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Uterine Sarcomas: An Updated Overview. Part 1: Smooth Muscle Tumors

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Abstract

Uterine sarcomas (USs) account for 3–9% of uterine malignant neoplasia and about 5% of all gynaecologic malignancies. Despite their low prevalence, these tumors stimulate a great interest because of their aggressiveness, poor prognosis and high mortality rate. According to the last World Health Organization (WHO) classification and the International Federation of Gynecology and Obstetrics Committee (FIGO) staging, USs are categorized as pure mesenchymal tumors (endometrial stromal sarcoma, leiomyosarcoma and undifferentiated uterine), and mixed tumors (carcinosarcoma and adenosarcoma). Due to their non-specific signs and symptoms, USs are commonly diagnosed in advanced stage, more often after surgery for a suspected leiomyoma. Although surgery followed by adjuvant therapies represent the common choices for USs, they show poor efficacy due to the early occurrence of metastasis, and the high resistance of tumors to radio- and chemotherapy. Presently, specific expression profiles and new cytotoxic agents are under investigation. In these reviews, we summarized clinical and pathological features, imaging characteristics, therapeutic approaches, genomic and molecular aberration associated with smooth muscle neoplasia (Part 1) and endometrial stromal neoplasia (Part 2); the goal is to understand the biology and the molecular signature of these tumors, in order to focus on their best management.

Keywords: uterine sarcomas, mesenchymal tumors, uterine malignant neoplasia, uterine smooth muscle neoplasia, leiomyomas, STUMP

1. Introduction: why these chapters?

Cancers of the female reproductive system (cervix uteri, corpus uteri, vulva, vagina, ovaries and fallopian tubes) are important causes of morbidity and mortality worldwide, accounting for almost 15% of all female neoplasia [1].

Uterine cancer is defined as any invasive neoplasm of the uterine corpus and represents the fourth most common malignancies in women, after breast, lung and colorectal cancer [2]. Uterine cancers originating from mesenchymal elements of the uterus are defined as uterine sarcomas (USs). They are very rare, representing about 5% of all gynaecologic malignancies and 3–9% of all uterine cancer [1, 2].

USs usually manifest in postmenopausal women. Obesity, diabetes mellitus, nulliparity and hypertension, considered as certain risk factors for the development of endometrial carcinoma, do not seem to have a crucial role in the genesis of USs [3]. Moreover, most authors reported a three times risk for USs developing in patients undergoing prolonged use of tamoxifen, a synthetic oestrogens (ERs) receptor agonist largely used in the management of women with oestrogens receptor-positive breast cancer [3]. Tamoxifen-related US usually occurs about 5 years following tamoxifen therapy and presents with a higher stage of disease [3].

Because of the rarity of USs, their histopathological heterogeneity and aggressiveness, there is a general lack of consensus regarding risk factors and treatment options [2].

The only certainty is that, if compared with the epithelial counterpart, uterine sarcoma is associated with a poor prognosis, a high rate of local recurrence and distant metastasis [1].

In this chapter, we systematically focus on each single type of USs, starting from epidemiological and etiological factors, going through clinical, morphological and molecular characteristics, differential diagnosis and prognostic features, finally achieving conventional and novel therapeutic approaches.

2. The mesenchyma

Mesenchyma consists of loosely packed and mobile cells embedded in a network of fibers and fluid called intercellular matrix. Mesenchymal cells are spindle-shaped, with oval nucleus and scant cytoplasm.

The loose nature of the mesenchymal cells allows them to easily migrate. Moreover, during embryogenesis and foetal development, their pluripotent nature makes them able to differentiate into a great variety of structures: bones, cartilage, teeth, blood cells, endothelial lining of blood and lymphatic vessels, and smooth muscles.

Mesenchyme derives from mesoderm germ layer and forms early during embryogenesis. Mesenchymal cells also derive from the neural crest, a specialized ectodermal structure. During

gastrulation, mesenchymal cells lose their adhesiveness and separate from the connected sheets of epithelial cells. This process is known as epithelial-mesenchymal transition (EMT). Some important events take place during interactions between mesenchymal and epithelial cells. Epithelial cells are often induced in changing their shape and arrangement in response to signals originating from mesenchymal cells [4].

During EMS, epithelial cells lose their polarity. Cell membranes and desmosomes dissolution, degeneration of cytocheratin filaments, increased cell resistance to apoptosis, and migration of new epithelial cells with mesenchymal phenotype also occur [4]. These changes are induced by the mechanical stimulation of migrating mesenchymal cells or by biochemical mechanisms [4].

EMT has to be considered as a physiological process, playing a role in the development of various embryo tissues, as well as in cells proliferation and tissue repair. EMT is also essential in driving folliculogenesis and ovulation [5]. It has been hypothesized that pathological process such as adenomyosis, endometriosis, malignant neoplasia and metastasis would derive from the dysfunction of EMT within the epithelial cells of the female reproductive system [6, 7].

EMT also participates in other pathological processes, including metastatization [8].

In cancer cell lines, cells gradually change from epithelial to spindle-like shape and acquire fibroblastic morphology [4]. During this process, the expression of epithelial markers decreases and the cells progressively acquire mesenchymal markers [4]. This mesenchymal signature facilitates the detachment of tumor cells, the proteolytic digestion of basement membrane, the vascular invasion, and the migration of circulating cells towards distant sites [8].

Little is still known about the detachment of circulating tumor cells from the cytoskeleton. It seems that EMT produces detyrosinated α -tubulin with the formation of microtubules-based membrane protrusions, which are distinct from the actin-based prolongations known as lamellipodia and filopodia. The new acquired protrusions make circulating tumor cells with mesenchymal phenotype able to attach to endothelial layers and to migrate towards distant sites [9].

Three types of EMT have been described. EMT type 1 plays an important role in the organogenesis; it also generates the primitive mesenchyma during embryogenesis. EMT type 2 is characteristic of pathological, non-neoplastic processes. Through EMT2, fibroblasts are recruited to repair tissue; EMT2 also causes fibrosis as a consequence of chronic inflammations (i.e. renal and hepatic fibrosis, Crohn's disease). It has been demonstrated that about one-third of the fibroblasts causing chronic glomerulonephritis, diabetic nephropathy, lupus nephritis and Alport syndrome occurring during renal fibrosis originates from tubular epithelial cells. They are recruited because of the damage of basement membrane. EMT type 3 allows tumor cells to dissociate, migrate and metastasize [9].

EMT is regulated by transcriptional and post-transcriptional mechanisms, particularly through downregulation of E-cadherin and overexpression of mesenchymal proteins such as vimentin and N-cadherin [9].

If mesenchymal cells would have a crucial role during morphogenesis, they often remain undifferentiated in adults. Undifferentiated mesenchymal cells, known as stem cells, exist in small

quantities in bone marrow, fat, muscles and in dental pulp of baby teeth. They retain the ability to differentiate into different kind of connective tissues for reparative or regenerative reasons [9].

Mesenchymal-epithelial transition (MET) is the reverse process by which mesenchymal cells acquire adhesive properties and arrange themselves into organized sheets. MET would also need to generate the so-called 'secondary epithelium' in various organs (i.e. kidney) [6]. When required, the secondary epithelium can re-differentiate towards mesenchymal tissues by mediation of several genes [6]. The switch EMT-MET would also induce neoplastic cells in acquiring a stem cell pattern. This pattern helps to prevent apoptosis and senescence, and would contribute to both immunosuppression and multidrug resistance [6]. These converted mesenchymal cells are not able to migrate toward the blood flow and cause local recurrence. In metastatic sites, in accordance with local microenvironment, an EMT-MET switch would occur. Restoration of epithelial features allows cells to arrange in clusters contributing to the stability of the metastatic focus.

3. Uterine sarcomas: the history

Sarcomas are malignant neoplasia occurring in any site of the body in which mesenchymal tissues are present. Because of their mesodermal origin, sarcomas are characterized by histological and cytogenetic heterogeneity. The histological classification of sarcomas is made according to tissue differentiation [1].

Homologous USs refer to mesenchymal tissues, which are normally found in the uterus, such as smooth muscle, endometrial stroma, vascular and fibrous tissue. Heterologous USs refer to mesenchymal tissues that are foreign to the uterus, such as cartilage, bone, skeletal muscle and fat.

In the past, sarcomas originating from different organs were grouped together; such classification demonstrated a scant utility from a clinical point of view [1]. Recently, basing on cells differentiation and growth pattern, the World Health Organization (WHO) proposed a separate histological classification for uterine neoplasia. Thus, uterine mesenchymal neoplasias were grouped as smooth muscle tumors and endometrial stromal tumors [10]. Uterine smooth muscle tumors are defined as benign and malignant neoplasms arising in the context of myometrium and composed of cells showing smooth muscle differentiation. Among these, benign leiomyoma, smooth muscle tumor of uncertain malignant potential (STUMP) and leiomyosarcoma (LMS) are listed [10].

Endometrial stromal tumors enclose all the neoplasia originating from the uterine endometrial stroma: endometrial stromal nodule (ESN), endometrial stromal sarcoma (ESS) and undifferentiated uterine sarcoma (UUS) [10] (**Figure 1**).

Nowadays, being carcinosarcoma (CS) considered as a dedifferentiated/metaplastic form of endometrial carcinoma, together with Müllerian adenosarcoma (MA), it is encompassed among the 'mixed epithelial and mesenchymal tumours' [11].

Tumor stage represents the most important prognostic factor for USs. In the past, USs were inadequately staged using the same 1988 staging system utilized for endometrial carcinoma.

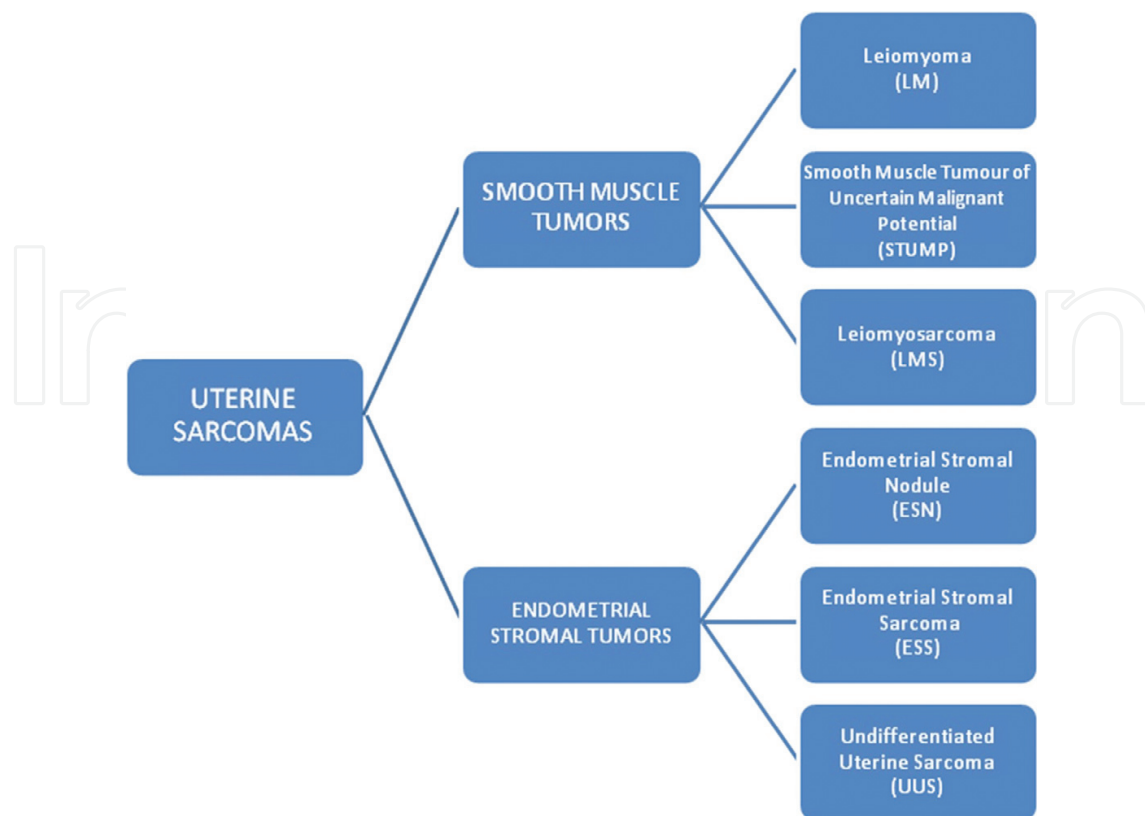


Figure 1. 2014 WHO classification of uterine sarcomas.

In 2009, a new International Federation of Gynecology and Obstetrics Committee (FIGO) staging system was specifically developed [12]. It comprises two sections, one for both leiomyosarcomas and endometrial stromal sarcomas and another for the adenosarcomas. The staging system used for carcinosarcomas is the same used for endometrial carcinomas.

4. The two great excluded

Müllerian adenosarcomas (MAs) account for 5.5–9% of all USs [1]. They are commonly seen in postmenopausal women, even if cases occurring in adolescents and young women are described. MA typically shows benign epithelial cells together with homologous/heterologous mesenchymal sarcomatous components. Neoplasia is often limited to the endometrium, since myometrial invasion is extremely rare. Malignant potential is low as well as histological grade at first presentation [1]. The 5-year survival rate for stage I is of about 76% [1]. MAs are polypoid in shape and may contain small internal cysts. Tumor cell necrosis, if present, represents the most important prognostic factor [1].

Carcinosarcoma (CS), also known as malignant mixed Müllerian tumor (MMMT), has been recently considered as a metaplastic carcinomas basing on a different derivation from a common monoclonal stem cell [13]. Clinical, pathological and molecular evidences would confirm the monoclonal origin of carcinosarcomas, which would further undergo both epithelial and mesenchymal differentiation during its development [13]. For other authors, a CS would

originate from a carcinoma undergoing sarcomatous metaplasia through a dedifferentiation process [14].

The peculiar molecular features of CSs, as well as their good response to adjuvant therapies, would confirm the epithelial derivation of these tumors which characteristically shows a high aggressiveness and a high frequency of lymph nodal and distant metastases. Thus, the prognosis of CS would depend on the carcinomatous component [15].

Noticeably, patients with MA and CS tend to be much older than patients bearing US [15].

5. Leiomyosarcoma

After the exclusion of CSs, leiomyosarcomas (LMSs) represent the most common USs (30%), being the endometrial stromal sarcomas the second (10–15%). Rhabdomyosarcoma, angiosarcoma and liposarcoma are extremely rare [1].

LMSs develop in the smooth muscle layer of the uterus, called myometrium; thus, malignant cells show smooth muscle differentiation.

5.1. Epidemiology

The worldwide annual occurrence rate of USs is 1.55–1.95 per 100,000 women. The peak of incidence is in the fifth decade (50–55 years), about 10 years later than leiomyoma. In younger women, the incidence of LMS strictly correlates with the use of tamoxifen in adjuvant breast cancer therapy [16].

The percentage of incidental LMS among women undergoing surgery for suspected leiomyoma increases with age, being about 0.2% in patients aging 31–40, 0.9% among those aging 41–50 years of age, about 1.4% in women aging 51–60 and 1.7% in patients ranging from 61 to 81 years of age [15].

LMS is most common in black race. The relative risk and incidence of both leiomyomas and LMS is two- to threefold greater in black women than in white ones [1].

5.2. Aetiology

The risk factors for LMS are still unknown. The role of obesity, nulliparity, hypertension and diabetes mellitus, recognized as influencing the development of other uterine malignancies, are uncertain yet. On the other hand, some evidences demonstrated that the use of tamoxifen for 5 years or more is associated with an increased relative risk of developing an LMS, although the absolute risk remains low [15]. Pelvic irradiation, a history of retinoblastoma in childhood, hereditary leiomyomatosis and renal cell carcinoma are other documented risk factors [15].

Finally, although it is now clear that the vast majority of LMSs arise independently, it is now accepted that a small percentage would derive from the transformation of a pre-existing leiomyomas [17].

5.3. Clinical features

Since pelvic examination cannot distinguish between leiomyoma and LMS, the pre-surgical differential diagnosis is very difficult. In both cases, symptoms are not specific. Patients often present with vaginal bleeding or discharge, lower abdominal mass and pelvic pain. Size, contour and mobility of the uterus along with any other possible findings (i.e. cervical abnormalities or vaginal nodules) should be evaluated during gynecological examination. A fixed mass is commonly suggestive of a malignant neoplasm, even if a malignant neoplasm not infiltrating the uterine serosa is often mobile. A rapidly growing solitary intramural or subserosal uterine mass should be suspected for an LMS, especially in the absence of hormonal stimulation or in non-pregnant women. LMS shows lymph nodal or haematogenous spreads. Lung represents the preferential site for distant metastasis. When local metastases occur, gastrointestinal or urinary symptoms may be associated [1].

5.4. Imaging

Imaging features for LMS are similar to those of leiomyoma.

At transvaginal ultrasound examination, LMS shows echogenic components mixed with anechoic areas due to necrosis. Color Doppler usually demonstrates irregular vessel distribution and low impedance to flow. All of these characteristics may also be found in leiomyomas [18].

Computed tomography (CT) is not able to differentiate between leiomyomas and LMS. A specific characteristic of LMS would be the absence of calcifications, which are usually seen in leiomyomas outgrowing their blood supply [19].

Magnetic resonance imaging (MRI) has been reported to have high sensitivity in LMS diagnosis, although specificity is low [19]. Contrast-enhanced MRI (CE-MRI) demonstrates significantly higher accuracy and specificity if compared with diffusion-weighted MRI (DW-MRI), while sensitivities are comparable [19].

Finally, even if the uptake of fluorodeoxyglucose (FDG) in positron emission tomography/CT (PET-CT) is usually high in LMS and low in leiomyomas, the use of this technique in differential diagnosis is limited, since leiomyomas can uptake FDG too [20].

In conclusion, although most studies demonstrated that pelvic ultrasound followed by MRI represents the most useful strategy in LMS diagnosis, the vast majority of the authors concluded that no pelvic imaging is able to reliably differentiate between LMS and leiomyomas.

5.5. Surgical specimens

LMS is commonly diagnosed after surgery for a suspected leiomyoma [1, 16, 19].

Although fine needle biopsy and curettage samples have been proposed as good diagnostic specimens, their use is limited. In the context of an LMS, areas showing histological features indistinguishable from those of leiomyoma may be seen. For this reason, histological diagnosis requires the evaluation of the entire neoplastic mass, obtained by myomectomy or hysterectomy [21].

In addition, since the distribution of atypia and mitosis is not homogeneous in the context of a malignant mesenchymal mass, an accurate estimation requires extensive sampling.

Intra-operative diagnosis on frozen section demonstrated to be limited too, although this technique remains essential to drive the extension of the surgery [21]. Hysterectomy may be performed by laparotomy or laparoscopy. Using laparotomy, the specimen is not morcellated. By laparoscopy, only the suspected mass is removed; in such cases, the specimen is morcellated and might favor dissemination of malignant cells within the peritoneal cavity [22]. Occasionally, smooth muscle cells have been found in pelvic washing after laparoscopic myomectomy [22].

5.6. Pathological findings

5.6.1. Macroscopic features

About 65% of LMSs are intramural, 20% are submucosal, 10% are subserosal and 5% originate from cervix. Characteristically, LMS presents as a large solitary mass, although the development of an LMS in a uterus harboring multiple leiomyomas is common [1]. Usually, LMS presents as a voluminous mass with a mean diameter of 10 cm. Its margins are often well defined, although focal infiltration of the adjacent myometrium may also be seen. Irregular margins and lacking of a clear line of demarcation separating LMS from normal myometrium usually indicate invasive behaviour. Because of the possible overlap in shape between LMS and ischemic degeneration of leiomyoma, most of smooth muscle neoplasms suspected to be malignant at imaging are found to be benign at microscopic evaluation [23]. Grossly, LMS is very different from leiomyoma, the former revealing a fleshy consistency, a bulging cut surface and a pearly white-to-gray color; necrotic and haemorrhagic foci are often seen. The typical whorled appearance of leiomyoma is always lacking. The presence of hemorrhage and necrosis should always be regarded as suspected for LMS. When cystic changes are present, samples should be mainly taken on the solid areas [1].

5.6.2. Microscopic features

LMS is composed of connected bundle cells showing smooth muscle differentiation. Nuclei are round with one or more prominent nucleoli. Multinucleated giant cells with osteoclast-like shape may be present (**Figure 2A**) [24]. The three cardinal microscopic features characteristics of LMS are tumor cell necrosis (**Figure 2B**), nuclear atypia (**Figure 2C**) and mitotic count >10/10 High Power Fields (HPFs) (**Table 1**). Even if all of these three cardinal features are usually detected in about 80% of typical LMS, the presence of two of three is sufficient to reach the diagnosis [1].

Three types of necrosis have been described in smooth muscle tumors: (1) ulceration with submucosal necrosis; (2) infarct-type necrosis, encountered in both benign and malignant neoplasms and (3) tumor cell necrosis, characterized by distinct and harshly demarcated necrotic zones, suddenly transiting towards non-necrotic zone [1, 26]. Tumor cell necrosis is specific for LMS and should also be distinguished from hyaline or degenerative necrosis, which can be seen in both leiomyomas and other types of sarcomas (**Table 2**) [26].

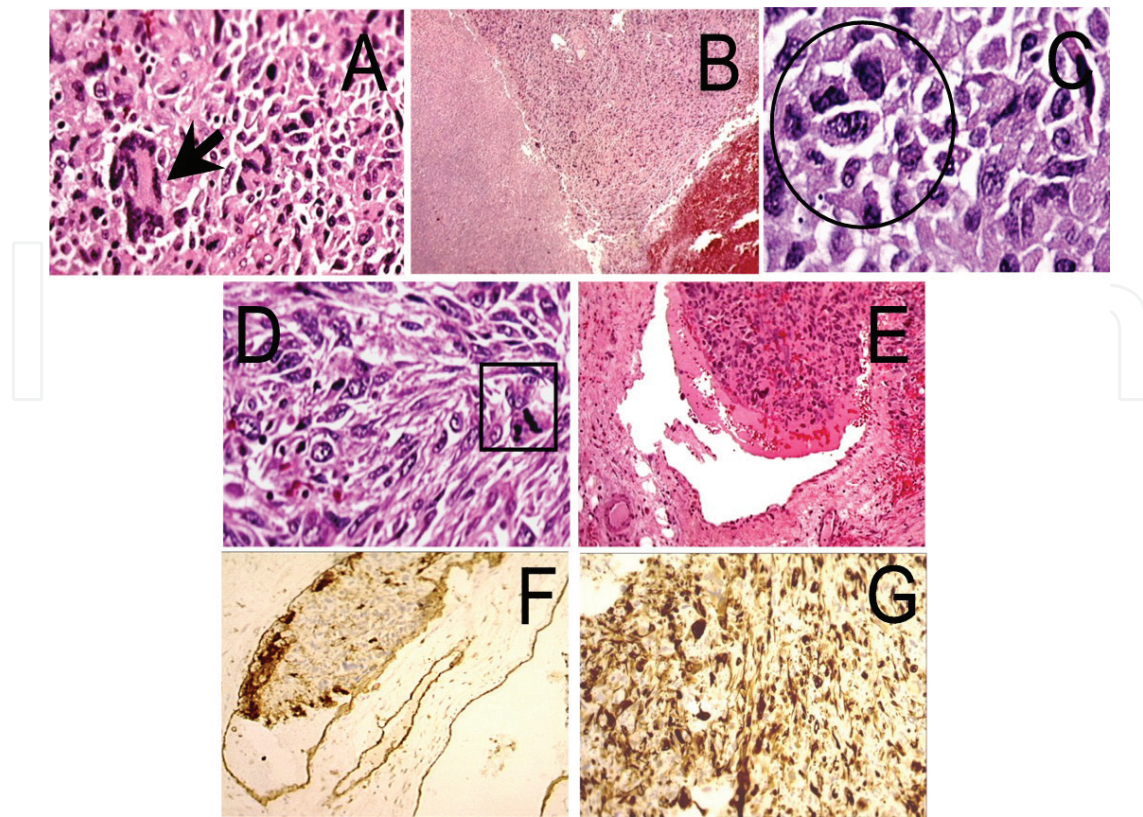


Figure 2. Uterine leiomyosarcoma. (A) Bundles of cells with smooth muscle differentiation, and multinucleated giant cells with osteoclastic shape (arrow), Ematoxilin-eosin (EE), 20x. (B) Tumor cell necrosis: Demarcated necrotic zones abruptly transiting towards non-necrotic zone; EE, 10x. (C) Nuclear atypia (circle), EE, 40x. (D) Mitosis (square), EE, 60x. (E) Vascular invasion with artery embolization, EE, 10x. (F) The wall of the vessel shows CD31 positivity, 10x. (G) Desmin positive stain in neoplastic cells, 10x.

If infarct-type necrosis is present, it should be evaluated in conjunction with nuclear atypia and mitoses (**Figure 2D**), since it is common in both benign and malignant neoplasms [1, 16].

Other features that should be included in the pathological assessment of uterine LMS are tumor size, presence of vascular invasion (**Figure 2E, F**), occurring in 10–27% of the cases, and status of surgical margins [26]. Hypercellularity does not discriminate between LMS and leiomyoma [1]. As previously shown, the specimen should be adequate to exactly evaluate the mitotic rate. To obtain adequacy is essential to analyze one section every 1–2 cm of tumor diameter, to count mitotic figures only in mitotically active areas at 60× magnification, and to evaluate five sets of 10 consecutive HPF, excluding degenerating cells [1]. Some drugs and hormones may induce histological changes mimicking necrosis; for example, iatrogenic cell necrosis in a histological background of atypical leiomyoma could lead to a wrong diagnosis of LMS. For this reason, pathologists should be informed of any therapies [1, 26]. A tumor lacking coagulative cell necrosis and nuclear atypia should be diagnosed as mitotically active leiomyoma in the presence of 5–20 mitoses/10 HPF, or as Stromal Tumor of Undetermined Malignant Potential (STUMP) when mitotic count is >20 mitoses/10 HPF. A tumor lacking coagulative necrosis but showing diffuse moderate–severe nuclear atypia should be considered as atypical leiomyoma when mitosis is <2/10 HPF, as STUMP when mitotic count is 2–10/

Tumor cell necrosis	Atypia	Mitosis/10 HPFs	Diagnosis
Present	Diffuse, moderate–severe	Any	Leiomyosarcoma
		≥10	Leiomyosarcoma
		<10	Leiomyosarcoma
Absent	Diffuse, moderate–severe	≥10	Leiomyosarcoma
		<10	Atypical leiomyoma
	None-mild	≥10	Leiomyoma
		<10	Mitotically active leiomyoma
	Focal, moderate–severe	<10	Leiomyoma with limited experience
		≤10	STUMP

HPF, high power fields; STUMP, smooth muscle tumor with uncertain malignant potential. (Modified from Ref. [25]).

Table 1. Diagnostic criteria for smooth muscle tumors.

Coagulative tumor cell necrosis	Hyalinizing necrosis
Common in malignant smooth muscle tumors	Common in leiomyomas
Sudden transition to vital to necrotic areas	Area of fibrous and granulation tissue between vital and necrotic areas
Necrotic cells look ghostly	No cell shadows are visible
Rare inflammation	Presence of immune complexes
Abrupt borders	Slight borders
Blood vessels are not involved	Blood vessels are involved by fibrin deposits; their walls are thickened
Hyperchromatic and atypical nuclei	Pale nuclei

Table 2. Types and characteristics of necrosis in smooth muscle tumors.

10 HPF, as LMS when mitoses are more than 10/10 HPF. A neoplasia showing coagulative necrosis without a significant nuclear atypia should be classified as STUMP when mitosis is less than 10/10 HPF, as LMS when at least 10 mitoses/10 HPFs are found. Finally, a tumor with coagulative necrosis and significant nuclear atypia, regardless of mitotic count, should be diagnosed as LMS [1].

In the past, Broder’s classification was one of the most used systems to grade LMS. It considered four categories: grade 1, mild cytological atypia; grade 2, more nuclear irregularity; grade 3, intermediate between grades 2 and 4; grade 4, the presence of bizarre cells. [27]. Other authors classified LMS basing on the level of differentiation (well, moderately and poorly

differentiated) [28]. A binary categorization into low- and high-grade categories was rarely used, since it has been demonstrated that it is quite impossible to recognize a low-grade uterine LMS at the time of diagnosis [28]. Presently, according to WHO, no grading should be performed for LMS [1].

5.6.3. Immunohistochemistry

Although immunohistochemistry (IHC) does not represent a necessary tool in LMS diagnosis, it may help in distinguishing LMS from other uterine malignancies (**Table 3**).

Desmin, h-caldesmon, smooth muscle actin and histone deacetylase 8 (HDAC8), the so-called smooth muscle markers, are usually expressed in LMS (**Figure 2G**), even if immunoreaction

Antibody markers	Typical LMS	Epithelioid LMS	Myxoid LMS	STUMP
<i>Smooth muscle actin</i>	+	±	+	
<i>Desmin</i>	+	±	±	
<i>h-caldesmon</i>	+	±	±	
<i>EMA</i>	+, patchy	+	+, patchy	
<i>CD10</i>	+, patchy	+, patchy	+, patchy	
<i>CD34</i>	—	—	—	
<i>CD44</i>	—	—	—	
<i>Cytokeratins</i>	+, patchy	+	—	
<i>HDAC8</i>	+	+	+	
<i>ER</i>	if +, better prognosis	if +, better prognosis	if +, better prognosis	±
<i>PR</i>	if +, better prognosis	if +, better prognosis	if +, better prognosis	±
<i>p53</i>	±	±	±	±
<i>p21</i>	if +, poor prognosis	if +, poor prognosis	if +, poor prognosis	+
<i>Bcl-2</i>	if +, better prognosis	if +, better prognosis	if +, better prognosis	if +, good prognosis
<i>MIB1</i>	poor prognosis for high percentage	poor prognosis for high percentage	poor prognosis for high percentage	Absent or low percentage
<i>p16</i>	if +, high risk of relapse	if +, high risk of relapse	if +, high risk of relapse	±
<i>Inhibin</i>	—	—	—	
<i>S100</i>	may be +	—	may be +	
<i>c-kit</i>	±	—	±	±
<i>Cyclin D1</i>				

LMS, leiomyosarcoma; STUMP, smooth muscle tumors of uncertain malignant potential.

Table 3. Immunohistochemical features of uterine smooth muscle neoplasia.

for one or more of these markers (particularly for desmin and h-caldesmon) can be lost or may be weak in some LMS variants, such as myxoid and epithelioid ones [29]. LMS is generally negative or focally positive for CD10, but it is still unknown whether CD10-positive foci have to be considered as areas of endometrial stromal differentiation within smooth muscle neoplasms [30].

LMS does not immunoreact with CD44, whereas leiomyoma and normal myometrium express this marker [1]. CD44 demonstrated sensitivity, specificity, and positive- and negative-predictive values near to 100%; thus, it is very useful in problematic cases [29]. Epithelial markers such as cytokeratins (CKs) and epithelial membrane antigen (EMA) may also be expressed in LMS, although their expression is weak and focal [29]. Focal positivity for CAM5.2 may also be seen.

Expression of estrogen (ER) and progesterone (PR) receptors has been reported in 57 and 43% of LMS cases, respectively; the corresponding percentage for leiomyoma is 78 and 88% [31]. In general, LMSs staining positive for ER and PR demonstrated to be less aggressive than the negative counterpart [31]. Positivity for c-kit may also be seen, although a variable proportion of LMS without c-kit mutation has been identified [1]. The percentage of MIB1-positive cells is usually high in LMS, if compared with leiomyomas. p53 positivity is detected in about 50% of LMS but not in leiomyoma [32]; tumors overexpressing p53 are more aggressive than those showing p53 negativity [32].

p16 antibody seems to be useful in distinguishing between benign and malignant uterine smooth muscle neoplasia. In particular, a strong and diffuse p16 positivity associated with p53 positivity would favor an LMS diagnosis. In addition, p16 expression seems to be strictly related to a highest risk of LMS relapse [33].

5.7. Histological variants of LMS

Several histological subtypes of LMS have been recognized, although it is unknown if this classification may have a clinical relevance.

Usual leiomyosarcoma is composed of fascicles of spindle-shaped cells with eosinophilic cytoplasm, resembling the normal myometrial smooth muscle.

A tumor lacking all the three main cardinal histological features seen for LMS should be diagnosed as leiomyoma (**Figure 3**); a tumor showing one of three main features should be categorized as atypical leiomyoma or STUMP [1].

Myxoid leiomyosarcoma is the less common variant. Grossly, it appears as a well-circumscribed, voluminous and gelatinous mass. Commonly, myxoid change is seen in about 30% of the tumor mass. Histologically, it differs from the classic form of LMS due to hypocellularity and myxoid stroma. A significant cytological atypia and a high mitotic activity are usually lacking [34]. Within myxoid areas, no more than 2 mitosis/10 HPFs are often seen, although a higher mitosis number may be present in the context of smooth muscle fascicles. Smooth muscle cells stain positive for smooth muscle markers (**Table 3**). Myxoid LMS usually shows clinically malignancy, since it is highly infiltrative [1].

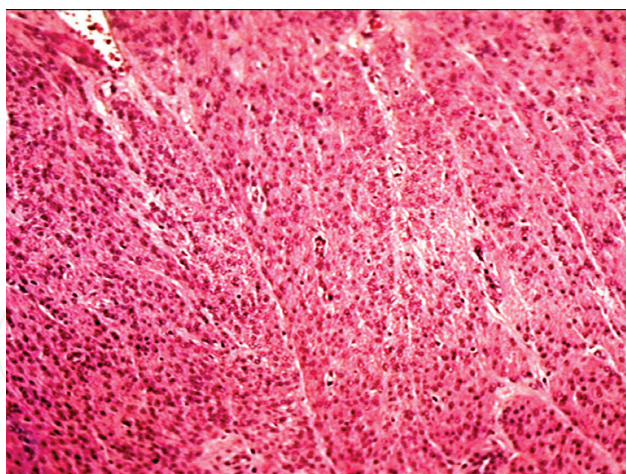


Figure 3. Typical leiomyoma. EE, 10x.

Epithelioid leiomyosarcoma is characterized by the presence of round-polygonal smooth muscle cells with abundant eosinophilic cytoplasm and round nuclei, arranged in nests, cords or plexiform patterns. The clinical behaviour of epithelioid tumors with a moderate mitotic activity (2–4 mitosis/10 HPFs) is not well understood. About 10% of epithelioid LMS larger than 6 cm recurred or metastasized [1]. These cases are classified as STUMP and need a careful follow-up [34].

Leiomyosarcoma with osteoclastic giant cells is a rare but more aggressive variant of LMS [1]. The background is similar to those of typical LMS; however, histiocytic CD68-positive cells may be detected admixed with smooth muscle cells staining positive for smooth muscle cell markers. Overall survival is <2 years after presentation, even with radiation or chemotherapy [1].

In **xanthomatous LMS**, smooth muscle cells show microvesicular and foamy cytoplasm.

The three cardinal features used to diagnose typical LMS are often hard to assess in epithelioid and myxoid variants [35]. In patients showing a worse prognosis, two or more of the following features are usually detected: tumor size of 5 cm or more, infiltration of the adjacent tissues, cytological atypia, high mitotic index, necrosis and lymph vascular invasion [35]. Particularly, cut-off values of 10 mitoses/10 HPFs, ≥ 4 mitoses/10 HPFs and ≥ 2 mitoses/10 HPFs are used for typical, epithelioid and myxoid LMS, respectively [16].

5.8. The 2009-revised FIGO staging system for LMS

Staging of LMSs is very important to drive treatment. The International Federation of Gynecology and Obstetrics Committee (FIGO) recognized that the old classification was no longer sufficient and that USs require an independent staging [35]. The old staging system looked at how far the cancer spreads; FIGO staging, essentially being a post-surgical staging, relies on histological examination.

Moreover, while FIGO staging is more precise in detecting tumors with a worse prognosis, staging by the American Joint Commission on Cancer (AJCC) demonstrates to be more

accurate in identifying patients with a good prognosis (**Table 4**). In general, neither the former nor the latest are able to provide an exact estimation of the overall survival for LMSs [36].

5.9. Diagnostic problems with LMS

Among uterine sarcomas, LMS represents a source of differential diagnostic problems, particularly with leiomyomas variants, which most often show macroscopic and histological features causing misdiagnosis [1]. This fact would be essentially due to the hormonal uterine milieu that would cause a high mitotic activity. A diagnosis of LMS would also signify a challenge for clinicians, because of problems with its management. As previously shown, among women undergoing hysterectomy or myomectomy for a myometrial mass, the prevalence of LMS is approximately 0.20% [37]. Thus, differential diagnosis between LMS and leiomyoma is the first step to move when a uterine mass is suspected. Since the risk of complications during hysterectomy exceeds the risk of incidental LMS, women with a suspected leiomyoma should be treated with a uterine-sparing surgical option [37]. Some conditions, which may be considered as associated with LMS, but not with leiomyoma, include older age and postmenopausal status. Being leiomyoma responsive to estrogen and progesterone, it frequently arises during reproductive age (below 20 years of age in black women, and between 30 and 40s in white women), while usually stabilizes or decreases in size in postmenopausal patients [37]. Basing on these considerations, a new or growing uterine mass in women above 40 years of age should be suspected for LMS, while the level of suspicion for malignancies may be lower in postmenopausal women undergoing oestrogens therapy [38]. Younger age cannot exclude a

FIGO stage	Definition	TNM Stage
I	Tumor limited to uterus	T1, N0, M0
IA	<5 cm	T1a, N0, M0
IB	>5 cm	T1b, N0, M0
II	Tumor extended to the pelvis	T2, N0, M0
IIA	Adnexal involvement	T2a, N0, M0
IIB	Tumor extends to extra -uterine pelvic tissue	T2b, N0, M0
III	Tumor invades abdominal tissues (not just protruding into the abdomen)	Any of the following
IIIA	One site	T3a, N0, M0
IIIB	More than one site	T3b, N0, M0
IIIC	Metastasis to pelvic and/or para-aortic lymph nodes	T1-T3, N1, M0
IV	Tumor invades bladder and/or bowel mucosa, and/or distant metastases	
IVA	Tumor invades bladder and/or bowel mucosa	T4, any N, M0
IVB	Distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes	any T, any N, M1

FIGO, International Federation of Gynecology and Obstetrics Committee; AJCC, American Joint Commission on Cancer.

Table 4. 2009-revised FIGO and AJCC (TNM) staging system for leiomyosarcomas.

diagnosis of LMS. On the other hand, a rapidly growing large uterine mass cannot unequivocally be associated to an LMS [38]. For all these reasons, histological examination represents the milestone to distinguish between leiomyoma and LMS.

Recent data reported an increased risk of undetected LMS among postmenopausal patients who underwent morcellation of uterine tissue [39]. Uterine sarcoma usually spreads via intra-abdominal, lymphatic or haematogenous routes. It is worth noting that some histological variants of leiomyomas may also disseminate. Thus, a careful diagnosis has to be done in the presence of a widespread disease. Failure of medical treatment with gonadotropin-releasing hormone agonist, or unsuccessful non-excisional procedures for a leiomyoma (such as uterine artery embolization), has been reported in some LMS cases [39].

Genetic studies demonstrated that, in a vast majority of cases, an LMS does not originate from a benign leiomyoma. LMS typically shows polyploidy and aneuploidy, while leiomyoma displays genetic rearrangements which are often shared by other benign neoplasms. On the other side, rare cases of leiomyoma progressing to LMS have been described [40]. In the absence of risk factors, the vast majority of the authors agree to manage women for a leiomyoma unless new symptoms develop. Conversely, a suspect of LMS should be put if women failing response to medical therapy or when new symptoms appear.

5.10. Differential diagnosis

5.10.1. LMS versus intravascular leiomyomatosis, benign metastasizing leiomyoma, disseminated pelvic leiomyomatosis

Intravascular growth, metastasis and pelvic dissemination are not included among the cardinal features driving LMS diagnosis. Thus, they cannot be used to distinguish an LMS from a leiomyoma. However, intravascular leiomyomatosis, benign metastasizing leiomyoma and disseminated pelvic leiomyomatosis do not show significant cytological atypia, tumor cell necrosis or a high mitotic count [1]. Recent findings demonstrated a distinctive genetic profile in benign metastasizing leiomyomas [41].

5.10.2. LMS versus endometrial stromal sarcoma with smooth muscle differentiation

In endometrial stromal sarcoma with smooth muscle differentiation, smooth muscle cells do not show necrosis or a significant mitotic activity. Moreover, these malignancies always contain an endometrial stroma usually lacking in LMS [1].

5.10.3. Epithelioid LMS versus poorly differentiated carcinoma

A diagnosis of carcinoma is favored when malignant cells are associated with endometrial hyperplasia. This diagnosis was also supported when neoplastic cells show positivity for keratin and negativity for desmin and h-caldesmon (**Table 3**) [1]. When a distinction is impossible to make, a diagnosis of 'undifferentiated malignant neoplasm' should be put. Electron microscopic examination may sometimes help.

5.10.4. LMS versus *gastrointestinal stromal tumor (GIST)*

Occasionally, GIST extends from the bowel wall simulating a fibroid. In such cases, differential diagnosis between GIST and leiomyoma may be problematic since both tumors show spindled cells without cytological atypia or mitotic activity.

Unlike LMS, GIST frequently shows spindle cells with cytoplasmic vacuoles, while the typical fascicular architecture of muscle cells is lacking. Desmin expression in GIST is rare, while both c-kit and CD34 expression are common. Basing on these evidences, the use of a panel including desmin, c-kit and CD34 may be helpful in differential diagnosis [36].

5.10.5. LMS versus *undifferentiated uterine sarcoma*

Recent data demonstrated that there are no universal histological criteria able to distinguish these two malignancies. In truth, it is also uncertain if there are significant clinical and therapeutic differences between them [36].

5.11. Molecular features

The oncogenic mechanisms leading to LMS remain unknown, even if the accumulation of multiple genetic events has been demonstrated. In general, the number of molecular features characteristic for LMSs is smaller if compared with those of endometrial stromal sarcomas.

Single nucleotide polymorphisms technique, gene expression arrays and DNA methylation analyses show genomic modifications and mosaicisms in LMS; cytogenetic analyses also demonstrated numerical and structural chromosomal abnormalities [42]. On the other hand, no or limited genomic aberrations have been found in leiomyomas [42]. Thus, genomic instability represents the hallmark of uterine smooth muscle malignancies [43]. The most frequent genomic loss found in LMS involves 10q, 11q, 13q and 2p chromosomal arms. Particularly, the loss of genetic material at chromosomal arms 1p, 14q, and 22q seems to be the same for both uterine LMS and gastrointestinal stromal tumors (GISTs) [43]. The most common genomic gains in LMS are Xp, 1q, 5p, 8q and 17p.91 [33]. Loss of heterozygosity (LOH) for long arm of chromosome 10 was found in about 50% of LMSs, but not in leiomyomas [43]. t(12;14)(q15;q23-24) translocation has been detected in a high proportion of leiomyomas but not in LMS [43]. Some LMSs demonstrated some types of X chromosome inactivation differing from those of leiomyomas. This fact would confirm the theory of the independent transformation processes occurring in LMS and leiomyoma [43]. Moreover, convincing evidences regarding the malignant transformation of certain type of leiomyomas, such as the bizarre variant, are still lacking. LMS also shows a significant higher frequency of allelic loss (FAL), if compared with leiomyoma (52 vs. 18%, respectively) [44]. All these findings would support the hypothesis that the pathways for LMS and leiomyoma are different [43]. Genetic instability would be the key to acquire sequential genetic changes and mutations. Although the vast majority of USs are sporadic, some germline mutations (i.e. mutation occurring in fumarate hydratase) are regarded as genetic risk factors for the development of both LMSs and leiomyomas [45]. Most authors put their attention on the mutations occurring in the gene named mediator complex subunit 12 (MED12), located at locus Xq13.1 [46]. MED12 protein complexes with MED13, CDK8 and cyclin D [46]. Mutations of Exon

2 in MED12 gene have been found in 70% of leiomyomas, particularly in the typical and mitotically active variants [46]. For this reason, MED12 mutation cannot be used to determine the behaviour of a smooth muscle neoplasia. The unique role of this marker would rely on the individuation of the smooth muscle differentiation within a mesenchymal neoplasia [46]. Overexpression of high-mobility group AT-hook 2 (HMGA2) protein, frequently mutated in uterine leiomyomas, seems to be inversely related to the presence of MED12 mutations [47].

By FISH analysis, TP53 mutations and PTEN deletions were detected in LMS, atypical leiomyoma and STUMP [34]. A high expression of topoisomerase 2A (TOP2A) has been found in a vast majority of LMSs, while low expression was seen in leiomyoma variants and STUMP [48]. Expression of Stathmin1 activating the phosphoinositide-3-kinase (PI3K) pathway was demonstrated to be significantly higher in LMSs, if compared with other uterine smooth muscle tumors. Thus, the absence of Stathmin1 would not support a diagnosis of LMS [49]. Being the expression of the mRNA-binding protein IMP3 higher in LMS than in benign smooth muscle neoplasia, it must be considered as a useful tool in differential diagnosis [50]. CDC7, CDC20, GTSE1, CCNA2, CCNB1, and CCNB2 are overexpressed in LMS, while K-ras is overexpressed in a small percentage of leiomyomas but not in LMSs [42]. MDM-2 oncogene negatively regulates apoptosis by (1) targeting p53 for ubiquitin-based degradation, (2) blocking p53 transcriptional activation domain and (3) shuttling p53 from the nucleus to the cytoplasm [42]. Amplification of MDM-2 has been reported in 10% of uterine LMS and in extra-uterine LMS, but not in leiomyomas [42]. The block of MDM-2 would enhance p53 function, thus providing a targeted therapeutic strategy. Abnormalities of the retinoblastoma-cyclin D pathway have been found in about 90% of LMSs [42]. All the above mentioned aberrant molecular patterns, the vast majority of which is different for LMSs and leiomyomas, confirm the different nature of these tumors. Cell cycle markers and proliferation proteins (p16, p21, p27, p53, PCNA, Ki-67 and PHH3) are presently under consideration. p16^{INK4a} has been found to be implicated in the genesis of LMS [51]. p16 binds to cyclin D/CDK4 complex regulating cell cycle through G1/S progression. p16-/CDK4A would act as a negative cell cycle regulator, by blocking cell cycle progression of neoplastic cells and accelerating cell senescence. Ki67 antigens identify both normal and neoplastic cells under proliferation. Recently, statistically significant higher level of both PCNA and Ki67 has been found in uterine LMSs in comparison with leiomyomas. The percentage of MIB1-positive cells would help to predict LMS prognosis and neoplastic spread [1].

In conclusion, among the several markers listed above, TOP2A, IMP3, Stathmin1, HMGA2 and MED12 are demonstrated to be promising in distinguishing between LMS and leiomyoma. Most studies recently focused on molecular markers able to predict progression risk and prognosis of a LMS. Slatter et al. correlated the presence of ALT and PML bodies (APBs) to a poor prognosis of LMS [52]. Next-generation sequencing confirmed the presence of ATRX mutations in LMS and their association with a poor survival [53]. RNA sequencing identified three distinct molecular subtypes of LMS; subtype II was demonstrated to have the worse prognosis [54]. Leiomodulin (LMOD1) and ADP-ribosylation factor-like 4 C (ARL4 C) are now considered as specific markers for LMS types I and II [54]. The expression of progesterone receptor has been recently included in FIGO staging as an independent prognostic factor for

stage I LMS [2]. On the other hand, overexpression of c-myc proto-oncogene does not correlate with smooth muscle tumor prognosis, since it has been detected in about 50% of both leiomyomas and LMSs [2].

Gene expression profiling individuated 203 probes, which were differentially expressed in primary and metastatic LMSs. Among these, OSTN, NLGN4X, NLGN1, SLITRK4, MASP1, XRN2, ASS1, RORB, HRASLS and TSPAN7 were overexpressed in primary LMSs, while TNNT1, FOLR3, TDO2, CRYM, GJA1, TSPAN10, THBS1, SGK1, SHMT1, EGR2 and AGT were overexpressed in metastatic LMSs [55]. By flow cytometry, about 70% of LMSs showed aneuploidy; thus, DNA ploidy may probably help in identifying cases with adverse prognosis [1]. CGH analysis demonstrated to be useful in distinguishing LMS from STUMP and in predicting the clinical behaviour of the latest [56].

In summary, most molecular markers have been studied in relation to LMSs progression and prognosis. However, large studies are still needed to validate their usefulness as possible therapeutic targets.

5.12. Therapeutic approaches

5.12.1. Surgery

Hysterectomy with tumor debulking may be considered the treatment of choice in patients with uterine LMS [1]. In postmenopausal women, hysterectomy and bilateral salpingo-oophorectomy represent the gold standard. Ovarian preservation may be considered in premenopausal patients with early stage LMS, limited to the uterus [57]. Patients without residual disease after surgical resection would have an improved survival if compared with those undergoing suboptimal surgical resection [57]. The role of lymph node dissection remains controversial, since lymphatic metastases occur only in a small percentage of cases, frequently associated with intra-abdominal disease. The incidence of retroperitoneal lymph node metastases is low in patients harboring a uterine LMS. On the other side, nodal metastasis has been reported in 50% of women with an LMS mass of 6–10 cm. This fact would suggest to also consider tumor size in planning surgical management. Presently, among postmenopausal women harboring an LMS larger than 5 cm its maximum diameter, lymph node dissection should be considered [57], although lymph nodes metastases were identified in 6.6–11% of women undergoing lymphadenectomy [1, 57].

In patients with localized metastases, complete metastasectomy enhances disease-specific survival. Particularly, in patients with pulmonary metastasis, metastasectomy would bring to a 5-year survival rate of 43–46.8%, with an overall 3-year disease-free survival rate of 27.8% [58].

As previously shown, since the vast majority of LMSs are diagnosed after surgery for a suspected benign uterine mass, it would be extremely important to avoid uterine morcellation or intraoperative rupture of the mass into the peritoneal cavity.

5.12.2. Adjuvant therapies

The role of postoperative adjuvant therapies remains controversial, since no study clearly confirmed their benefits in the management of uterine LMSs. Radiation does not show a significant impact on the overall survival, although it seems to have a role in controlling local

disease, local recurrences and in palliation [59]. In general, CT with a single agent did not demonstrate a significant improvement of the LMS outcome, with limited clinical benefits. Moreover, only tumors with ER/PR receptors may respond to hormonal therapy [59]. Adjuvant chemotherapy is not standardly administered in patients who underwent hysterectomy for LMS confined to the uterus (stages I and II) [60]. The management of advanced uterine LMS is now based on a first-line regimen including Doxorubicin/Doxorubicin plus Ifosfamide [61]. The use of Gemcitabine or Gemcitabine plus Docetaxel produced conflicting results [61]. A French randomized study by Pautier et al. demonstrated a better 3- and 5-year disease-free survival in patients with multiagent CT, in comparison with women receiving RT alone [62]. Conversely, the use of multiagent CT or the combination of CT and RT proved to be associated with a significant increase in toxicity [62]. Trabectedin is a tetrahydroisoquinoline alkaloid. Trabectedin interferes with several transcription factors, DNA-binding proteins and DNA repair pathways, thus resulting in G2-M cell-cycle arrest and apoptosis [63, 64]. The two main advantages to use Trabectedin would rely on (1) therapeutic benefits that can be maintained by extending the use beyond six cycles and (2) reliable tolerability. All these findings would underline the possible role of Trabectedin in the management of advanced/persistent/recurrent LMS, although this drug has not been approved by the Food and Drug Administration yet [65, 66]. Some authors reported the cytoreductive surgery with hyperthermic intraperitoneal CT (CRS-HIPEC) as a promising treatment to achieve prolonged survival for peritoneal spreading LMS [67]. In general, chemotherapeutic protocols do not lead to a clinically significant response in high-grade LMS cases; on the other side, palliative CT is a rationale approach to improve the quality of life in patients with advanced unresectable disease.

A trial by the European Organization for Research and Treatment of Cancer failed to demonstrate some benefits of adjuvant RT in treating patients with LMS in stages I and II after surgery [68, 69]. These data were also confirmed by SEER (Surveillance, Epidemiology, and End Results) database [70]. On the other side, a retrospective study from Sanpath et al. demonstrated an improved outcome in women receiving RT after surgery, in comparison with surgery alone [71]. Finally, a consensus by the Gynecologic Cancer InterGroup (GCIG) established that adjuvant RT does not confer survival benefits to patients undergoing complete resection of uterus-limited LMS. Moreover, in advanced or recurrent LMS, RT may only have a minor role [72].

5.13. Spread and metastases

Although LMS shows metastatic potential and a high rate of recurrence, patients usually present with early stage of disease. If present, the extension of the LMSs outside the uterus occurs into the pelvis. About 3% of LMS at stages I and II show lymph nodes involvement, as a consequence of intraperitoneal spreading. A high proportion of patients without lymph nodes involvement would develop distant metastasis, the favored site being lung, brain, liver and bone. Direct extension to cervix and vagina is commonly observed [1].

5.14. Prognostic factors and survival

LMSs are often associated with a poor prognosis. A 5-year disease-specific survival is about 20–30%; a 5-year survival rate is 50–60% in stage I and 15% in more advanced stages. Death frequently occurs within 2 years from diagnosis, although a long disease-free interval was

described for low-stage LMS confined to the uterus [1]. In stage I, tumor size represents the most important prognostic factors [20]. Age at presentation and mitotic index remain controversial. In a large Norwegian report including 245 uterine LMSs confined to the uterus, tumor size and mitotic rate demonstrated to be useful in stratifying patients in different prognostic groups [73]. In truth, correlation between survival, patients' age, clinical stage, tumor size, the presence/absence of necrosis, mitotic rate, the degree of nuclear pleomorphism and vascular invasion varies among the different studies. Presently, nuclear pleomorphism, high mitotic rate, extensive tumor cell necrosis, vascular invasion, a size greater than 5 cm and non-spindle morphology are considered negative prognostic factors in low-stage LMS [1]. Prognostic significance of DNA ploidy and TP53 expression has been described, although confirmation is still needed [74]. Ancillary parameters such as p53, p16, Ki67 and Bcl-2 have also been explored, but results are still confusing. Recurrences are seen in 53–71% of the cases. All patients with extra pelvic metastasis usually die within 6 years from diagnosis [1].

5.15. Future perspectives

The genetic heterogeneity of the uterine LMSs makes the identification of driver mutations and therapeutic targets more difficult [75]. Recently, recurrent mutations of alpha thalassaemia/mental retardation syndrome X-linked (ATRX) gene have been detected. Although ATRX inhibitors might be considered as new possible therapeutic targets, their benefits are still to be defined [76, 77]. Since MDM2 inhibitors have proven to be efficient in preclinical settings, agents such as AMG232 and RG7112 are currently under investigation in a variety of cancer types [78].

In summary, the standard treatment for both early and advanced uterine LMSs remains the hysterectomy. In postmenopausal women, bilateral salpingo-oophorectomy and complete cytoreduction of the tumor with adherent structures, even if not infiltrated, are recommended. For uterus-limited disease (early stage), neoplastic mass should be removed en bloc. Metastasectomy should be considered in patients with metastatic LMS. Adjuvant RT and CT should not be considered in routine practice, especially in women in which tumor has been completely removed. CT with a single agent (Doxorubicin, Gemcitabine and Trabectedin) or in combination might be promising in patients with advanced, persistent or recurrent LMS. Presently, many efforts are focused to define the molecular etiology of LMS, in order to provide a better care for this highly lethal neoplasia.

5.16. Key points

- Uterine leiomyomas represent the most common gynecological benign neoplasia. Uterine sarcoma is rare. The percentage of incidental LMS among women undergoing surgery for suspected leiomyoma ranges from 0.2 to 1.7% and increases with age.
- Among women in reproductive age, a rapidly enlarging uterine mass should not be suspected for LMS. A new or growing uterine mass in postmenopausal women needs further evaluation.

- Leiomyomas do not appear to progress to sarcoma, with the exception of some histological variants.
- No pelvic imaging is undoubtedly able to distinguish between leiomyoma and LMS.
- It is not recommended to perform hysterectomy to exclude malignant neoplasm. Conversely, hysterectomy is suggested when the presence of LMS is strongly suspected by MRI, in the presence of multiple risk factors or when thoracic imaging demonstrated lung metastases.
- The influence of adjuvant therapy on survival is uncertain. RT may be useful in controlling local recurrences; CT with doxorubicin or docetaxel/gemcitabine should be considered as the first-line choice in advanced or recurrent disease.
- Multidisciplinary evaluation of LMS is essential.

6. Uterine smooth muscle tumors of uncertain malignant potential

Uterine smooth muscle tumors, which cannot be unequivocally diagnosed as benign or malignant, are designated as STUMPs [79]. STUMPs represent a heterogeneous group of neoplasia with a borderline behaviour. Because of their rarity and the evolving knowledge about them, the proper management of patient bearing STUMP represents a dilemma. The lack of uniform diagnostic criteria may often result in STUMP over diagnosis. The term 'STUMP' was first used by Kempson et al., in 1973 [80]. He clustered STUMPs into three groups, basing on cytological atypia, tumor cell necrosis and mitosis (**Figure 4A, B**):

1. Atypical leiomyoma with a low risk of recurrence: diffuse moderate–severe atypia, <10 mitosis MFs/10 HPFs and no tumor cell necrosis.
2. Atypical leiomyoma with limited experience: focal moderate-severe atypia, <20 mitosis/10 HPFs and no tumor cell necrosis.
3. Smooth muscle tumor with a low malignant potential: absent-mild nuclear atypia, mitosis less than 10/10 HPFs and the presence of tumor cell necrosis.

Later, Kempson et al. classified STUMPs as those tumor with a mitotic count major than 15 mitosis/10 HPFs [81, 82]. The largest study on uterine STUMP was done by Guntupalli et al. [83], which grouped STUMPs into five categories:

Group 1: the presence of tumor cell necrosis, the absence of atypia, and mitotic count <10/10 HPFs.

Group 2: the absence of tumor cell necrosis, diffuse atypia and mitotic count <10/10 HPFs.

Group 3: the absence of tumor cell necrosis, the absence of atypia and mitotic count >20/10 HPFs.

Group 4: hypercellularity and mitotic count >4/10 HPFs.

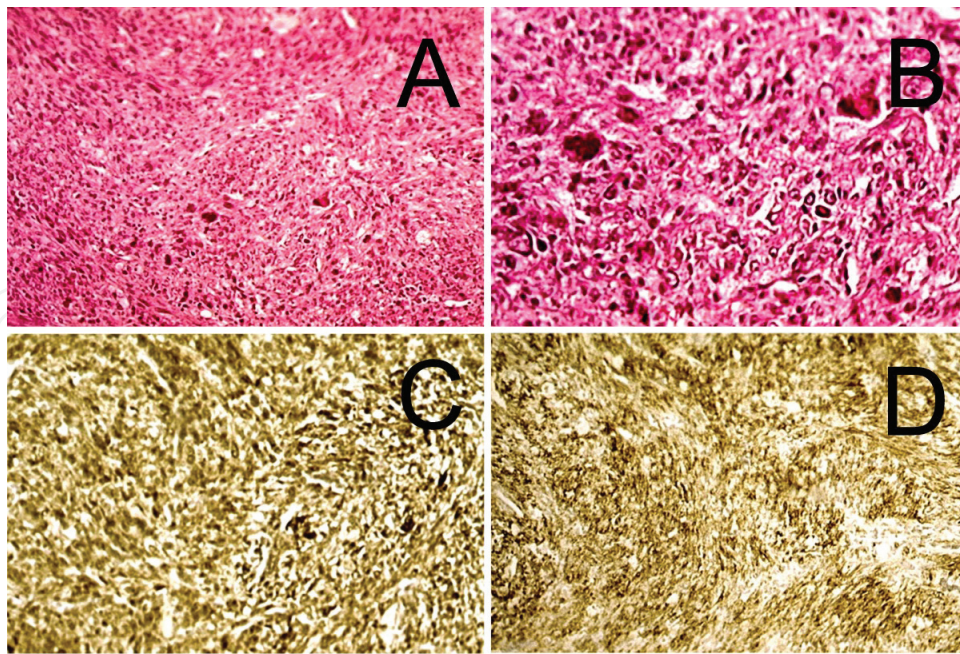


Figure 4. Uterine smooth muscle tumor of uncertain malignant potential (STUMP). (A) Overview, EE, 4x. (B) Nuclear atypia, EE, 20x. (C) p16 positive stain, 10x. (D) Smooth muscle actin positive stain, 10x.

Group 5: irregular margins or vascular invasion at the periphery of the tumor.

Mitotically active leiomyoma, considered as benign variants of leiomyoma, differs from STUMP due to the lacking of recurrences and metastases outside the pelvis [83]. On the opposite side, the difference between LMS and STUMP would rely on the aggressive clinical course, with early recurrence and metastases of the former, and on lower tumor growth and possible delayed recurrence of the latter [83]. The clinical presentation of STUMPs resembles signs and symptoms of uterine leiomyomas: rapidly growing pelvic mass, abnormal uterine bleeding, pelvic pain and vaginal discharge. Risk factors are still unclear, as well as clinical behaviour. The mean age at diagnosis is 45 years and the vast majority of patients are premenopausal women [84].

6.1. Pathological findings

Recent studies characterized the natural history of smooth muscle neoplasms. Physiologically, myometrial stem cells induce cells proliferation and tissue regeneration through strictly regulated processes [85]. Uterine smooth muscle cells undergo multiple cycles of growth and involution induced by oestrogens and progesterone stimulation. These cells also receive paracrine signaling from stem cells, in order to regulate physiologic process [85]. Genetic mutations and chromosomal rearrangements in myometrial stem cells would be induced by repeated endocrine and paracrine stimulation [85]. Mutations and genetic rearrangements would cause unregulated cells proliferation driving smooth muscle tissue towards a spectrum of neoplasia ranging from leiomyomas to LMSs [86]. In particular, the deletion of the short arm of chromosome 1 (1p) has been associated with a possible malignant behaviour of myometrial cells [87].

6.2. Diagnostic imaging

No reliable method is able to pre-operatively distinguish between benign and malignant behaviour of STUMP. Although some MRI features may differentiate tissue intensity, these elements are not specific. Similar to leiomyoma, STUMPs demonstrate homogeneous low signal on T2-weighted images. On the other hand, STUMP and leiomyosarcoma often present with areas of heterogeneous high T2 signal intensity. Recent data would suggest how the combination of hypointense T1 signal, moderate T2 signal intensity and high signal intensity on diffusion-weighted imaging (DWI) might be indicative of a leiomyoma variant or STUMP [88]. The utility of positron emission tomography/computed tomography (PET/CT) is still to be defined.

6.3. Immunohistochemistry

A panel of antibodies such as p16, p53, p21 and Ki-67/MIB1 may be helpful in distinguishing STUMP from leiomyoma and LMS (**Figure 4C**) [1]. Ki-67/MIB1 and p53 expressions are significantly higher in LMS if compared with STUMP. p16 shows a significant increased expression starting from leiomyoma to LMS. Smooth muscle actin is positive in STUMP (**Figure 4D**). A significant difference has been found in PR expression when comparing STUMP and leiomyosarcoma. Bcl-2 is more frequently expressed in leiomyomas with respect to STUMP and LMS. Finally, the expression of Bcl-2 in STUMP is indicative of a good prognosis [89].

6.4. Therapeutic approaches

6.4.1. Surgery

No standard protocols for the management of patients with suspected STUMP have been defined. Present recommendations are based on guidelines for LMS. Considering the high risk of recurrence, hysterectomy represents the gold standard for women completing their childbearing. Myomectomy followed by hysterectomy after childbearing is suggested in patients who desired maternity. Since STUMPs may show delayed recurrences, patients with surgically removed STUMP should get CT of chest, abdomen and pelvis at baseline, followed by physical examinations every 6 months for 5 years. When myomectomy is performed for fertility sparing, US evaluation every 6 months, followed by yearly MRI and chest X-ray for 5 years have been proposed [89].

6.4.2. Adjuvant therapies

The usefulness of adjuvant therapy for STUMP is not clear yet, since few studies have been performed. In general, due to the low recurrence rate of these neoplasias, no role has been suggested. If recurrence occurs, surgical excision of the mass is followed by adjuvant therapy, such as pelvic RT. CT (with Doxorubicin and Cisplatin), Medroxyprogesterone or GnRH should be performed [89]. In the presence of metastasis and in premenopausal patients, some authors suggest achieving hormonal suppression to prevent STUMP progression [89].

6.5. Prognosis

STUMP recurrences are observed in about 7% of the cases. The median of survival after recurrence is higher in STUMP than in LMS. In truth, recurred STUMP should be biologically considered as low-grade LMS, even if this diagnosis cannot be achieved until a recurrence develops [90]. In this context, the number of mitosis seems to have the highest value in predicting the clinical behaviour and the prognosis of STUMP [91]. STUMP metastases are rare. They commonly occur in lungs, although the involvement of bones has also been described [1].

In conclusion, the management of STUMPs remains controversial. In general, patients with STUMP should be counseled regarding the potential risk of recurrence. Moreover, because of the risk of metastases even many years after the initial diagnosis, patients with STUMP require a long-term surveillance [92]. These considerations highlight the need of a multidisciplinary approach, which includes gynecologists, gynecological pathologists and oncologists, to early detect disease and to establish the correct management. Finally, the future research should put the attention on the detection of an ideal biomarker, able to predict the outcome of STUMPS and to personalize both surgical and oncological strategies.

6.6. Key points

- STUMPs represent a heterogeneous group of neoplasia and a gray area in diagnostic pathology of uterine sarcomas.
- The vast majority of STUMPs demonstrated a benign behaviour, although follow-up with adjuvant therapy is strongly recommended.
- Immunohistochemistry with Ki67/MIB1 and p53 antibodies may help stratify the prognosis.

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References

- [1] Mutter GL, Prat J, editors. *Pathology of the Female Reproductive Tract*. 3th ed. London: Churchill Livingstone Elsevier; 2014
- [2] Prat J, Mbatani N. FIGO cancer report 2015. Uterine sarcomas. *International Journal of Gynecology & Obstetrics*. 2015;**131**:S105-S110
- [3] Yildirim Y, Inal MM, Sanci M, Yildirim YK, Mit T, Polat M, Tinar S. Development of uterine sarcoma after tamoxifen treatment for breast cancer: Report of four cases. *International Journal of Gynecological Cancer*. 2005;**15**:1239-1242
- [4] Bilyk O, Coatham M, Jewer M, Postovit L-M. Epithelial-to-mesenchymal transition in the female reproductive tract: From normal functioning to disease pathology. *Frontiers in Oncology*. 2017;**7**:145-165
- [5] Kim YS, Yi BR, Kim NH, Choi KC. Role of the epithelial-mesenchymal transition and its effects on embryonic stem cells. *Experimental & Molecular Medicine*. 2014;**46**:108-113
- [6] Gurzu S, Turdean S, Kovacs A, Contac AO, Jung I. Epithelial-mesenchymal, mesenchymal-epithelial, and endothelial-mesenchymal transitions in malignant tumors: An update. *World Journal of Clinical Cases*. 2015;**3**:393-404
- [7] Liu F, Zhou Y, Zhou D, Kan M, Niu X, Zhang Z, Zhang D, Tao L, He L, Zhan L, Liu Y. Whole DNA methylome profiling in lung cancer cells before and after epithelial-to-mesenchymal transition. *Diagnostic Pathology*. 2014;**9**:66-75. DOI: 10.1186/1746-1596-9-66
- [8] Zhang JX, Mai SJ, Huang XX, Wang FW, Liao YJ, Lin MC, Kung HF, Zeng YX, Xie D. MiR-29c mediates epithelial-to-mesenchymal transition in human colorectal carcinoma metastasis via PTP4A and GNA13 regulation of β -catenin signaling. *Annals of Oncology*. 2014;**25**:2196-2204. DOI: 10.1093/annonc/mdu439
- [9] Polyak K, Weinberg RA. Transitions between epithelial and mesenchymal states: Acquisition of malignant and stem cell traits. *Nature Reviews. Cancer*. 2009;**9**:265-273
- [10] IARC Publications. *Pathology and Genetics of Tumors of the Breast and Female Genital Organs*. World Health Organization Classification of Tumours Available at: <http://www.iarc.fr/en/publications/pdfs-online/pat-gen/bb4/>. [Accessed: September 1, 2017]
- [11] McCluggage WG. Uterine carcinosarcomas (malignant mixed Mullerian tumors) are metaplastic carcinomas. *International Journal of Gynecological Cancer*. 2002;**12**:764-767
- [12] Prat J. FIGO staging for uterine sarcomas. *International Journal of Gynecology & Obstetrics*. 2009;**104**:177-178
- [13] Oliva E, Carcangiu ML, Carinelli SG, Ip P, Loening T, Longacre TA. Mesenchymal tumours. In: Kurman RJ, Carcangiu ML, Herrington CS, Young RH, editors. *WHO Classification of Tumours of Female Reproductive Organs*. 4th ed. Lyon: IARC; 2014. pp. 135-147

- [14] Prat J, Mbatani N. Uterine sarcomas. *International Journal of Gynecology & Obstetrics*. 2015;**131**:S105-S110
- [15] Kobayashi H, Uekuri C, Akasaka J, Ito F, Shigemitsu A, Koike N, Shigetomi H. The biology of uterine sarcomas: A review and update. *Molecular and Clinical Oncology*. 2013;**1**:599-609
- [16] Kuo-Chang W, Huann-Cheng H, Peng-Hui W, Yi-Jen C, Ming-Shyen Y, Heung-Tat N, the Taiwan Association of Gynecology Systematic Review Group. Uterine sarcoma part I-uterine leiomyosarcoma: The topic advisory group systematic review. *Taiwanese Journal of Obstetrics & Gynecology*. 2016;**55**:463-471
- [17] Mittal KR, Chen F, Wei JJ, Rihvani K, Kurvathi R, Streck D, Dermody J, Toruner GA. Molecular and immunohistochemical evidence for the origin of uterine leiomyosarcomas from associated leiomyoma and symplastic leiomyoma-like areas. *Modern Pathology*. 2009;**22**:1303-1311
- [18] Testa AC, Di Legge A, Virgilio B, Bonatti M, Manfredi R, Mirk P. Which imaging technique should we use in the follow up of gynaecological cancer? *Best Practice & Research. Clinical Obstetrics & Gynaecology*. 2014;**28**:769-791
- [19] Rha SE, Byun JY, Jung SE, et al. CT and MRI of uterine sarcomas and their mimickers. *AJR. American Journal of Roentgenology*. 2003;**181**:1369-1374
- [20] Arleo EK, Schwartz PE, Hui P, McCarthy S. Review of leiomyoma variants. *AJR. American Journal of Roentgenology*. 2015;**205**:912-921
- [21] Milad MP, Milad EA. Laparoscopic morcellator-related complications. *Journal of Minimally Invasive Gynecology*. 2014;**21**:486-491
- [22] Toubia T, Moulder JK, Schiff LD, Clarke-Pearson D, O'Connor SM, Siedhoff MT. Peritoneal washings after power morcellation in laparoscopic myomectomy: A pilot study. *Journal of Minimally Invasive Gynecology*. 2016;**23**:578-581
- [23] de Almeida TG, da Cunha IW, Maciel GAR, Baracat EC, Carvalho KC. Clinical and molecular features of uterine sarcomas. *Medical Express*. 2014;**1**:291-297
- [24] Aru A, Norup P, Bjerregaard B, Andreasson B, Horn T. Osteoclast-like giant cells in leiomyomatous tumors of the uterus. A case report and review of the literature. *Acta Obstetrica et Gynecologica Scandinavica*. 2001;**80**:371-374
- [25] Kurman RJ, Ellenson H, Lora R, Brigitte M, editors. *Blaustein's Pathology of the Female Genital Tract* 2011. pp. 453-527
- [26] Oliva E. Practical issues in uterine pathology from banal to bewildering: The remarkable spectrum of smooth muscle neoplasia. *Modern Pathology*. 2016;**29**:S104-S120
- [27] Pautier P, Genestie C, Rey A, Roche B, Lhommé C, Haie-Meder C, Duvillard P. Analysis of clinicopathologic prognostic factors for 53 American College of Obstetricians and

Gynecologists. ACOG practice bulletin. Alternatives to hysterectomy in the management of leiomyomas. *Obstetrics and Gynecology*. 2008;**112**:387-400

- [28] Soslow RA. Uterine mesenchymal tumors: A review of selected topics. *Diagnostic Histopathology*. 2008;**14**:175-188
- [29] Oliva E, Young RH, Amin MB, Clement PB. An immunohistochemical analysis of endometrial stromal and smooth muscle tumors of the uterus: A study of 54 cases emphasizing the importance of using a panel because of overlap in immunoreactivity for individual antibodies. *The American Journal of Surgical Pathology*. 2002;**26**:403-412
- [30] Moinfar F, Azodi M, Tavassoli A. Uterine sarcomas. *Pathology*. 2007;**39**:55-71
- [31] Leita MM, Soslow RA, Nonaka D, Olshen AB, Aghajanian C, Sabbatini P, Dupont J, Hensley M, Sonoda Y, Barakat RR, Anderson S. Tissue microarray: Immunohistochemical expression of estrogen, progesteron, and androgen receptors in leiomyomata and leiomyosarcoma. *Cancer*. 2004;**101**:11455-11462
- [32] Anderson SE, Nonaka D, Chuai S, Olshen AB, Chi D, Sabbatini P, Soslow RA. p53, epidermal growth factor, and platelet-derived growth factor in uterine leiomyosarcoma and leiomyomas. *International Journal of Gynecological Cancer*. 2006;**16**:849-853
- [33] Hosh M, Antar S, Nazzal A, Warda M, Gibreel A, Refky B. Uterine sarcoma: Analysis of 13,089 cases based on surveillance, epidemiology, and end results database. *International Journal of Gynecological Cancer*. 2016;**26**:1098-1104
- [34] Zhang Q, Ubago J, Li L, Guo H, Liu Y, Qiang W, Kim JJ, Kong B, Wei JJ. Molecular analyses of 6 different types of uterine smooth muscle tumors: Emphasis in atypical leiomyoma. *Cancer*. 2014;**120**:3165-3177
- [35] Nagai T, Takai Y, Akahori T, Ishida H, Hanaoka T, Uotani T, Sato S, Matsunaga S, Baba K, Seki H. Novel uterine sarcoma preoperative diagnosis score predicts the need for surgery in patients presenting with a uterine mass. *Springerplus*. 2014;**3**:678-684
- [36] Seddon BM, Davda R. Uterine sarcomas- recent progress and future challenges. *European Journal of Radiology*. 2011;**78**:30-40
- [37] Pritts EA, Vanness DJ, Berek JS, Parke W, Feinberg R, Feinberg J, Olive DL. The prevalence of occult leiomyosarcoma at surgery for presumed uterine fibroids: A meta-analysis. *Gynecological Surgery*. 2015;**12**:165-177
- [38] Sabry M, Al-Hendy A. Medical treatment of uterine leiomyoma. *Reproductive Sciences*. 2012;**19**:339-353
- [39] Wright JD, Tergas AI, Burke WM, Cui RR, Ananth CV, Chen L, Hershman DL. Uterine pathology in women undergoing minimally invasive hysterectomy using morcellation. *Journal of the American Medical Association*. 2014;**312**:1253-1255
- [40] Morton CC. Genetic heterogeneity among uterine leiomyomata: Insights into malignant progression. *Human Molecular Genetics*. 2007;**16**:7-13

- [41] Nucci MR, Drapkin R, Cin PD, Fletcher CD, Fletcher JA. Distinctive cytogenetic profile in benign metastasizing leiomyoma: Pathogenetic implications. *The American Journal of Surgical Pathology*. 2007;**31**:737-743
- [42] Davidson B, Micci F. Molecular characteristics of uterine sarcomas. *Expert Review of Molecular Diagnostics*. 2017;**17**:515-522
- [43] Miyata T, Sonoda K, Tomikawa J, Tayama C, Okanura K, Maehara K, Kobayashi H, Wake N, Kato K, Hata K, Nakabayashi K. Genomic, epigenomic, and transcriptomic profiling towards identifying omics features and specific biomarkers that distinguish uterine leiomyosarcoma and leiomyoma at molecular levels. *Sarcoma*. 2015;**2015**:412-425
- [44] Quade BJ, Wang TY, Sornberger K, et al. Molecular pathogenesis of uterine smooth muscle tumors from transcriptional profiling. *Genes, Chromosomes & Cancer*. 2005;**40**:97-108
- [45] Lehtonen HJ, Kiuru M, Ylisaukko-Oja SK. Increased risk of cancer in patients with fumarate hydratase germline mutation. *Journal of Medical Genetics*. 2006;**43**:523-526
- [46] Matsubara A, Sekine S, Yoshida M, et al. Prevalence of MED12 mutations in uterine and extrauterine smooth muscle tumours. *Histopathology*. 2013;**62**:657-661
- [47] Bertsch E, Qiang W, Zhang Q, Espona-Fiedler M, Druschitz S, Liu Y, Mittal K, Kong B, Kurita T, Wei JJ. MED12 and HMGA2 mutations: Two independent genetic events in uterine leiomyoma and leiomyosarcoma. *Modern Pathology*. 2014;**27**:1144-1153
- [48] Baiocchi G, Poliseli FL, de Brot L, Mantoan H, Schiavon BN, Faloppa CC, Vssallo J, Sores FA, Xunha W. TOP2A copy number and TOP2A expression in uterine benign smooth muscle tumours and leiomyosarcoma. *Journal of Clinical Pathology*. 2016;**69**:884-889
- [49] Allen MM, Douds JJ, Liang SX, Desouki MM, Parkash V, Fadare O. An immunohistochemical analysis of stathmin 1 expression in uterine smooth muscle tumors: Differential expression in leiomyosarcomas and leiomyomas. *International Journal of Clinical and Experimental Pathology*. 2015;**8**:2795-2801
- [50] Barlin JN, Zhou QC, Leitao MM. Molecular subtypes of uterine leiomyosarcoma and correlation with clinical outcome. *Neoplasia*. 2015;**17**:183-189
- [51] Mills AM, Ly A, Balzer BL, Hendrickson MR, Kempson RL, McKenney JK, Longacre TA. Cell cycle regulatory markers in uterine atypical leiomyoma and leiomyosarcoma: Immunohistochemical study of 68 cases with clinical follow-up. *The American Journal of Surgical Pathology*. 2013;**37**:634-642
- [52] Slatter TL, Hsia H, Samaranyaka A. Loss of ATRX and DAXX expression identifies poor prognosis for smooth muscle tumours of uncertain malignant potential and early stage uterine leiomyosarcoma. *The Journal of Pathology: Clinical Research*. 2015;**1**:95-105
- [53] Yang CY, Liao JY, Huang WJ. Targeted next-generation sequencing of cancer genes identified frequent TP53 and ATRX mutations in leiomyosarcoma. *American Journal of Translational Research*. 2015;**7**:2072-2081

- [54] Guo X, Jo VY, Mills AM. Clinically relevant molecular subtypes in leiomyosarcoma. *Clinical Cancer Research*. 2015;**21**:3501-3511
- [55] Davidson B, Abeler VM, Førsund M. Gene expression signatures of primary and meta-static uterine leiomyosarcoma. *Human Pathology*. 2014;**45**:691-700
- [56] Croce S, Ribeiro A, Brulard C. Uterine smooth muscle tumor analysis by comparative genomic hybridization: A useful diagnostic tool in challenging lesions. *Modern Pathology*. 2015;**28**:1001-1010
- [57] Duffaud F, Ray-Coquard I, Salas S, Pautier P. Recent advances in understanding and managing leiomyosarcomas. *F1000Prime Reports*. 2015;**7**:55-62
- [58] Clavero JM, Deschamps C, Cassivi SD, Allen MS, Nichols FC, Barrette BA. Gynecologic cancers: Factors affecting survival after pulmonary metastasectomy. *The Annals of Thoracic Surgery*. 2006;**81**:2004-2007
- [59] Giuntoli RL, Metzinger DS, DiMarco CS. Retrospective review of 208 patients with leiomyosarcoma of the uterus: Prognostic indicators, surgical management, and adjuvant therapy. *Gynecologic Oncology*. 2003;**89**:460-469
- [60] Mancari R, Signorelli M, Gadducci A, Carinelli S, De Ponti E, Sesana S. Adjuvant chemotherapy in stage I-II uterine leiomyosarcoma: A multicentric retrospective study of 140 patients. *Gynecologic Oncology*. 2014;**133**:531-536
- [61] Momtahn S, Curtin J, Mittal K. Current chemotherapy and potential new targets in uterine leiomyosarcoma. *Journal of Clinical Medicine Research*. 2016;**8**:181-189
- [62] Pautier P, Floquet A, Gladieff L, Bompas E, Ray-Coquard I, Piperno-Neumann S. A randomized clinical trial of adjuvant chemotherapy with doxorubicin, ifosfamide, and cisplatin followed by radiotherapy versus radiotherapy alone in patients with localized uterine sarcomas (SARCGYN study). A study of the French sarcoma group. *Annals of Oncology*. 2013;**24**:1099-1105
- [63] Hensley ML, Barrette BA, Baumann K, Gaffney D, Hamilton AL, Kim JW. Gynecologic cancer InterGroup (GCIG) consensus review: Uterine and ovarian leiomyosarcomas. *International Journal of Gynecological Cancer*. 2014;**24**:61-66
- [64] Le Cesne A, Blay JY, Domont J, Tresch-Bruneel E, Chevreau C, Bertucci F, et al. Interrup-tion versus continuation of trabectedin in patients with soft-tissue sarcoma (T-DIS): A randomized phase II trial. *The Lancet Oncology*. 2015;**16**:312-319
- [65] Monk BJ, Blessing JA, Street DG, Muller CY, Burke JJ, Hensley ML. A phase II evaluation of trabectedin in the treatment of advanced, persistent, or recurrent uterine leiomyosarcoma: A gynecologic oncology group study. *Gynecologic Oncology*. 2012;**124**:48-52
- [66] Le Cesne A, Yovine A, Blay JY, Delaloge S, Maki RG, Misset JL, et al. A retrospective pooled analysis of trabectedin safety in 1132 patients with solid tumors treated in phase II clinical trials. *Investigational New Drugs*. 2012;**30**:1193-1202

- [67] Randle RW, Swett KR, Shen P, Stewart JH, Levine EA, Votanopoulos KI. Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy in peritoneal sarcomatosis. *The American Surgeon*. 2013;**79**:620-624
- [68] Wang PH, Wen KC, Yen MS. Challenges in the management of recurrent endometrial cancer. *Journal of the Chinese Medical Association*. 2016;**79**:171-177
- [69] Reed NS, Mangioni C, Malmstroom H, Scarfone G, Poveda A, Pecorelli S. Phase III randomised study to evaluate the role of adjuvant pelvic radiotherapy in the treatment of uterine sarcomas stages I and II: An European Organisation for Research and Treatment of Cancer Gynaecological cancer group study (protocol 55874). *European Journal of Cancer*. 2008;**44**:808-818
- [70] Wright JD, Seshan VE, Shah M, Schiff PB, Burke WM, Cohen CJ. The role of radiation in improving survival for early-stage carcinosarcoma and leiomyosarcoma. *American Journal of Obstetrics and Gynecology*. 2008;**199**:536-543
- [71] Sampath S, Schultheiss TE, Ryu JK, Wong JY. The role of adjuvant radiation in uterine sarcomas. *International Journal of Radiation Oncology, Biology, Physics*. 2010;**76**:728-734
- [72] D'Angelo E, Prat J. Uterine sarcomas: A review. *Gynecologic Oncology*. 2010;**116**:131-139
- [73] Abeler VM, Royne O, Thoresen S, et al. Uterine sarcomas in Norway. A histopathological and prognostic survey of a total population from 1970 to 2000 including 419 patients. *Histopathology*. 2009;**54**:355-564
- [74] Layfield LJ, Liu K, Dodge R, Barsky SH. Uterine smooth muscle tumor Utility of classification by proliferation, ploidy and prognostic markers versus traditional histopathology. *Archives of Pathology & Laboratory Medicine*. 2000;**124**:221-227
- [75] Raish M, Khurshid M, Ansari MA. Analysis of molecular cytogenetic alterations in uterine leiomyosarcoma by array-based comparative genomic hybridization. *Journal of Cancer Research and Clinical Oncology*. 2012;**138**:1173-1186
- [76] Mäkinen N, Aavikko M, Heikkinen T, Taipale M, Taipale J, Koivisto-Korander R. Exome sequencing of uterine leiomyosarcomas identifies frequent mutations in TP53, ATRX, and MED12. *PLoS Genetics*. 2016;**12**:10-13
- [77] Yang CY, Llau JY, Huang WJ, Chang YT, MC C, Lee JC. Targeted next generation sequencing of cancer genes identified frequent TP53 and ATRX mutations in leiomyosarcoma. *American Journal of Translational Research*. 2015;**7**:2072-2081
- [78] Carry JC, Garcia-Echeverria C. Inhibitors of the p53/ hdm2 protein-protein interaction-path to the clinic. *Bioorganic & Medicinal Chemistry Letters*. 2013;**23**:2480-2485
- [79] Ip PP, Cheung AN, Clement PB. Uterine smooth muscle tumors of uncertain malignant potential (STUMP): A clinicopathologic analysis of 16 cases. *The American Journal of Surgical Pathology*. 2009;**33**:992-1005

- [80] Kempson RL. Sarcomas and related neoplasms. In: Noris HJ, Hertig AT, Abel MR, editors. *The Uterus*. Baltimore: Williams and Wilkins; 1973. pp. 298-215
- [81] Bell SW, Kempson RL, Hendrickson MR. Problematic uterine smooth muscle neoplasms. A clinicopathologic study of 213 cases. *The American Journal of Surgical Pathology*. 1994; **18**:535-558
- [82] Rosai J, editor. *Rosai and Ackerman's Surgical Pathology*. 10th ed. Amsterdam: Elsevier; 2011. ISBN: 9780323248662
- [83] Guntupalli SR, Ramirez PT, Anderson ML, Milam MR, Bodurka DC, Malpica A. Uterine smooth muscle tumor of uncertain malignant potential: A retrospective analysis. *Gynecologic Oncology*. 2009; **113**:324-326
- [84] Kalogiannidis I, Stavrakis T, Dagklis T, Petousis S, Nikolaidou C, et al. A clinicopathological study of atypical leiomyomas: Benign variant leiomyoma or smooth muscle tumor of uncertain malignant potential. *Oncology Letters*. 2016; **11**:1425-1428
- [85] Quade BJ, Robboy SJ. Uterine smooth muscle tumors. In: Robboy SJ, Mutter GL, Prat J, editors. *Robboy's Pathology of the Female Reproductive Tract*. 2nd ed. Oxford: Churchill Livingstone Elsevier; 2009. pp. 474-492
- [86] Bulun SE. Uterine fibroids. *The New England Journal of Medicine*. 2013; **369**:1344-1355
- [87] Mehine M, Kaasinen E, Heinonen HR, Mäkinen N, Kämpjärvi K, Sarvilinna N, Aavikko M. Integrated data analysis reveals uterine leiomyoma subtypes with distinct driver pathways and biomarkers. *Proceedings of the National Academy of Sciences of the United States of America*. 2016; **113**:1315-1320
- [88] Sahdev A, Sohaib SA, Jacobs I, Sheperd JH, Oram DH. MR imaging of uterine sarcomas. *AJR*. 2001; **177**:1307-1311
- [89] White MP, Rahimi S, Garely A, Buhl A, Dean RM. Uterine smooth muscle tumors of uncertain malignant potential (STUMP): Review of pathophysiology, classification, diagnosis, treatment, and surveillance. *Journal of Community Health*. 2017; **2**:4-10
- [90] Ip PP, Cheung AN. Pathology of uterine leiomyosarcomas and smooth muscle tumours of uncertain malignant potential. *Best Practice & Research. Clinical Obstetrics & Gynaecology*. 2011; **25**:691-704
- [91] Vahedpoor Z, Khamechian T, Zandi N. Uterine smooth muscle tumors of uncertain malignant potential (STUMP) mistaken with ovarian tumor in a female with polio: A case report. *Journal of Obstetrics Gynecology and Cancer Research*. 2017; **2**:1-3
- [92] Canciani GN, Burbos N, Duncan TJ, Lonsdale R, Nieto JJ. Late presentation of metastatic smooth muscle neoplasm of the uterus with low malignant potential. *Journal of Gynecologic Oncology*. 2012; **23**:69-71

