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ORIGINAL RESEARCH

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Diagnostics and treatment of uterine sarcomas: challenges of a low-volume tertiary centre

Andrej Cokan[1], Eva Timošek[1,*], Tamara Serdinšek[2]

[1]Department for Gynaecological and Breast Oncology, University Medical Centre Maribor, 2000 Maribor, Slovenia
[2]Department for General Gynaecology and Urogynaecology, University Medical Centre Maribor, 2000 Maribor, Slovenia

***Correspondence**
eva.timosek@ukc-mb.si
(Eva Timošek)

Abstract

Uterine sarcomas are rare diseases with no specific characteristics on imaging, so preoperative diagnosis remains challenging. The diagnostics is usually performed before treatment of what is supposed to be a benign tumour and therefore not at referral centres. We performed a retrospective study of patients with uterine sarcoma treated at our centre between 2012 and 2022. We aimed to analyse the preoperative management and clinical characteristics of the tumours, and to propose appropriate clinical pathways for these patients in small countries with a low number of inhabitants. We identified 21 women with the average age of 59 $\pm$ 11 years. The most common clinical symptom was vaginal bleeding (61.9% of patients). Uterine sarcoma was confirmed in 42.9% of patients prior to primary surgery. Tumours were classified as leiomyosarcomas (38.1%), as low-grade endometrial stromal sarcomas (ESS) (23.8%), as high-grade or undifferentiated ESS (19%), as liposarcomas (4.8%), and as adenosarcomas (14.3%). 81% of patients were operated as having uterine tumour, of which 14.3% had either enucleation or morcellation of the tumour/uterus due to presumed uterine fibroma. 33.3% of all patients had a primary metastatic disease when presented at our centre, and 28.6% had a recurrent disease. In patients with a follow-up period of 5 years or more, the overall survival (OS) was 46.2%. Our results confirmed that the clinical and histopathological characteristics of uterine sarcomas are very diverse. As their incidence is extremely rare when compared to benign fibroids, the main challenge remains in defining the criteria to select which patients should be referred for further diagnostics and treatment to tertiary centres before surgical procedure. Specifically in small countries, an additional challenge is the fact that even a single referral centre is still a low volume centre.

Keywords

Uterine sarcoma; Uterine sarcoma treatment; Low-volume centre

1. Introduction

Uterine sarcomas are rare heterogeneous mesenchymal malignant tumours, representing 3–7% of malignant tumours of the uterine corpus that mainly affect patients between 50 and 70 years of age [1]. They arise from the myometrium or from the endometrium connective tissue elements. The College of American Pathologists classifies the sarcomas by the following types: leiomyosarcoma (LMS), which is the most common and accounts for approximately 63% of all uterine sarcomas, endometrial stromal sarcoma (low grade (LG-ESS) and high grade (HG-LSS)), undifferentiated endometrial stromal sarcoma (U-ESS), adenosarcoma (AS), and other rarer subtypes [2]. Sarcomas present a diagnostic and therapeutic challenge. On ultrasound, these tumours are usually round, with central necrosis, highly vascularized, and do not have calcifications, yet it remains difficult to reliably differentiate them from myomas. Contrast-enhanced ultrasound (CEUS), computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) can be used to aid with the diagnosis and targeted biopsy, while hysteroscopy or dilation and curettage can also be considered [3]. Treatment is primarily surgical, especially in early stages, with en-bloc hysterectomy with bilateral adnexectomy. In general, uterine sarcomas have poor prognosis—existing treatment methods, such as surgery, chemotherapy and radiotherapy are not very effective. Therefore, the 5-year survival rate exhibits suboptimal outcomes, varying across distinct subtypes and ranging from 54.3% to 85.3% [4].

According to the latest data from our national cancer database in Slovenia, there were 396 new cases of malignant tumours of the uterine corpus in 2019, which means that there were probably only approximately 15 cases of uterine sarcomas in the entire country, which should be treated and managed in the tertiary-level hospitals [5]. While uterine sarcomas are rare, uterine fibroids are most common pelvic tumours in women, and differentiation between the two can be very challenging. As many as 20–40% of women

have fibroids, and these are treated in both secondary- and tertiary-level hospitals. Almost 30% of the uterine sarcoma are associated with a preoperative diagnosis of a uterine fibroid [6]. Therefore, the major challenge is defining the "red flag" criteria that are accurate and user friendly for general gynaecologists that treat several women per month with benign fibroids and will encounter only one or two malignant tumours in their whole career. Furthermore, small countries encounter an additional specific problem of having small numbers of cases even if all patients are referred to one tertiary centre.

This study aims to analyse the preoperative management and clinical characteristics associated with uterine sarcoma as well as to propose more appropriate clinical pathways for these patients in low-volume centres or countries.

2. Materials and methods

2.1 Aims of the study

The primary aim of the study was to determine the signs and symptoms, preoperative diagnostic tools, and other clinical characteristics of patients with uterine sarcoma referred to or treated at our institution. The secondary aim was to suggest a clinical pathway for patients with solid uterine tumours using "red flag" signs and how to manage them in a tertiary centre in a small country.

2.2 Study population

We performed a single-institution retrospective study including all consecutive female patients with histopathologically confirmed uterine sarcoma that were treated at our tertiary centre between 2012 and 2022. The data were extracted from the hospital's computerised medical records. The patients were staged and treated at the Department for Gynaecological Oncology and Breast Oncology or sent to our multidisciplinary team from another department or secondary-level hospital. Women with a previously confirmed uterine sarcoma diagnosis and incomplete data for analysis were excluded.

2.3 Data collection

The following data were obtained for each patient: (i) age at diagnosis, (ii) time since the diagnosis (less than five years and five or more years), (iii) preoperative signs, symptoms and diagnostic procedures, (iv) histopathological type of sarcoma, (v) preoperative histopathological confirmation of uterine sarcoma, (vi) preoperative stage of the disease, (vii) type of primary treatment, (viii) accidental enucleation or morcellation of the tumour, (ix) presence of lymphovascular invasion, (x) type of adjuvant treatment, (xi) presence of primary metastatic disease, (xii) disease recurrence, (xiii) treatment of disease recurrence, (xiv) secondary surgery.

2.4 Statistical analysis

We performed a statistical analysis using SPSS Statistics software 25.0 (IBM, Armonk, NY, USA). Descriptive statistics were calculated on basic patient characteristics. Pearson's chi-square/Fisher's exact tests were used to compare categorical data between groups. Kaplan-Maier analysis was performed to OS curves. We defined progression-free survival (PFS) as the period during and after the primary treatment with no clinical or imaging signs of sarcoma relapse/progression and OS as the period since the diagnosis of gynaecological sarcoma to the date of the last follow-up or death. Statistical significance was set at a p-value < 0.05.

3. Results

Using our inclusion criteria, we identified 21 women with uterine sarcoma treated or managed at our Department from 2012 to 2022. Their average age was 59 $\pm$ 11 years (range 39–84 years), 15 (71.4%) of them were postmenopausal. Their average body mass index was 29.8 $\pm$ 6.6 kg/m^2 (range 20–39 kg/m^2). The median number of deliveries was 2 (range 0–3), abortions 0 (range 0–2) and extrauterine pregnancies 0 (range 0–1). Seven patients (33.3%) were diagnosed less than five years ago, and 14 (66.7%) patients were diagnosed five or more years ago. The most common clinical symptom was vaginal bleeding, which was present in 13 (61.9%) patients. Nine (42.9%) patients had only one symptom, 10 (47.6%) patients had two or more symptoms or signs, and one had no symptoms. Initial clinical signs and symptoms are presented in Table 1. Five (23.5%) women had a gynaecological history of concomitant uterine fibroma. Tumor sizes, determined through preoperative imaging, spanned a range from 28 to 120 millimeters.

TABLE 1. Initial clinical signs and symptoms.

Clinical sign/symptom	Number of patients (N = 21)	Percentage
Vaginal bleeding	13	61.9
Rapidly growing uterine mass	10	47.6
Pelvic pain	6	28.6
Renal colic pain	1	4.8
Anaemia	1	4.8
Uterine fibroids	1	4.8
Hydronephrosis	1	4.8

Clinical and/or radiologic suspicion of sarcoma was preoperatively histopathologically confirmed in 9 (42.9%) patients, 4 (19%) of these with dilation and curettage, 2 (9.5%) of these with hysteroscopy and 3 (14.3%) of these with tumour biopsy. Six (66.7%) patients who had sarcomas diagnosed with biopsy were presented at the multidisciplinary team board before any oncological treatment. Among them, two were metastatic at the time of diagnosis. Five (55.6%) were completely staged before treatment, with imaging of the thorax and abdomen. One patient underwent only a pelvic ultrasound before the surgery. In this patient, LMS was confirmed postoperatively.

Six (28.6%) patients had only one preoperative investigation, while others had two or more. Preoperative imaging investigations that were performed are presented in Table 2. Nine (42.9%) patients were presented at our multidisciplinary team meeting prior to any type of primary treatment.

TABLE 2. Performed preoperative imaging investigations.

Preoperative investigations	Number of patients (N = 21)	Percentage
Transvaginal ultrasound	17	81.0
Chest X-ray	7	33.3
Abdominal ultrasound	4	19.0
Chest CT	7	33.3
Abdominal CT	10	47.6
Pelvic MRI	2	9.5

CT: computed tomography; MRI: magnetic resonance imaging.

Histopathologically, 8 (38.1%) tumours or biopsy specimens were defined as LMS, 5 (23.8%) as LG-ESS, 4 (19%) as HG- or U-ESS, 1 (4.8%) as liposarcoma, and 3 (14.3%) as AS. Data on lymphovascular invasion (LVI) were available for 14 patients, 4 of those (19% of all patients) had signs of LVI during the histopathological examination. The average number of mitoses per high-power field was 20 (range 2–98).

Primary surgery was performed in 17 (81%) patients. Among them, six patients were histopathologically diagnosed with sarcoma before the surgery. Three patients had total abdominal hysterectomy with bilateral salpingo-oophorectomy, two had total abdominal hysterectomy with bilateral salpingo-oophorectomy and pelvic lymphadenectomy, and one patient had total laparoscopic hysterectomy.

Seven (33.3%) patients were treated as having benign fibroid. One patient had myomectomy with morcellation, one patient had hysterectomy with morcellation, three patients had total abdominal hysterectomy, and two patients had laparoscopic hysterectomy without morcellation. Two patients (25%) were presented at multidisciplinary team meetings before the first operation. Both patients who underwent morcellation remain alive, and only one experienced a local recurrence in the pelvis. This recurrence was managed through secondary cytoreduction, followed by adjuvant radiotherapy.

Almost two thirds of our patients had a tumour limited to the uterus, 4 (19%) had a FIGO (The International Federation of Gynecology and Obstetrics) stage I, and 9 (42.9%) had a stage II disease. On the other hand, 7 (33.3%) patients had a primary metastatic disease. Besides surgery as a primary treatment, other primary treatment modalities were chemotherapy in 1 (4.8%) patient, palliative radiotherapy in 2 (9.5%) patients, and hormonal therapy in 1 (4.8%) patient. Adjuvant treatment was indicated in 7 (33.3%) patients who underwent chemotherapy (14.3%), radiotherapy (9.5%), or a combination of both (9.5%).

Six women (28.6%) experienced disease recurrence, constituting 42.9% of those without primary metastatic disease. Notably, only one patient with disease recurrence had undergone prior morcellation. The recurrences were predominantly distant, with three occurrences in the pulmonary region, one in the spleen and abdominal wall, and two in the pelvic region (including one after prior morcellation). Progression-free survival within this group exhibited a range of 3 to 29 months. Secondary cytoreduction was conducted at a different institution and proved feasible in 2 of the patients, accounting for 33.3% of all recurrences. Among them, one received adjuvant radiotherapy, and the other underwent adjuvant chemotherapy along with hormonal therapy. The remaining cases were managed with either chemotherapy or palliative radiotherapy. In one patient, specific treatment was hindered by a poor performance status, while information regarding the treatment of another patient was unavailable as it was administered at a different institution.

4. Discussion

Our results confirmed that symptoms and signs of uterine sarcomas are diverse and not specific. The vaginal bleeding was, however, the most frequent symptom. When the histopathological diagnosis was known before the surgery, all patients were managed accordingly. Morcellation/enucleation of the tumours or of the uterus were therefore observed only among women with no clinical or radiological suspicion of sarcoma—they were all treated as having benign fibroids.

Symptoms are usually not specific and include vaginal bleeding, abdominal discomfort, and pain [7], which is in concordance with our findings—the most common symptoms were vaginal bleeding and pelvic pain. Risk factors associated with sarcomas include enlargement of the tumour in the postmenopausal period, long-term use of tamoxifen, pelvic irradiation, a history of childhood retinoblastoma, and hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome [8–11]. Most commonly, a clinical suspicion is made when a rapidly growing leiomyoma or rapidly growing uterus is detected, especially in postmenopausal women. However, there is no consensus on the definition of rapid growth [12]. There are also no validated clinical or radiological criteria that can accurately distinguish benign from malignant myometrial tumours. Some morphological ultrasound characteristics of sarcomas differ from their benign counterparts, such as irregular margins, cooked aspect, irregular cystic areas, regular cystic areas, colour score, and absence of acoustic shadowing [13]. CT and MRI can help differentiate sarcomas, but also frequently cannot reliably exclude one [12]. Pathognomonic signs on CT and MRI include uterus enlargement with extensive necrosis and haemorrhage, central zones of low attenuation can be seen, as well as infiltration into the surrounding tissues. In the case of ESS, polypoid endometrial mass can often be detected. Although CT, MRI, and positron emission tomography/CT with fluorodeoxyglucose (FDG) are not exceedingly suitable for evaluating primary tumours, they can be helpful for staging purposes [12]. In cases of preoperative vaginal bleeding, some patients may undergo curettage or endometrial biopsy. However, it is crucial to note that these procedures can yield a false negative result in approximately 50% of cases. Consequently, a negative biopsy result does not conclusively rule out leiomyosarcoma [12]. While factors such as symptoms, risk factors, and diagnostic tools can help identify indicators of a sarcoma, the low prevalence of

the disease limits the effectiveness of screening measures to increase the positive predictive value to a clinically useful level. This likely accounts for the considerable variability in presentation patterns associated with uterine sarcoma and underscores the challenge of reliably identifying such cases before hysterectomy [14].

As mentioned, benign uterine fibroids are common tumours and affect every fourth or fifth woman. Morcellation is usually required in patients with large or numerous fibroids [15]. Since fibroids are so prevalent, the European Society for Gynecologic Oncology (ESGO) issued a statement stating that eliminating the technique of morcellation could lead to increased morbidity in low-risk patients and is therefore advisable after a thorough preoperative evaluation and discussion with patients [16]. Considering this, special attention must be paid to peri- and postmenopausal women with newly onset symptoms, particularly uterine bleeding or enlargement. They should be evaluated immediately, and malignancy, including LSS, should be excluded, especially if morcellation is planned. Preoperative biopsy should be performed, even though the sensitivity of this method to detect sarcoma is low [16]. This holds significance as unprotected morcellation elevates the risk of dissemination and recurrence in both smooth uterine muscle of uncertain malignant potential (STUMP) and uterine sarcomas [17].

In our study, 71.4% of patients were postmenopausal, and only one was asymptomatic. Eight patients in total (36.4%) underwent comprehensive staging, including imaging of the abdomen and thorax, prior to the initial surgery. Additionally, two patients underwent complete staging post-primary surgery for fibroids. In 42.9% of patients, sarcoma was confirmed before the treatment. Only 42.9% of patients were presented at the multidisciplinary team meeting before the treatment. In three patients, sarcoma was diagnosed after previous surgery for fibroids, namely after myomectomy (in one case) or after morcellation (in two cases).

The most important challenge remains the specification of symptoms and signs that could have a role of "red flag" signs, helping general gynaecologists in deciding which patient to refer for further diagnostics and treatment. According to our and previously published results, these could be: abnormal vaginal bleeding, especially in postmenopausal women with solid uterine tumours, rapidly growing new tumours, especially if these cause symptoms of pressing neighbouring organs (urinary symptoms, urinary retention, colorectal symptoms, deep vein thrombosis with or without pulmonary embolism). As shown by our results, when women having clinical or radiological suspicion of sarcoma were referred to a department dedicated to gynaecologic oncology, they were all presented to the preoperative multidisciplinary team and treated accordingly. Nevertheless, it is almost impossible to identify all sarcomas preoperatively. This is especially true for the younger population, in which symptoms and signs are non-specific. This population remains highly challenging mainly because benign symptomatic fibroids are common and because avoiding minimally invasive surgery is associated with higher complication rate.

Furthermore, working in a country with a low number of inhabitants presents another important drawback. Even if somehow complete centralisation of care is achieved, there is still a low number of cases per centre. This is especially important for radiologists and pathologists, as surgical treatment is relatively easy when the disease is confined to the uterus. According to our experience, it is most valuable for small countries that pathologists have a regular established pathway for second opinions between institutions and abroad. The same holds for radiologists and clinicians. We would therefore recommend each tertiary centre in a small country to have an established routine pathway for consultations with a large sarcoma centre abroad.

This is, to our knowledge, the first analysis of uterine sarcoma in our country after an updated International Federation of Gynaecology and Obstetrics (FIGO) classification. A paper from our institution was published in 2013, but in that cohort of uterine sarcoma, there were 40.9% of patients with carcinosarcoma, so we could not compare those patients with our cohort [18].

There are also some limitations of our work. Firstly, the study is a single-centre retrospective study with a low number of included patients. Secondly, since a large proportion of the patients were diagnosed outside our Department, data regarding ultrasound characteristics and other diagnostic tools were either incomplete or partially missing. Further, the heterogeneity of the cases can lead to unreliable conclusions regarding statistical comparisons and survival analyses. In addition, a major limitation of our study was the loss of follow-up information for those patients that were referred for adjuvant therapy, which was at that time performed in a different tertiary centre.

5. Conclusions

The article presented 10-year data on the diagnostics and management of uterine sarcoma in a low-volume setting in a country with two million inhabitants. The analysis is limited by its retrospective nature and the small number of patients included; nevertheless, we have shown that the real challenge of managing these patients is the heterogeneity of tumours themselves and their clinical presentation. Whenever possible, patients with suspected or confirmed uterine sarcomas should be referred to speciality centres with expertise in diagnostics and management of uterine sarcomas.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

AUTHOR CONTRIBUTIONS

AC—conceptualization; AC, ET and TS—data curation, formal analysis, investigation, writing-original draft preparation; writing-review and editing and supervision. All authors have read and agreed to the published version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

As this was a retrospective study, patients signed informed consent to analyze their anonymous data for statistical purposes, so an ethical approval from the institutional review board was not necessary and therefore not obtained.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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