UTERINE LEIOMYOSARCOMA: About 13 Cases and Review of the Literature

TERRAB FZ\textsuperscript{1}, ALLOUCH F.\textsuperscript{1}, GHAMAD S.\textsuperscript{1}, BOUHAFA T.\textsuperscript{1}, ALAMI Z.\textsuperscript{1} and HASSOUNI K.\textsuperscript{1}

Abstract
The uterine leiomyosarcoma (LMS) is a rare cancer arising from the smooth myometrial cells. The LMS is clinically aggressive malignancy, accounting for 2% to 6% of uterine malignancies and a very low annual incidence.

Object of the study: To evaluate management and outcome of the treatment of uterine leiomyosarcoma.

Patients and methods: Retrospective study of a series of 13 patients treated for uterine leiomyosarcoma in the department of radiotherapy of CHU Hassan II, Fes between 2012 and 2016

Results: The condition is rarely suspected preoperatively, diagnosis is usually made on histological examination of the operative specimen. The outcome is related to the mitotic activity of the tumour and to the infiltration of nearly structures. Surgery is the only effective treatment, chemotherapy is ineffective, adjuvant radiotherapy improves local control of the tumour but has no incidence on survival.

Conclusion: In the absence of an effective adjuvant treatment, uterine leiomyosarcoma bears a poor prognosis with the only exception of small non infiltrating tumours with a low mitotic activity.

Keywords
Uterine sarcoma; Uterine leiomyosarcoma; hysterectomy, radiotherapy, chemotherapy

Introduction
The leiomyosarcoma (LMS) is a very rare uncommon uterine cancer, has an incidence ranging from 0.5 to 3.3 per 100,000 women per year, with a further incidence of sarcomas in women with myomas at rapid growth of 0.27%, representing 1-1.3% of all uterine malignancies and about 5% of uterine sarcomas\textsuperscript{1}. Generally, LMS arises within the myometrium, from the smooth muscle cells, clinically aggressive smooth muscle malignancy. The histological diagnosis of leiomyosarcoma is based on prominent cellular atypia, abundant mitoses (\(\geq 10\) per 10 high power fields), and areas of coagulative necrosis. LMS is a so aggressive tumor associated with a high risk of recurrence and death, regardless of a stage at presentation: 2% -6% of uterine malignancies have poor prognosis and annual incidence is 1.7 per women\textsuperscript{2}. Uterine LMS is usually detected during the fifth or sixth decades of life. Malignant alteration occurs mainly in postmenopausal women and is rarely asymptomatic. The main presenting symptoms of uterine LMSs are abnormal vaginal bleeding, pain in the lower abdomen and a pelvic or abdominal mass.\textsuperscript{3}

Patients and methods
We collected 13 patients followed and treated for uterine leiomyosarcoma in the department of radiotherapy of CHU Hassan II, Fes between 2012 and 2016. Statistical analysis was obtained using Excel and SPSS computer software. The significance level of all observed differences was set for all statistical tests at a probability value \(p \leq 0.05\).

Results
The mean age of our patients at diagnosis was 58.38 years (from 40 years to 81 years). The circumstances of discovery were in order of frequency: vaginal bleeding (100% cases), pelvic pain (85% cases), and a pelvic mass (20% cases). The ultrasound performed in 8 women showed: a uterus increases in size and irregular contours in 6 women, an aspect of myoma in necrobiosis in 2 women. Pelvic MRI was performed in 7 women. The hysterosalpingography was performed twice. Only one biopsy curettage was done, without being diagnosed. As part of the extension assessment, all women benefited from a TAP CT scan. All patients underwent total hysterectomy with or without preservation of annexes, pelvic lymph node dissection was performed in 4 patients, and lumbar-aortic lymph node dissection was performed in a single patient.

At the anatopathological examination, the average tumor size was 14 cm with extremes of 8 to 26 cm, with a whitish appearance at the cut and a soft consistency. On microscopic examination, the most consistent signs were the increase number of mitoses and the presence of cellular atypia. 8 patients received an adjuvant pelvic radiotherapy: vaginal curietherapy (7Gy) and external radiotherapy on the pelvis (50Gy in 25 fractions of 2Gy / Fr, 5 days out of 7). One patient received adjuvant chemotherapy with Doxorubicin monotherapy. 4 patients had metastatic locations and received palliative chemotherapy: 2 patients were treated with the combination of Docetaxel and Gemcitabine and 2 patients were treated with paclitaxel and carboplatin. After
an average follow-up of 20 months, 7 patients are alive and in complete remission, 5 deaths and one case lost of sight.

**Discussion**

**Epidemiology**

The frequency of occurrence of uterine leiomyosarcoma is 0.67 / 100000 women per year older than 20 years. The average age of onset is 58.3 years, which is very close to those reported in the literature.

**Clinical**

The three most frequent signs found in our observations as in the literature are genital hemorrhage, pelvic pain and pelvic mass.

**Paraclinical**

**Ultrasound** The contribution of ultrasound is very limited in terms of uterine leiomyosarcoma. Indeed, there is no pathognomonic echographic sign of uterine leiomyosarcoma, in general, they present themselves as irregular masses, voluminous, heterogeneous and poorly defined. Doppler regains a very high systolic peak and a slight increase in the diastolic component at the periphery of the tumor.

**MRI** The MRI is useful to differentiate between benign and malignant myometrial tumors. The combination of the characteristics of an intermediate signal T2, faint signal b 1000, and the low signal on the CDA is diagnosed in 92.4% of cases of malignancy.

**Hysterosalpingography** May be evocative in front of a uterine cavity increased in size with polycyclic gap with clear contours and hollow intra-lesional notches. Biopsy curettage is diagnosed only when the tumor reaches the endometrium, the rate of positive diagnosis in case of leiomyosarcoma varies between 15 to 35% according to the authors.

**Pathological anatomy** The macroscopic aspect of the LMS is in 90% of cases that of a single nodule forming an intramyometrial mass with a defined growth limit. In section, the tumor is pink to pale gray and has necrotic and hemorrhagic zones. The diagnosis of uterine leiomyosarcoma (LMSU) is difficult to make. Facing a smooth muscle tumor, the diagnosis of malignancy is based on three characteristics: necrosis, moderate to severe cytological atypia and mitotic activity which is consistent with our series. The cells are arranged in long bundles intersecting at right angles. They have abundant and eosinophilic cytoplasm, often fibrillar, possibly containing a vacuole notching the nucleus. There are three histological forms: the LMS in its typical form and two variants: epithelioid and myxoid. In immunohistochemistry, 50% of LMS are positive with an antidesmin antibody that has good specificity. The other markers expressed are global muscle actin (HHF35), smooth muscle actin and h-caldesmone, which has good specificity and is expressed by 85% of LMS. Finally, hormone receptors (HR) are also frequently expressed in uterine LMS, which can lead to a uterine origin when the diagnosis is made on a metastasis and may also constitute a potential therapeutic target.

**Prognostic factors** The dominant prognostic factor is the mitotic activity of the tumor. The prognosis is as much darker as the mitotic activity is high. The stage clearly influences the evolution of cancer. In the analysis of the SEER database, the five-year LMSU survival rates by stage were 75.8% for stage I, 60.1% for stage II, 44.9% for stage III, and 28.7% for stage IV. The median overall survival (OS) for stage IV is in the range of 12 to 16 months depending on the studies. Lack of necrosis and peri-tumoral hyalinization are factors of good prognosis. The young age as well as the perimenopause are factors of good prognostic for all the authors.

**Treatment**

**Treatment of early stages**

The standard treatment for LMSU is surgical. However, the rates of pelvic and extrapelvic relapse are respectively 16.6 and 42%. The objective of treatment at the localized stage is therefore to obtain local eradication of the disease and to avoid locoregional or metastatic relapse.

**Surgery** Surgery is often a diagnostic step but also the first therapeutic time for uterine sarcomas. Recommendations were published in 2003. These recommend, if the diagnosis of sarcoma is evoked, performing an exploration with surgical staging and a block hysterectomy, without fragmentation, associated with bilateral adnexectomy. Glandular dissection is only recommended in the presence of macroscopic lymphadenopathy. In the event of discovery following a myomectomy, fragmented surgery or subtotal hysterectomy and / or in the absence of annexectomy, a surgical revision must be performed in order to complete the procedure and perform the adnexectomy if it is not made.

**Adjuvant radiotherapy** In the EORTC phase III study, pelvic adjuvant radiotherapy (50 Gy) reduced the locoregional relapse rate: 22% in the radiotherapy group versus 40% in the observation group (p = 0.004), patients with stage I or II uterine sarcoma. This difference in local control did not translate into a difference in survival without relapse or difference in SG. All the other series published on adjuvant radiotherapy in uterine sarcomas are consistent with these results, its indication is to be discussed on a case-by-case basis, in a multidisciplinary consultation meeting (RCP).

**Adjuvant chemotherapy** The utility of adjuvant chemotherapy in LMSUs is debated and the rarity of this pathology makes it difficult to perform randomized trials. The first randomized phase III study, published in 1985, comparing adjuvant chemotherapy with adriamycin to the absence of adjuvant chemotherapy did not show a significant difference in terms of recurrence-free survival, progression-free survival, and median OS. A non-comparative, single-center phase II study evaluated the efficacy of adjuvant chemotherapy with gemcitabine and docetaxel in 23 patients who underwent complete resection of stage I to IV LMS. For 18 patients with stage I or II disease, the three-year PFS was 59% which seemed better than the retrospective series without adjuvant chemotherapy at the same center (35%
Treatement of advanced and metastatic stages

In this situation, the main treatment is chemotherapy. In case of oligometastatic situation, it is advisable to discuss the file in RCP in order to decide of local treatments in addition to the chemotherapy, a multidisciplinary management being able to improve the prognosis. Targeted therapies were also studied in this situation.

First-line Chemotherapy

The most commonly used protocols associate doxorubicin with ifosfamide or dacarbazine. The reference molecule in the first line of LMSU treatment is, as for all sarcomas, doxorubicin.

After the first-line chemotherapy

Several options are available, mainly monotherapies that are preferred in this context to limit toxicity and maintain a good quality of life. In practice, trabectedin, gemcitabine and dacarbazine are the second or higher choice molecules of LMSUs.

Targeted therapy

Hormone therapy is a therapeutic option for tumors expressing HR. Its place in maintenance treatment after first-line chemotherapy should be studied. Anti-angiogenic agents have shown an interesting activity in LMSUs, they allow mainly stabilizations in LMSUs with a low objective response rate; their use can be envisaged during a progression after one or two lines of chemotherapy.

Conclusion

Leiomyosarcoma is a rare cancer, that the prognosis remains dark. The preoperative diagnosis is rarely done, it is most often presented in the form of a simple myome or necrobiosis. The main prognostic factor is mitotic activity. The treatment is dominated by surgery. Radiotherapy only reduces local recurrence without changing survival and chemotherapy has not proven effective.

References


