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Uterine Sarcoma

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Abstract : *Our study's aim was to evaluate the epidemiology, clinicopathological features, diagnosis difficulties, treatment and prognosis of uterine sarcomas. The retrospective study of eight cases of uterine sarcoma was conducted in the department of gynecology and obstetrics I, university hospital Hassan II, Fes. The age range of presentation was from 46 to 70 years. The main presenting symptoms and clinical signs present at diagnosis are vaginal bleeding, pelvic pain and pelvic mass. Imaging procedure consisted on ultrasonography in the eight cases, hysteroscopy with biopsy in 03 case, tomography in 01 cases and magnetic resonance imaging in 03 case. The diagnosis of leimyosarcoma was established preoperatively in one case through biopsy. All patients except the one, had first intention surgery, Postoperative pathohistologic analysis showed that leiomyosarcoma was present in 05 cases, endometrial sarcoma in 03 case. All patients were sent to the hospital of Oncology in Fez for additional treatment, 04 patients were lost to view, three patients benefited from adjuvant radiotherapy, the outcome was favorable for 02 patients, the other showed a recurrence 2 years after the initial diagnosis, they received palliative chemotherapy. Uterine sarcomas are a heterogeneous group of rare gynecological malignant neoplasms. Our finding about frequency of leiomyosarcoma (62,5%) correlate with curent data, followed by endometrial stromal sarcomas 37.5%. Generally diagnosis is established after surgery. Actually, the gold standard is hystero salpingo ovariectomy associated with postoperative radiotherapy. Place of chemotherapy is still discussed.*

Keywords: Leimyosarcoma, Magnetic resonance, Hysteroscopy, Treatment

Introduction:

Uterine sarcomas are rare tumors, representing only 4-9% of malignant tumors of the uterus **(1,2)**. They are a heterogeneous group of tumors that include schematically three histological subtypes: leiomyosarcomas, endometrial stromal sarcomas and adenosarcomas.

One of the common characteristics of uterine sarcomas, except for low-grade stromal sarcomas, is that they have a bad prognosis, with a high rate of local recurrence and, especially, of metastatic recurrence (usually in the lungs).

Surgery occupies a central place in the management of uterine sarcomas. There are many publications on adjuvant treatments, but few of them concern prospective trials.

Optimal postoperative management is not fully defined. A better knowledge of prognostic factors through the study of new series of patients would allow to propose adjuvant treatments adapted to the evolutionary profile of each patient.

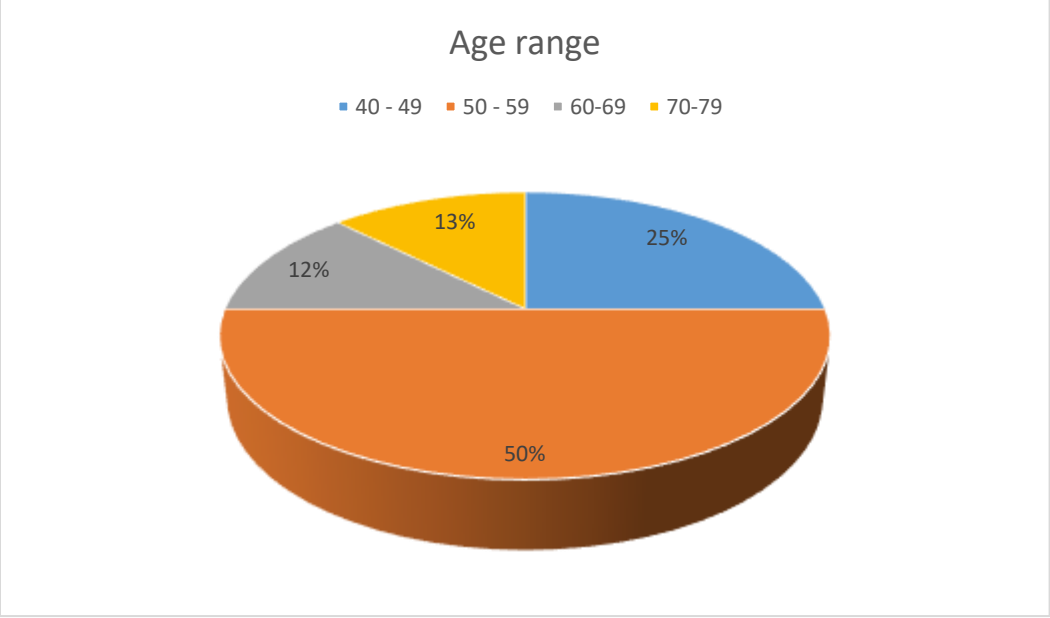
Who histological classification (2003)

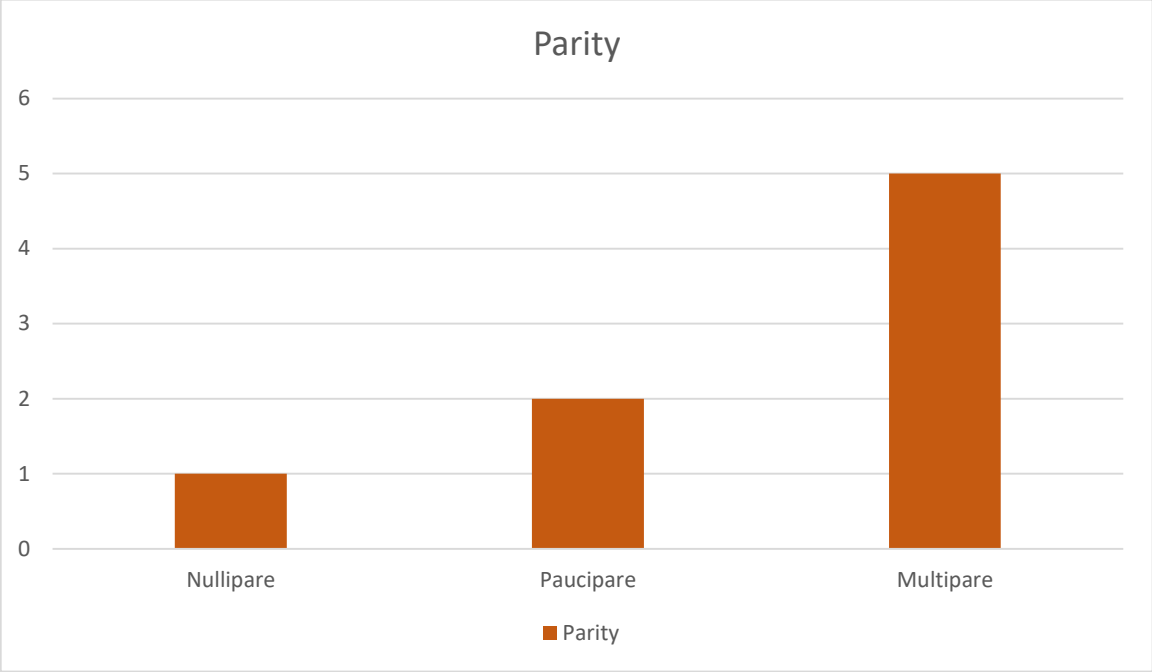
MESENCHYMAL TUMORS	
ENDOMETRIAL STROMAL TUMOR	**VARIOUS MESENCHYMAL TUMORS**
Low grade endometrial stromal sarcoma	Mixed endometrial stromal and smooth muscle tumor
Nodule of the endometrial stroma	Perivascular epithelial cell tumor
Undifferentiated endometrial sarcoma	Adenomatoid tumor
MYOMETRICAL SMOOTH MUSCLE TUMOR	Other malignant mesenchymal tumors
Leiomyosarcoma	Other benign mesenchymal tumors
Smooth muscle tumor of uncertain malignant potential	
Leiomyoma	
MIXED EPITHELIAL AND MESENCHYMAL TUMORS	
CARCINOSARCOMA	ADENOFIBROMA
[illegible]	[illegible]

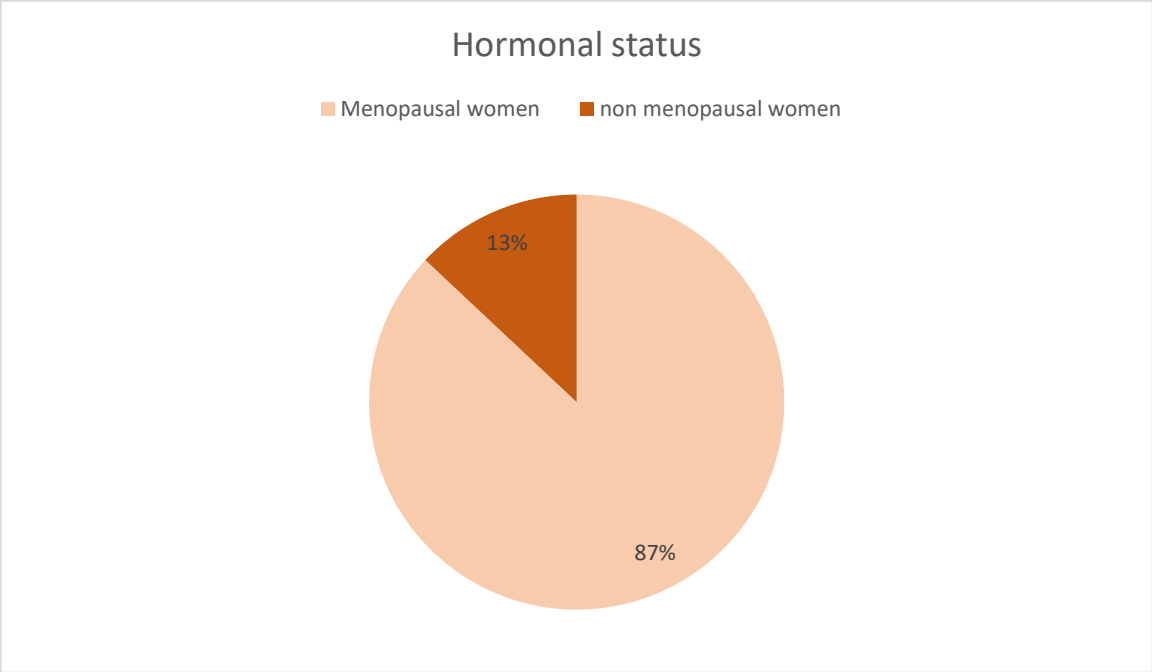
	Homologous	Heterologous
Pure	Leiomyosarcoma Endometrial stromal sarcoma	Rhabdomyosarcoma Chondrosarcomea Osteosarcoma Liposarcoma
Mixed	Mixed mesenchymal malignant tumors with homologous components (carcinosarcomas, adénosarcomas)	Mixed mesenchymal malignant tumors with heterelogous components (mixed mesodermal tumours)

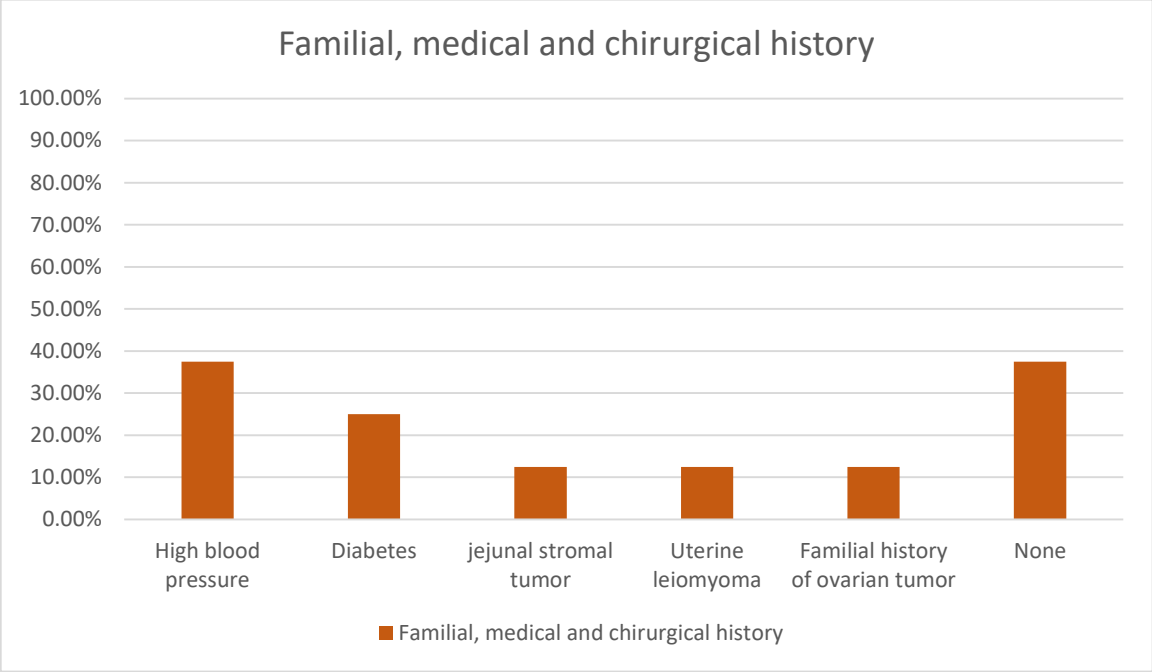
Uterine sarcomas are classified according to whether they are pure (presence of mesenchymal malignant cells only) or mixed (presence of mesenchymal and epithelial cells) and whether they are homologue (presence of malignant cells derived from mesenchymal cells normally present in the uterus) or heterologue (presence of malignant cells derived from mesenchymal cells normally absent from the uterus) **(3,4)**

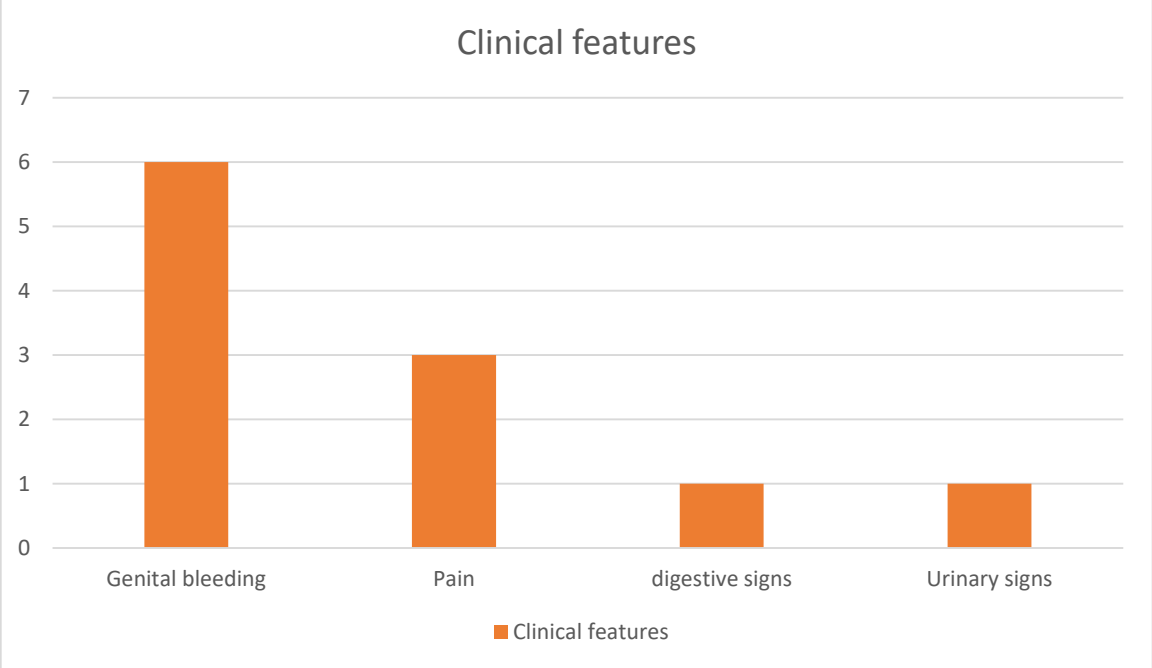
Cases report : 8 cases

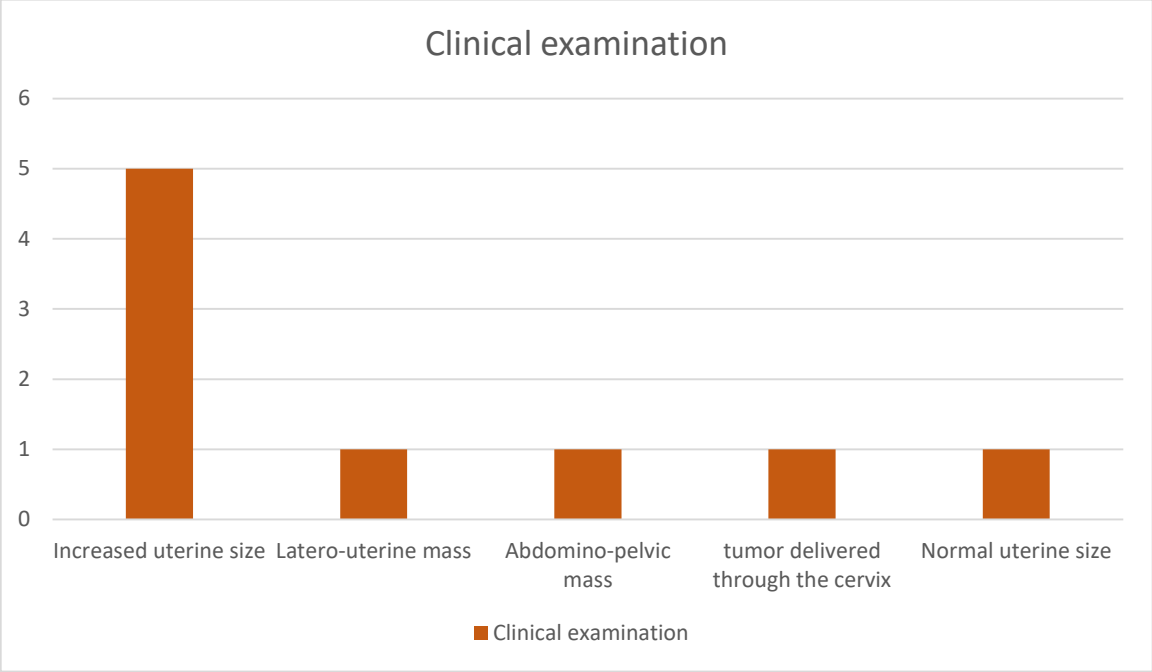


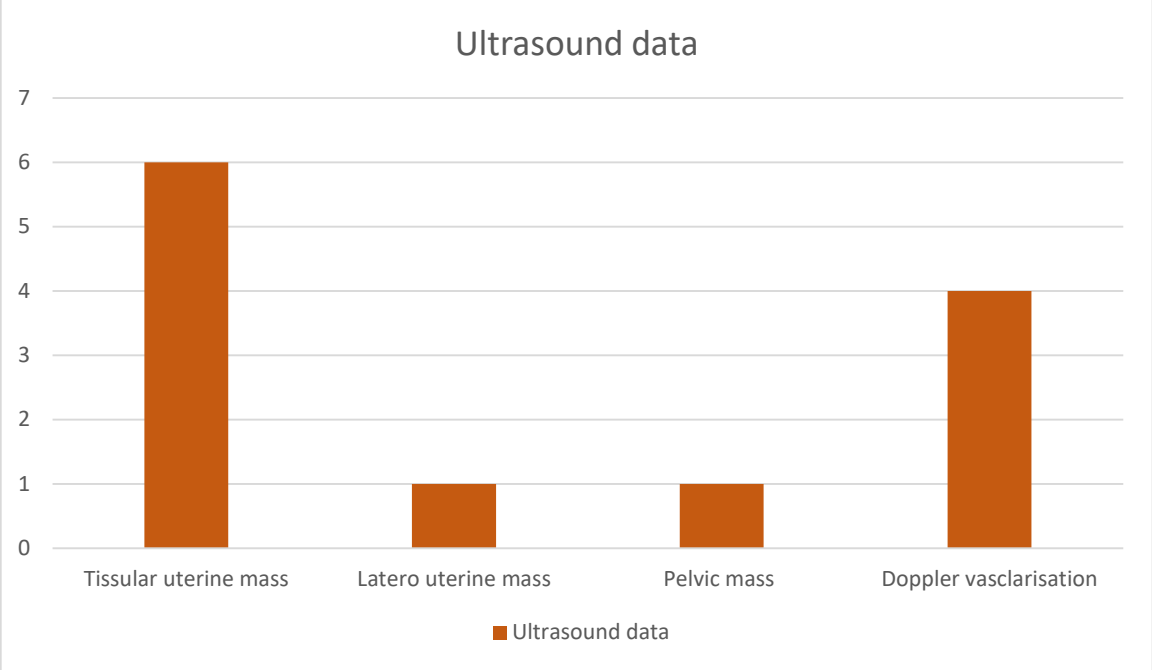

Parity
6
5
4
3
2
1
0
Nullipare
Paucipare
Multipare
Parity

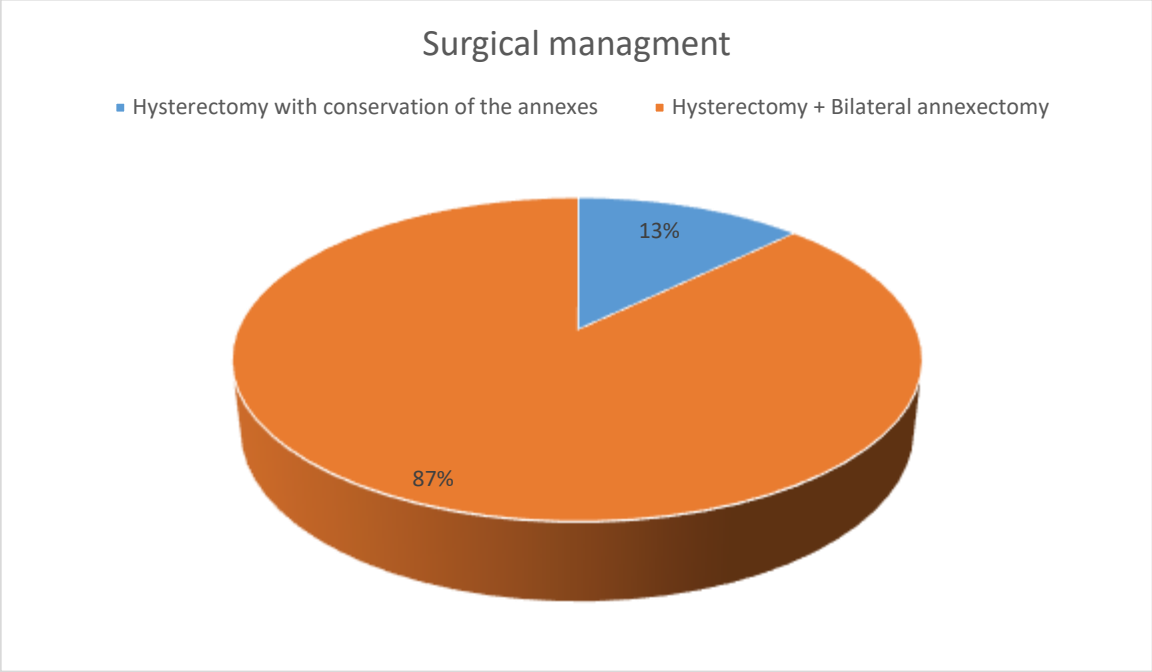

Hormonal status
Menopausal women
non menopausal women
13%
87%

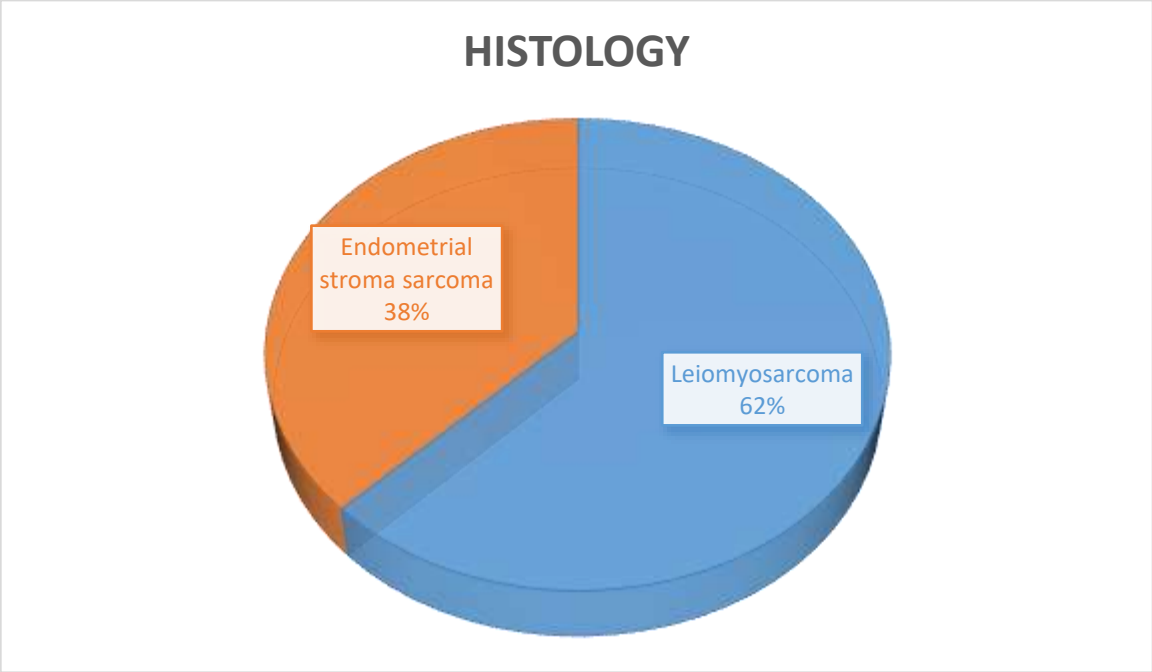

Familial, medical and chirurgical history
100.00%
90.00%
80.00%
70.00%
60.00%
50.00%
40.00%
30.00%
20.00%
10.00%
0.00%
High blood pressure
Diabetes
jejunal stromal tumor
Uterine leiomyoma
Familial history of ovarian tumor
None
Familial, medical and chirurgical history

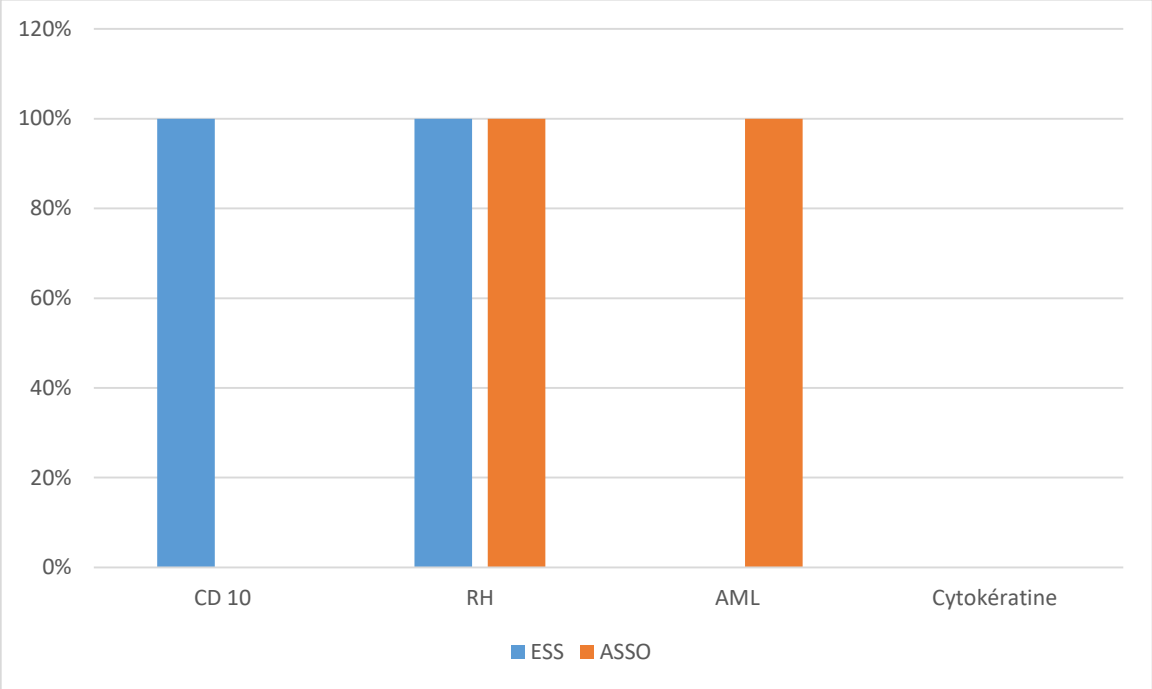

Clinical features
7
6
5
4
3
2
1
0
Genital bleeding
Pain
digestive signs
Urinary signs
Clinical features

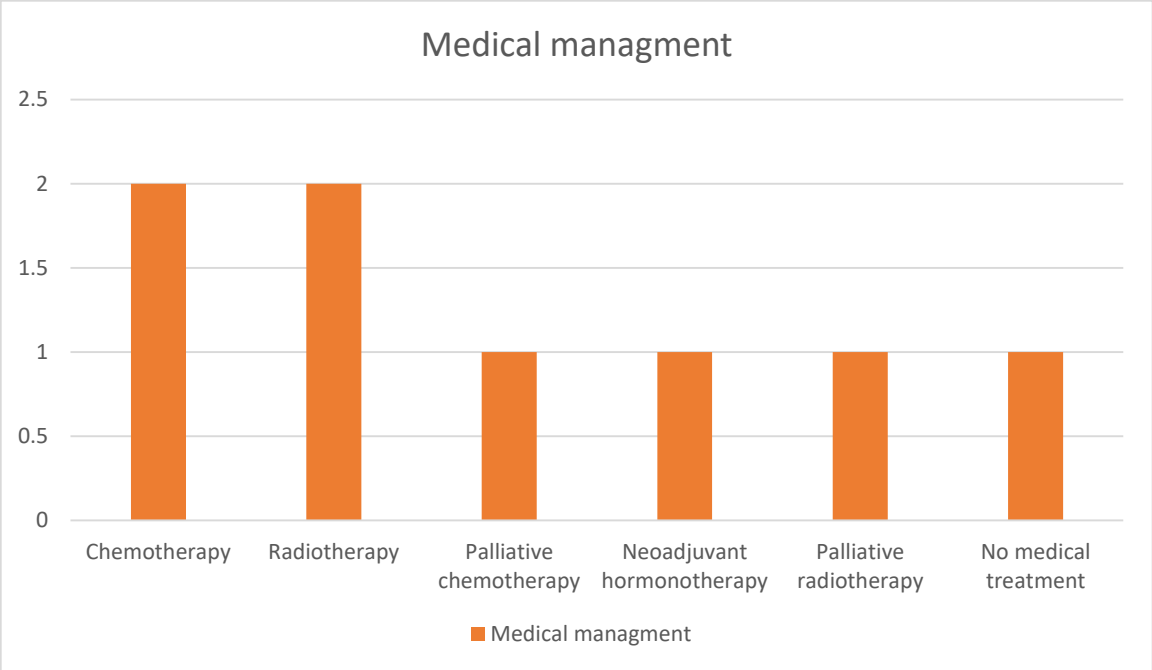

Clinical examination
6
5
4
3
2
1
0
Increased uterine size
Latero-uterine mass
Abdomino-pelvic mass
tumor delivered through the cervix
Normal uterine size
Clinical examination

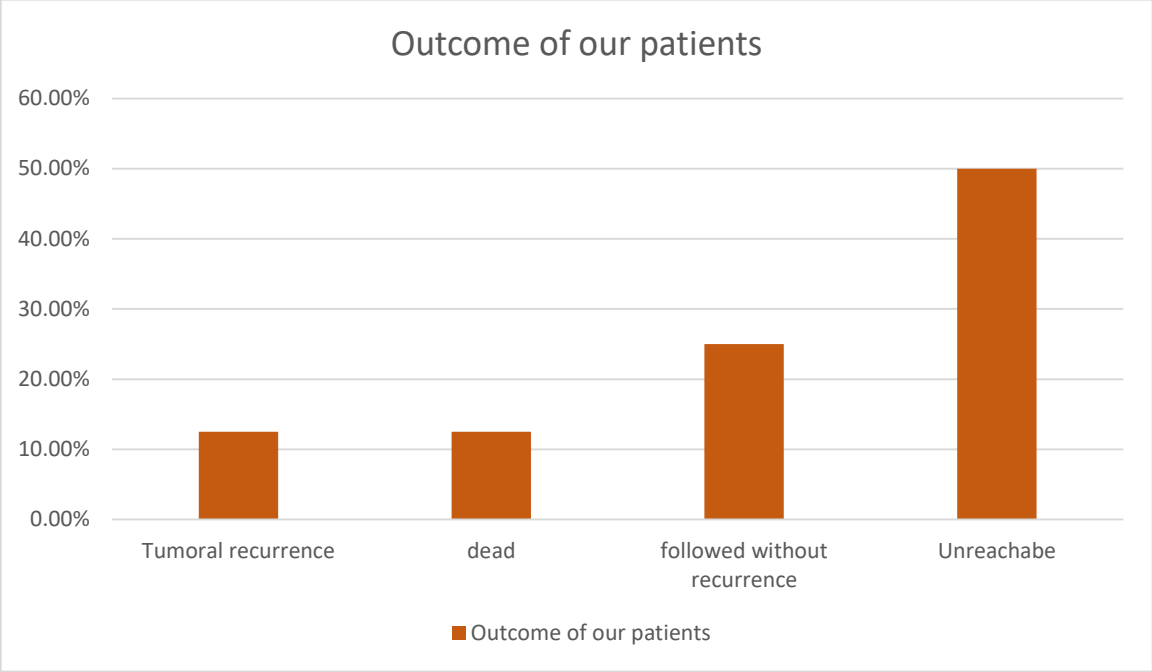

Ultrasound data
7
6
5
4
3
2
1
0
Tissular uterine mass
Latero uterine mass
Pelvic mass
Doppler vasclarisation
Ultrasound data

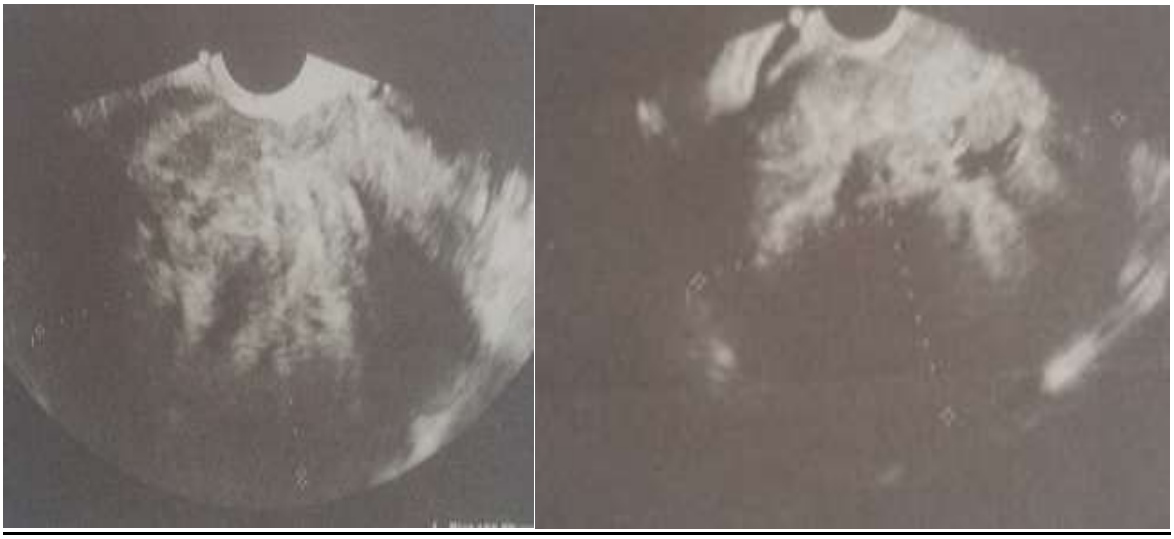

Surgical managment
Hysterectomy with conservation of the annexes
Hysterectomy + Bilateral annexectomy
13%
87%


HISTOLOGY
Endometrial stroma sarcoma 38%
Leiomyosarcoma 62%

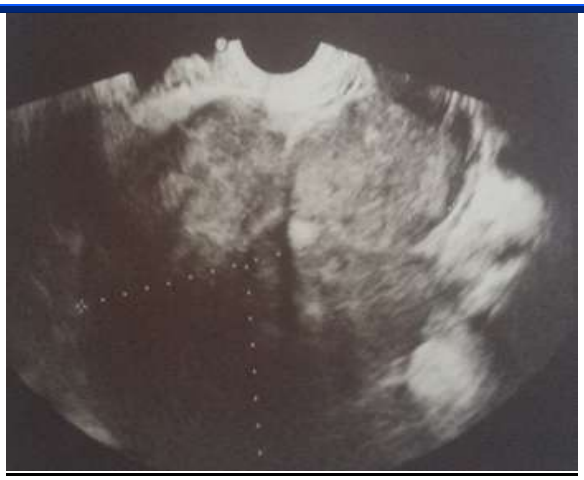

120%
100%
80%
60%
40%
20%
0%
CD 10
RH
AML
Cytokératine
ESS
ASSO


Medical managment
2.5
2
1.5
1
0.5
0
Chemotherapy
Radiotherapy
Palliative chemotherapy
Neoadjuvant hormonotherapy
Palliative radiotherapy
No medical treatment
Medical managment

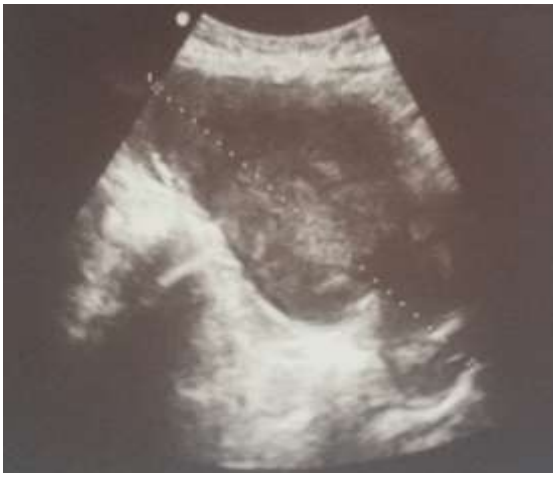




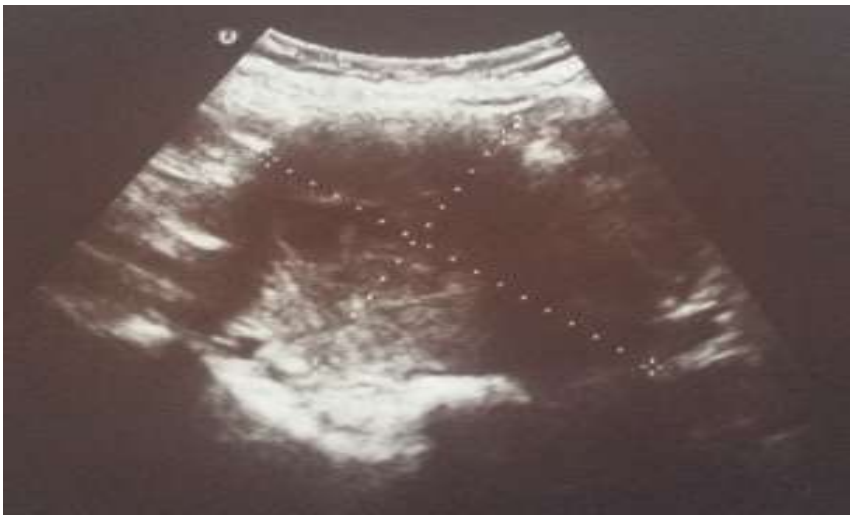
Ultrasound aspect of LMS: heterogeneous echogenic pelvic image of 107/86 mm



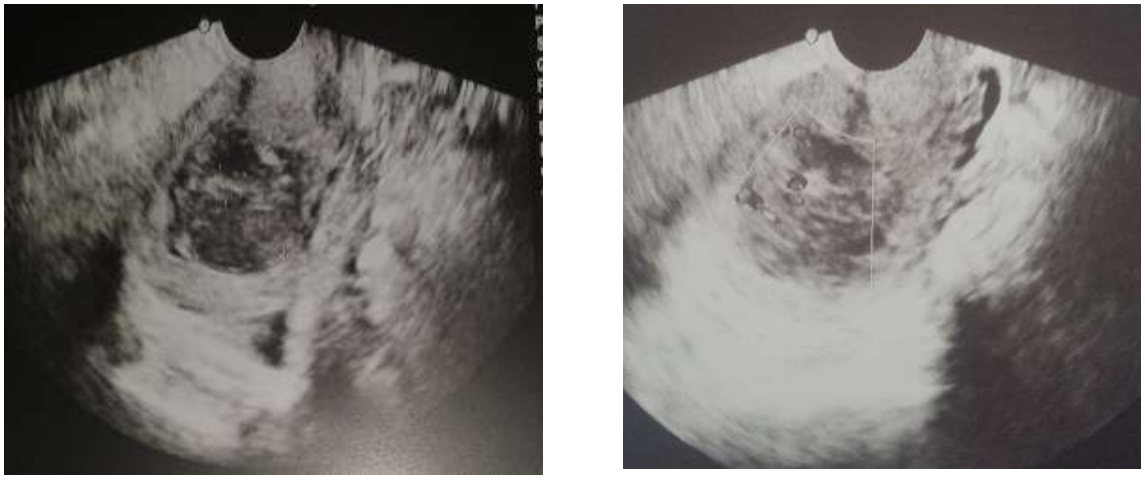
Ultrasound aspect of ESS: heterogeneous echogenic image probably on the myometrial wall



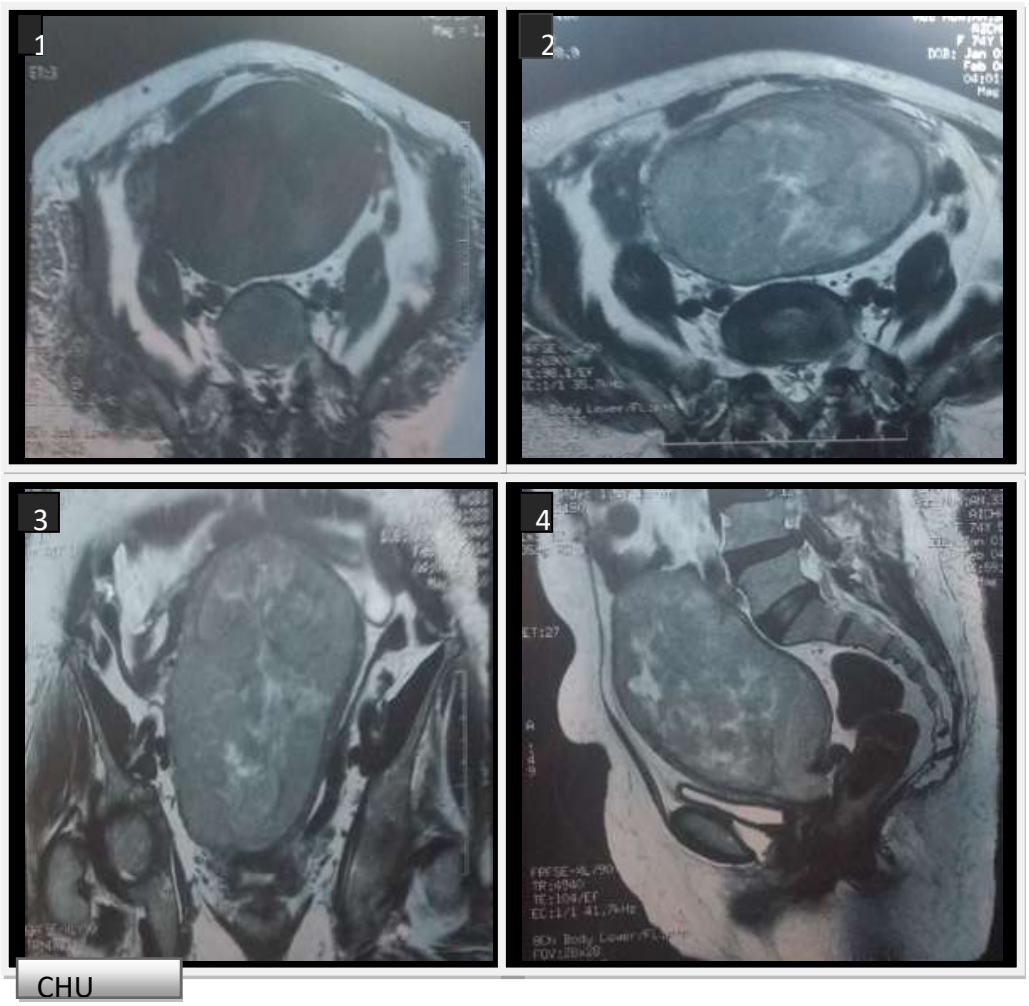
Ultrasound aspect of ESS: increased uterus size, with heterogeneous wall



Ultrasound aspect of LMS: heterogenous image taking the doppler

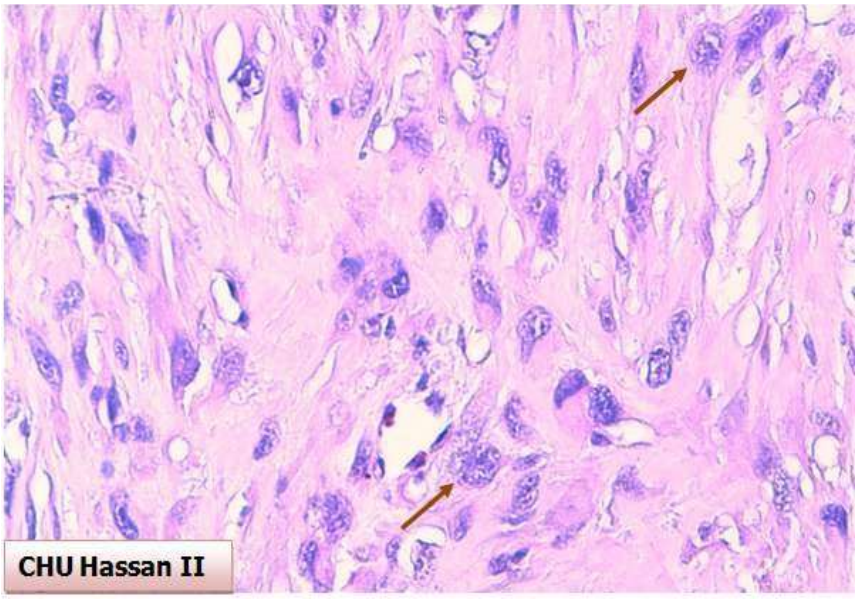


Ultrasound aspect of LMS: echogenic heterogenous intracavitary image, vascularized by doppler, measuring 27x24 mm

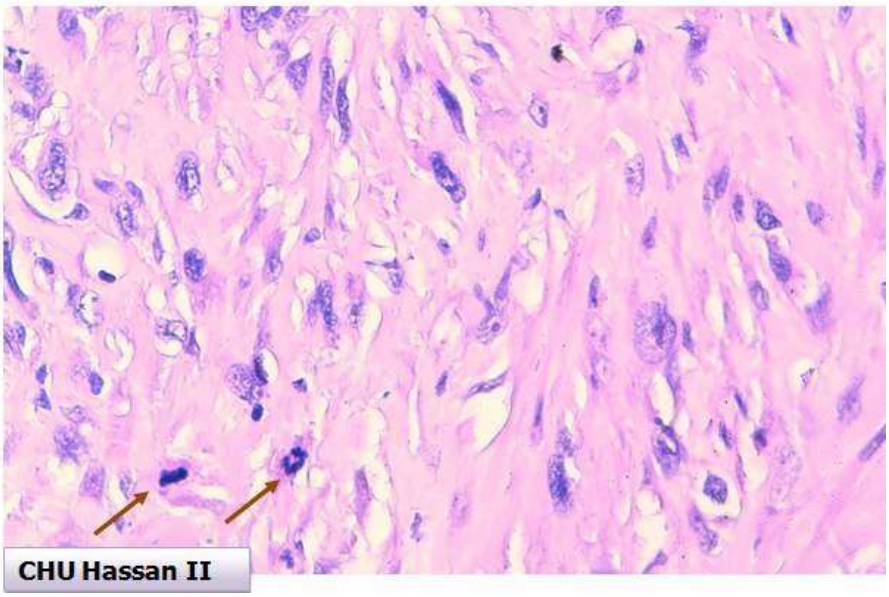


MRI aspect of low grade endometrial stromal sarcoma.
Increased of uterine size, containing a voluminous heterogenous mass, which is in isosignal T1 and hypersignal T2, invading myometrium, reaching the serosa in heterosignal in all sequencies with hemorragic areas, measuring 13/10/9,5 cm. It prolpases through the cervix.

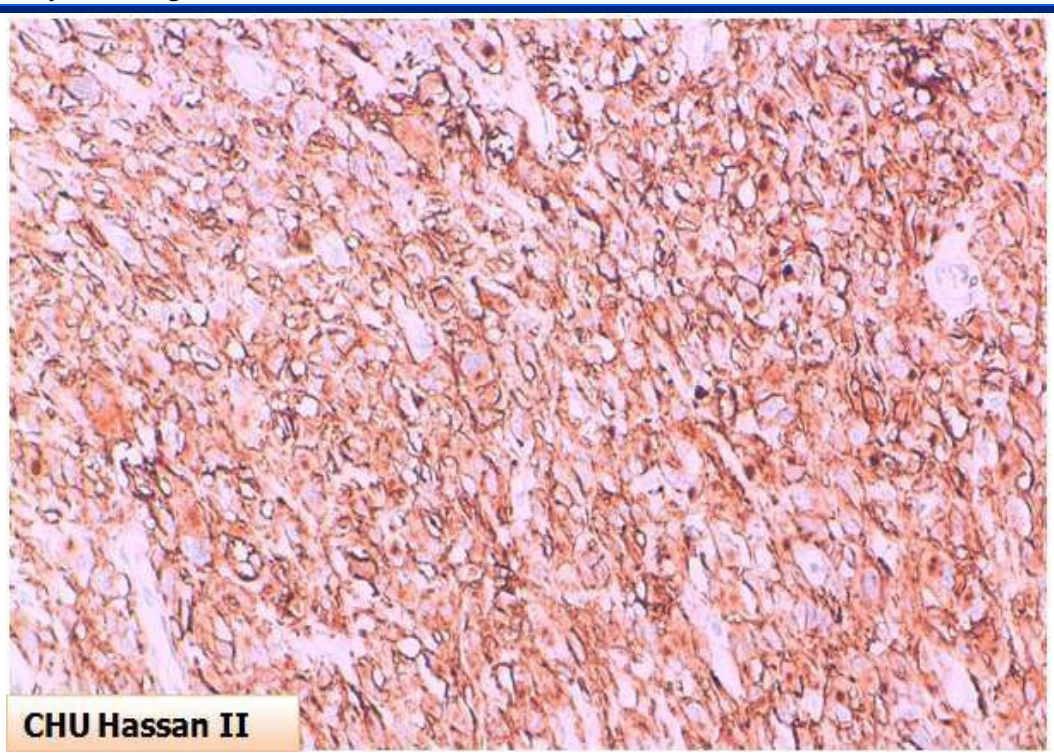
1- Axial section in T1 sequence
2- Axial section in T2 sequence
3- coronal section in T2 sequence
4- sagittal section in T2 sequence



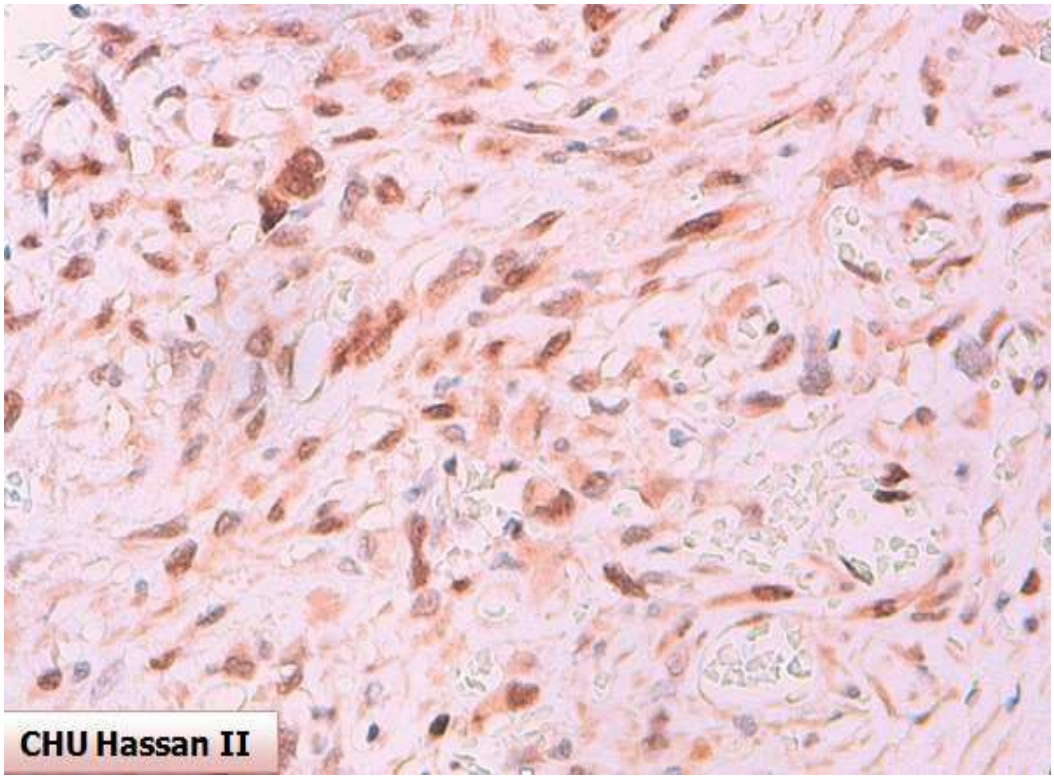
HES x 40: Endometrial stroma sarcoma with cytonuclear atypia



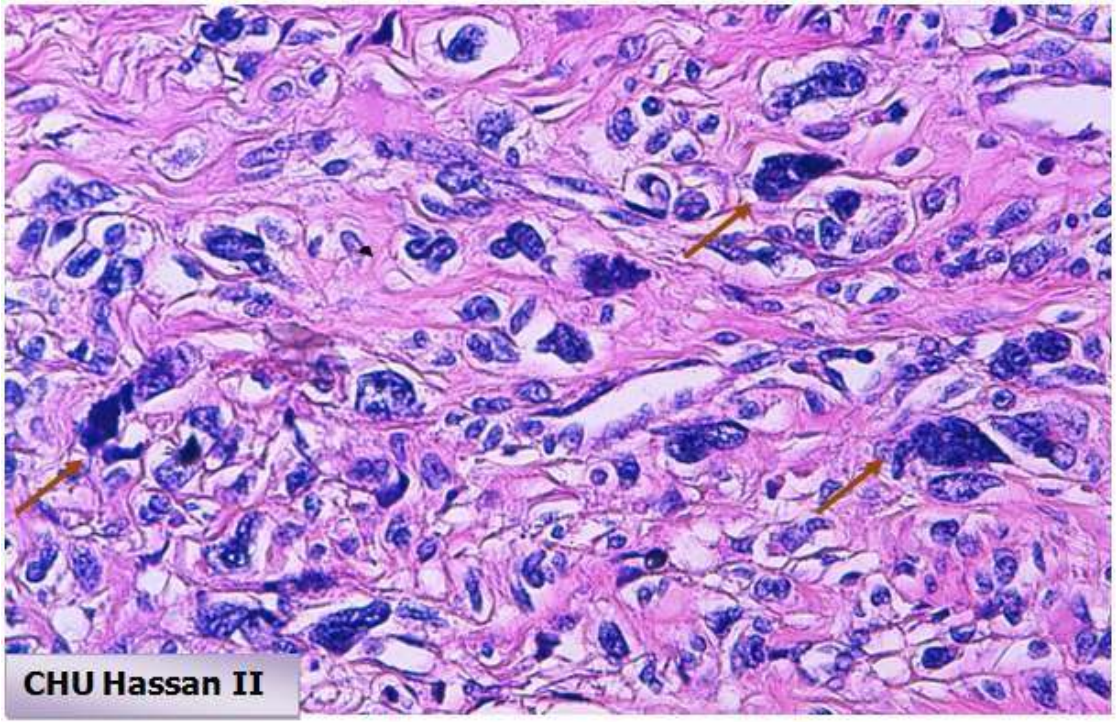
HES x 40: Endometrial stromal sarcoma presenting mitosis



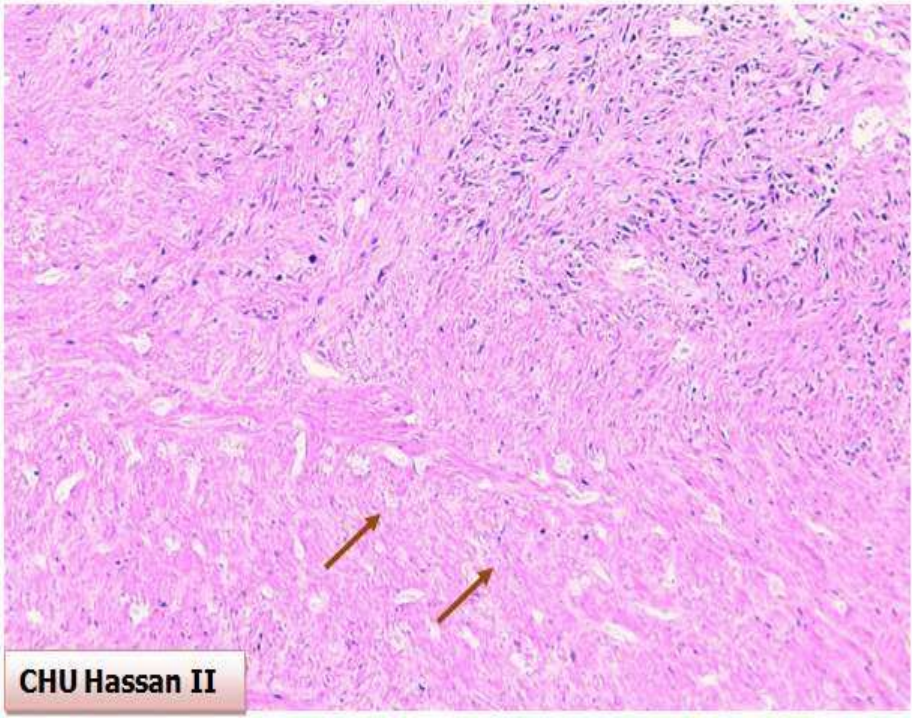
Stromal sarcoma: Positive immunomarking by Anti CD10 antibody



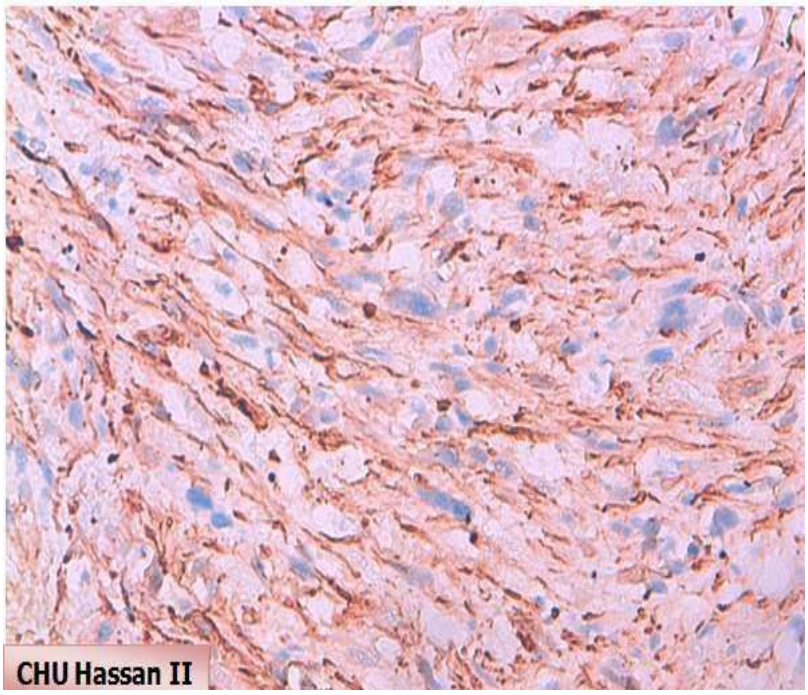
Stromal sarcoma: Positive immunomarking by oestrogenic receptors



Leiomyosarcoma presenting pleiomorphisme



HES x 10: Leiomyosarcoma dissociated by necrosis areas



Leiomyosarcoma: Positif immunomarking by anti Hcaldesmone antibody

Discussion:

Uterine sarcomas are rare tumors. The diagnosis is most often made postoperatively. It represents 0.1 to 0.5% of lesions operated with a preoperative diagnosis of uterine fibroids. They are characterized by a great diversity in histopathology and by clinical heterogeneity. And the prognosis remains poor. **(5,6)**

Ultrasound cannot differentiate uterine sarcomas from fibroids. MRI, and in particular dynamic sequences after injection of gadolinium, can help in the diagnosis by showing lesions that enhance early after injection, and the existence of intra-lesional areas of necrosis is also very specific.

The diagnosis must be made early since the tumor stage is the major prognostic factor. The improvement of the preoperative diagnosis of these cancers will require a better understanding of these tumours by the clinician who should know how to evoke uterine sarcoma in front of any "fibroid uterus" of atypical presentation or evolution, especially in postmenopausal women.

Immunohistochemically, leiomyosarcomas express connective markers such as smooth muscle actin (SMA), desmin, h-caldesmone and histone deacetylase 8 (HDCA8).

Epithelial leiomyosarcomas can express epithelial markers such as cytokeratin and epithelial membrane antigen (EMA). **(7,8)**

Many authors conclude that h-caldesmone has the best specificity and desmin and AML have the best sensitivity in smooth muscle differentiation.

Vimentin, which is also a mesenchymal cell marker, is often positive in leiomyosarcoma.

Immunostaining of SMLs for CD10 antigen is most often weak or absent.

Estrogen, progesterone, and androgen receptor expression in leiomyosarcomas ranged from 0 to 100%. The expression of

the ratio of RE-α /RE-β in SMLs was 0.06 in a study conducted by Rodriguez et al. in 2011. **(9,10)**

Furthermore, the expression of proliferation markers, Ki-67, p16, and p53 proteins, and the hyaluronic acid receptor CD44 distinguish leiomyosarcomas from benign leiomyomas.

Ki67 expression is often associated with poor prognosis, in contrast to bcl-2 expression, which is thought to be associated with longer survival.

Loddenkemper et al. demonstrated moderate to strong oxytocin receptor expression in 100% of the tumor in 05cas/08cas LMS studied, and weak positivity in 10-20% of the other 03 LMS. This could be an important contribution to the differential diagnosis between leiomyosarcoma and stromal tumors. **(11,12)**

Cytogenetically, the first chromosomal aberrations in uterine leiomyosarcoma were described in 1988.

Since then, many studies have been conducted to identify genetic disturbances in these tumors, but the results are limited by their rarity and there are no common abnormalities in all leiomyosarcomas. The most frequently reported anomalies are:

- 1p13 ~1pter translocations and deletions

- Monosomies of chromosomes 18 and 22

- Monosomy of chromosome 6 -Loss of chromosome 18, 22

- Polyploidy by partial or total gain of chromosome 8

- A gain in the long arm of chromosome 1 concerning the region 1q21-1q22

- Expression of the proto-oncogene C- Kit.

- Recently A. COOSEMANS et al. have identified the expression of the WT1 gene located on chromosome 11p 13 confirming the results of Sotobori et al. in 2006. This gene has been the subject of several targeted therapy studies and could constitute an interesting alternative in the adjuvant treatment of uterine sarcomas. **( )**

TNM and FIGO Classifications :

Stage	**TNM**	**FIGO Stage**	**Stage description***
I	T1	I	The cancer is growing in the uterus, but has not started growing outside the uterus. It has not spread to nearby lymph nodes (N0) or to distant sites (M0).
IA	T1a N0 M0	IA	The cancer is only in the uterus and is no larger than 5 cm across (about 2 inches) (T1a). It has not spread to nearby lymph nodes (N0) or to distant sites (M0).

IB	T1b N0 M0	IB	The cancer is only in the uterus and is larger than 5 cm across (about 2 inches). (T1b). It has not spread to nearby lymph nodes (N0) or to distant sites (M0).
II	T2 N0 M0	II	The cancer is growing outside the uterus but is not growing outside of the pelvis (T2). It has not spread to nearby lymph nodes (N0) or to distant sites (M0).
IIIA	T3a N0 M0	IIIA	The cancer is growing into tissues of the abdomen in one place only (T3a). It has not spread to nearby lymph nodes (N0) or to distant sites (M0).
IIIB	T3b N0 M0	IIIB	The cancer is growing into tissues of the abdomen in 2 or more places (T3b). It has not spread to nearby lymph nodes (N0) or to distant sites (M0).
IIIC	T1-T3 N1 M0	IIIC	The cancer is growing in the body of the uterus and it might have spread into tissues of the abdomen, but is not growing into the bladder or rectum (T1 to T3). The cancer has spread to nearby lymph nodes (N1), but not to distant sites (M0).
IVA	T4 Any N M0	IVA	The cancer has spread to the rectum or urinary bladder (T4). It might or might not have spread to nearby lymph nodes (Any N) but has not spread to distant sites (M0).

IVB	Any T Any N M1	IVB	The cancer has spread to distant sites such as the lungs, bones, or liver (M1). The cancer in the uterus can be any size and may or may not have grown into tissues in the pelvis and/or abdomen (including the bladder or rectum) (any T) and it might or might not have spread to nearby lymph nodes (Any N).

The contribution of ultrasound is very limited in uterine sarcomas. There is no pathognomonic ultrasound sign for uterine sarcoma, which is most often a heterogeneous lesion with a double solid and non-specific cystic component.

In 88% of uterine leiomyosarcomas, endovaginal color Doppler finds signs of neovascularization both in the center of the tumor and in the periphery. **(13,14)**

Pulsed Doppler analysis reveals small irregular vessels randomly dispersed with very high velocity and low impedance flows (IR: Resistance Index =0.37+/-0.03).

Performed under anesthesia, it can be diagnostic or therapeutic, it can be indicated in the assessment of metrorrhagia or to perform a directed biopsy.

The typical MRI pattern of uterine sarcomas is a large uterine mass with an intense or moderate signal in T2-weighted sequence and a hyposignal in T1. The existence of contrast enhancement superior than myometrium at 60 seconds, heterogeneous, with necrotic patches is an argument in favor of a sarcomatous origin. **(15,16)**

Given the rarity of this pathology, the therapeutic strategy for uterine sarcomas is not consensual.

Treatment is based primarily on surgery, pelvic radiotherapy, brachytherapy and chemotherapy. Although their prognosis is worse than soft tissue sarcomas, these tumors have a comparable evolutionary profile and by extension, the place of adjuvant treatments is often modelled on soft tissue. **(17,18)**

Surgery remains the main treatment for uterine sarcomas and must be radical. It allows for the assessment of the extension and removal of the uterine tumor and possibly extra uterine metastases. The indications for the various adjuvant therapies remain highly debated. Current recommendations are in favour of adjuvant radiotherapy. Most authors agree that adjuvant irradiation brings a benefit in terms of local control. Even if the benefit on survival is not certain, a decrease in the number of pelvic recurrences, often accompanied by pain, may justify the prescription of adjuvant radiotherapy. This benefit is often expected for high-grade tumors**. (19,20)**

The value of chemotherapy remains uncertain. Indications should be discussed case by case depending on the characteristics of the tumor, age, general condition and the patient's wishes.

Conclusion:

Uterine sarcomas are rare tumors with poor prognosis. There diagnosis is almost established postoperatively. The histopathologic analysis is the main important pattern to diagnostic these tumors. While awaiting for more effective chemotherapy protocols or therapeutic strategies. Early diagnosis is essential because patients' survival is correlated to tumour stage.

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