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Uterine Sarcomas Future Challenges a Systematic Review

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ABSTRACT

According to current bibliography, uterine sarcomas represent a controversial entity among malignant lesions of female genital tract.

Age of the patient, histologic type, grading and staging of the lesion, obesity, smoking and lymph vascular infiltration reflect as most important predisposition factors concerning ultimate therapeutic mapping, especially in women of reproductive age.

After histologic establishment of lesion staging, multidisciplinary approach seems mandatory in order to discover postoperative pathways.

Series of chemotherapy, radiotherapy or hormonal therapy consist corner stone of postoperative treatment in cases of advanced stages with depicted metastatic lesions.

Aim of our study reflects assiduous presentation and depiction of pathophysiologic pathways of such lesions strongly accompanied with proper therapeutic strategy.

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Introduction

According to current bibliography and substantial growth of medical depiction many cases of controversial reflection are capable of being proper diagnosed and assiduously treated.

Uterine sarcomas (US) consist a rare malignant entity originated of mesenchymal parenchyma estimated about 8% of uterine malignancies [1].

Uterine sarcomas classification depends on tissue origin and is being divided into four subcategories.

Leiomyosacromas arising from smooth muscle in myometrium, endometrial stroma sarcomas from endometrial stroma divided into high and low grade, undifferentiated endometrial sarcomas and mixed tumors such as Mixed Mullerial tumors or adenosarcomas [2].

Ultimate scope concerning proper diagnosis and treatment is strongly accompanied with assiduous imaging findings depiction and histologic evaluation of the lesion.

In many cases diagnostic curettage increases the diagnostic potential and confirms the lesion staging. Age of the patient, histologic type, grading and staging of the lesion, obesity, smoking and lymph vascular infiltration reflect as most important redisposition factors concerning ultimate therapeutic mapping, especially in women of reproductive age [3].

Series of chemotherapy, radiotherapy or hormonal therapy consist corner stone of postoperative treatment in cases of advanced stages with depicted metastatic lesions [4].

Optimal diagnosis of US remains in many cases a controversial entity. Abdominal MRI (Magnetic Resonance) along with atomic history and physical examination consists cornerstone regarding distinction of US and other uterine tumors such as endometrial carcinoma [5].

Leiomyomas reflected as well defined hypo signal entities at T2 sequences, comparing with intra-tumoral hyper signal at T1 and T2 sequences in cases of US, depiction very triggering [6]. Namimoto et al, suggested that in T2 sequences concerning abdominal MRI depiction, the mean tumor-myometrium contrast ratio consisted enlarged increased in cases of US comparing with benign lesions such as endometrial myomas [7]. (Table I)

Table I: MRI Features of Uterine Sarcomas, Leiomyoma and Endometrial Sarcoma

	LMS	ESS	UES	AS	Leiomyoma	Endometrial carcinoma
Localization	Myometrium	Generally endometrium; can be located in myometrium	Generally endometrium; can be located in myometrium	Endometrium	Myometrium	Endometrium
Margins	Irregular and ill-defined	Irregular and nodular	Markedly irregular and nodular	Regular and well demarcated	Regular	Regular or irregular
T1 signal	Hypointense and heterogeneous (hemorrhage, calcifications)	Hypointense	Heterogeneous	Predominantly hypointense, heterogeneous	Low-to-intermediate signal; high signal foci – hemorrhagic degeneration	Hypo-to-isointense signal to normal endometrium
T2 signal	Intermediate-to-high signal	Hyperintense and heterogenous; bands of low signal corresponding to preserved myometrium	Heterogeneous (extensive hemorrhage and necrosis)	Multiseptated cystic appearance; can show multiple small hyperintense foci	Low signal (non-degenerated); high signal – cystic, myxoid degeneration	Hyperintense and heterogeneous relative to normal endometrium
Contrast enhancement	Early and heterogenous	Moderate (more intense than endometrial carcinoma) and heterogeneous	Marked (generally more intense than normal myometrium) and heterogeneous	Marked (generally isointense compared to normal myometrium) and heterogeneous	Variable	Hypointense compared to normal myometrium
DWI	Generally more restriction (lower ADC values) than leiomyomas	High signal and low ADC	High signal and low ADC	Low signal (low grade nature)	Variable; generally higher ADC values than LMS	High signal and low ADC

LMS, leiomyosarcoma; ESS, endometrial stromal sarcoma; UES, undifferentiated endometrial sarcoma; AS, adenosarcoma; DWI, diffusion-weighted imaging; ADC, apparent diffusion coefficient.

On the contrary, in cases of degenerated myomas, concerning depiction of T2 sequences, many hyper signal spots have been detected [8]. Sings of potential malignancy and sarcomatous transformation depicted in abdominal MRI estimated central necrosis, formation of angiogenesis and cellular capability [9].

To the best of our knowledge, many cases are extremely controversial and histologic establishment, probably through diagnostic curettage consists final evaluation.

Material and Method

Assiduous systematic review concerning the classification, predisposition factors and pathophysiologic mechanisms of uterine sarcomas. Many conducted studies have been sampled through specific data bases such as PubMed and Cochrane data base.

Future challenges have been registered as well, focusing on patients of reproductive age with potential, concerning the lesion staging, fertility preservation. New therapeutic protocols which have been implemented, did not indicate promising results.

In such controversial issues, multidisciplinary approach seems in many cases mandatory, in order to establish proper therapeutic mapping.

Discussion

Myomas represent the most common benign entity in women of reproductive age [10]. Classification of uterine myomas is focusing on size, anatomic location and clinical features. (Figure I) We present four subtypes of uterine myomas diving into intramural (located inside the uterine cavity), subserosal (under the uterine serosa), pedunculated, cervical and intraligamentary (inside the broad ligament) [11].

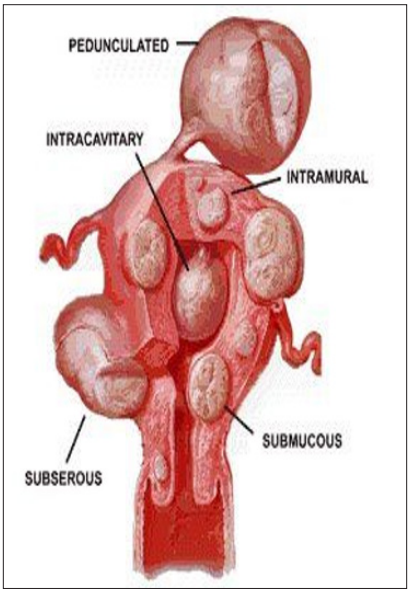

Figure I: Classification of uterine myomas. Indman P, Contemporary OB/GYN, July 8,2011.

Clinical features of uterine myomas reflect vaginal bleeding, abdominal pain with episodes of cystitis or severe bladder infection and defecation due to colon and rectum pressure [12]. All types of uterine myomas arise from smooth uterine muscle with benign origin.

On the contrary, in cases of rapid myomas growth, obesity, diabetes mellitus, malignant transformation, cystic necrosis and degeneration lead to sarcomatous transformation with configuration changes concerning proper therapeutic mapping.

Uterine sarcomas consist rare entity accounting about 10% of uterine malignancies exhibit poor prognosis [13]. After histologic establishment of the lesion, optimal treatment consists surgical intervention with total hysterectomy and bilateral salpigoopherectomy accompanied with series of chemotherapy and radiotherapy.

Many studies have been conducted in order to find molecular pathways such as genomic profiling leading to assiduous information concerning precision achievement, optimal treatment and therapeutic selection [14].

Many histologic types of uterine sarcomas, especially those with severe and extremely poor prognosis are examples of potential genetic mutations.

Along with atomic history, physical examination and imaging findings especially depiction from abdominal MRI, genetic profiling can solve many controversial issues regarding optimal diagnosis and treatment.

Many conducted studies have been indicated cases of loss or function mutations or homozygous establishment of TP53, RB1 and ATRX alterations [15].

On the other hand, increased incidence of BRCA 2 has been detected in cases of uterine sarcomas, pointing the significance of screening tests [16].

Hyperthermic intraperitoneal chemotherapy (HIPEC) represents an alternative noninvasive method approaching advanced stages of ovarian cancer or uterine sarcomas, especially cases of multiple recurrence [17].

Diffusion of peritoneal cavity with chemotherapeutic agents in increased temperature, can lead to satisfactory decrease of residual cancer volume. Hormonal therapy consists ultimate scope in postsurgical mapping in several types of uterine sarcomas [18].

In cases of low grade endometrial stroma sarcomas (LGESS), progestins reflect proper hormonal therapy.

Due to positive progesterone receptors, progestins such as megestrol acetate and medroxyprogesterone depict hormonal mapping in cases of recurrent disease or metastatic lesions of LGESS, regarding their antioestrogenic activity and increase of stroma proliferation [19].

mTOR/AKT/PIEK consists a very important signal regarding the transcription and proliferation of cancer cells.

Focusing on this entity, many studies managed to isolate the control protein responsible for all these activities and produce its inhibitor.
Most well know m TOR inhibitor represents rapamycin or better Sirolimus, adjusting and inhibiting the protein transcription [20].

Unfortunately, in many cases of uterine sarcomas long term studies did not point promising results depicting controversial issues.

On the contrary, many clinical trials haven conducted in order to investigate pathologic response signals concerning adjuvant therapy in cases of metastatic lesions or recurrent malignant entities. (Table II)

Table II: Overview of Clinical Trials with Sarcoma

Reference	Entities	Stage	Trial-phase	Design	Prcgression-free survival	Overall survival
Omura *et al.* [1985]	Uterine sarcoma	I, II	II *n* = 156	adriamycin 60 mg/m² q 21 *versus* observation	no significant difference	73 months *versus* 55 months; *p* = ns
Pautier *et al.* [2012]	Uterine leiomyosarcoma	I, II	II *n* = 81	doxorubicin 50 mg/m² d1, ifosfamide 3 g/m²/day d 1–2 and cisplatin 75 mg/m² d3,q 21 -> RT versus RT	3 year PFS: 51% versus 40%; *p* = 0.0048	3-year OS: 81% versus 69%; *p* = 0.41
Hensley *et al.* [2013]	Uterine leiomyosarcoma	I, II	II *n* = 47	gemcitabine 900 mg/m² days 1 and 8 plus docetaxel 75 mg/m² d8 -> doxorubicin 60 mg/m² q21	2-year PFS: 78%	
Harter *et al.* [2011]	Uterine/ ovarian sarcoma	I–IV and relapse	II *n* = 40	Pegylated liposomal doxorubicin 40 mg/m² plus carboplatin AUC 6 q28	8.6 months	29.5 months
Demetri *et al.* [2009]	Lipo-/leiomyo-sarcoma	relapsed	II *n* = 270	trabectidin 1,5 mg/m²(q21, 24 h) versus trabectidin 0.58 mg/m² (q1W, 3 h)	3.3 months versus 2.3 months; *p* = 0.0418	13.9 months versus 11.8 months, *p* = 0.1920
Maki *et al.* [2007]	Soft tissue sarcoma	metastatic	II *n* = 122	gemcitabine 900 mg/m² days 1, 8 plus docetaxel 75 mg/m² d8, q21 *versus* gemcitabine 1,200 mg/m² (1+8,q3w)	6.2 months versus 3.0 months; *p* = 0.02	17.9 months versus 11.5 months; *p* = 0.03
Garcia del Muro *et al.* [2010]	Soft tissue sarcoma	advanced	II *n* = 113	dacarbacine 500 mg/m², gemcitabine 1,800 mg/m²(q2w) versus dacarbacine 1,200 mg/m² (q21	16.3 months versus 8.2 months; *p* = 0.014.	4.2 months versus 2 months; *p* = 0.005
Van der Graaf *et al.* [2012]	Soft tissue sarcoma	metastatic	III *n* = 362	pazopanib 800 mg once daily versus placebo	4.6 months versus 1.6 months; *p* < 0.0001	12.5 months versus 10.7 months; *p* = 0.25
Chawla *et al.* [2011]	Soft tissue + bone sarcoma	relapsed, maintenance	III *n* = 711	ridaforolimus 12.5 mg (d1-d5,q2w) versus placebo	14.5 versus 17.7 weeks; *p* = 0.0001	21.4 months versus 19.2 months; *p* = ns
Schöffski *et al.* [2011]	Soft tissue sarcoma	metastatic	II *n* = 128	eribulin 1.4 mg/m² (d1-d8,q21)	2.1–2.6 months (depending on his:ologic subtype)	6 months OS: 52.9–86.8% months (see above)

ns, not significant; OS, overall survival; PFS, progression-free survival.

To the best of our knowledge, uterine sarcomas consist a controversial and in many cases very difficult entity, being depicted only through histopathologic evaluation.

Definitely, more studies must be conducted in order to establish primary diagnosis and assiduous therapeutic strategy.

Disclosure of Interest
Author declares any financial interest with respect to this manuscript.

Conclusion
Uterine sarcomas represent a rare entity, which in many cases can lead to poor prognosis affecting overall survival and patient's quality of life.

Optimal treatment depends on imaging findings depiction, especially abdominal MRI. Multidisciplinary approach seems mandatory in order to establish proper therapeutic mapping. Future therapeutic management reflects promising signals towards optimal target therapy.

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