34 (85%) and 6 (15%) patients underwent complete and ovarian preservation

surgery, respectively. Notably, 33 (82.5%), 13 (32.5%), and 5 (12.5%) patients received adjuvant chemotherapy, radiation therapy, and hormone treatment, respectively. Lymph node dissection was performed in 15 (37.5%) patients (positive rate: 7.4%), 16 (40%) patients underwent omentectomy (positive rate: 10%), and 12 (30%) patients underwent peritoneal lavage cytology (positive rate: 0%). Eighteen (45%) patients had lymphovascular space invasion, 13 (32.5%) patients had uterine fibroids, and 11 (27.5%) patients were diagnosed with endometriosis. Moreover, the levels of CA125 in the serum were measured prior to and following treatment. The median PFS and OS were 9 and 24 months, respectively. Eventually, 29 (72.5%) patients experienced relapse and 19 (47.5%) patients expired due to the disease.
CONCLUSION: Patients with advanced HG-ESS (stage II-IV) were associated with poor prognosis. The minimum value of CA125 and endometriosis were independent risk factors for PFS. The stage of disease, size of the tumor, minimum and average values of CA125, menopause, history of uterine leiomyoma, and endometriosis were independent risk factors for OS. The combination of surgery with radiotherapy and chemotherapy may improve the PFS of patients in the early stage of the disease.

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