ENDOMETRIAL STROMAL TUMORS: AN OBSERVATIONAL STUDY

STUDY PROTOCOL

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Background and Rationale

Uterine sarcomas are a rare heterogeneous group of tumors of mesenchymal origin, accounting for <10% of uterine malignancies **(1)** as well as of all soft tissue sarcomas **(2).**

Endometrial stromal tumors are rare uterine neoplasm of endometrial stromal origin that account for less than 2% of all uterine tumors **(3).** The newly released 2014 WHO classification system recognizes four categories: endometrial stromal nodule (ESN), low-grade endometrial stromal sarcoma (LGESS), high-grade endometrial stromal sarcoma (HGESS) and undifferentiated uterine sarcoma (UUS) **(4).**

- Endometrial stromal nodule is a rare benign tumor of the uterus. The two largest series published to date showed no recurrences after a follow-up period of up to 16 years and 17.8 years, respectively. **(5, 6).** It is a well-circumscribed lesion of variable size, non or minimally infiltrating the myometrium, which may occur as an intramural mass or as a polypoid mass protruding into the endometrial cavity **(4)**. Hysterectomy is the gold standard in cases of ESN or low-grade endometrial stromal tumors, considering their theoretic ability to infiltrate and become malignant **(7)**. Anecdotal evidence is available on hormonal therapy for endometrial stromal nodules, which may allow preserving the reproductive function. A few case reports have shown promising results, using fertility-preserving treatments such as local excision, endocrine therapy, and photodynamic therapy in young women with low-grade endometrial stromal sarcomas **(8, 9).**

- Low-grade endometrial stromal sarcoma is the second most common uterine malignant mesenchymal tumor. It is a slowly growing lesion with an indolent clinical course exhibiting infiltrative growth into the myometrium and/or lymphovascular spaces. LGESS exhibit a rearrangement of the JAZF1 gene in approximately 60% of cases. It is marked by multiple and/or late relapses, some occurring as late as 20 years after hysterectomy. Stage is the most important prognostic factor: the 5-year disease specific survival for stages I and II is 90%, compared to 50% for stage III and IV **(4)**. Hysterectomy with bilateral salpingo-oophorectomy is standard treatment for localized ESS **(7, 8)** even if leaving the ovaries in situ does not worsen survival, so that it could be proposed to young women **(9, 10-13)** Morcellation should be avoided because of the risk of spreading **(10, 11).** Systematic lymphadenectomy does not improve the outcome **(14-15).** There have been several reports on the use of adjuvant hormonal therapy but its prognostic efficacy over starting it at the time of relapse is unproven **(16, 17, 18).** Although in the lack of evidence, repeat surgery for recurrent disease looks beneficial, considering the indolent course and the hormone sensitivity of the disease **(19, 20)**. Case reports and small series have provided evidence for the efficacy of hormonal therapy in the advanced disease, and indeed it is the main systemic treatment for ESS. Low esponse rates to chemotherapy have been reported, and chemotherapy should only be prescribed when the armamentarium of hormonal therapies is exhausted **(21-25).** The role of radiotherapy is limited: a modest benefit in locoregional control can be achieved without survival improvement, so that radiation therapy may be considered in the presence of local risk factors after surgery or as a palliative treatment when systemic treatment and/or surgery are not able to reduce symptoms **(26).**

- High-grade endometrial stromal sarcoma is a malignant tumor of endometrial stromal derivation with high-grade, uniform round-cell morphology. Currently, the term HGESS is reserved for those rare stromal sarcomas exhibiting this kind of morphology and harboring a t(10;17)(q22;p13) rearrangement with YWHAE/NUTM2A/B gene fusion. HGESS exhibits a relatively distinctive immunophenotype that includes overexpression of CyclinD1 and absence of expression of ER and PR. In comparison to LGESS, patients present with earlier and more frequent recurrences, with frequent extrauterine disease at initial presentation. Prognosis of YWHAE-rearranged cases seems to be intermediate between that of LGESS and UUS **(4)**. There are no prospective or retrospective clinical trials to investigate treatment in HGESS, because of this new classification.

- Undifferentiated uterine sarcoma is a high-grade mesenchymal malignancy arising from the endometrium or the myometrium lacking specific differentiation, often exhibiting high degree of nuclear pleomorphism. UUS tends to exhibit highly complex karyotypes. This is a highly aggressive tumor, typical of elderly patients. More than 60% of patients present with metastatic disease **(4).** The standard treatment for UUS is total hystero-oophorectomy **(7, 8, 14, 15**). Due to its aggressiveness, UUS is often treated with chemotherapy as an adjuvant, though in the lack of studies. The Gynecologic Oncology Group reported a response rate of 33% among 21 patients treated with Ifosfamide in a phase II study **(27).**

Given the many open questions regarding the natural history of these diseases, their pathologic classification and their best treatment, considering their rarity (particularly of some entities), we set up this observational study as a global effort aimed to clarify the open questions. This study focuses on a rare subgroup within the rare family of uterine sarcomas; a global effort would be highly required in order to understand more about their biology, their natural history and antitumor activity of different treatment options.

Objectives

This project has the following objectives:

- to provide new data on the natural history of endometrial stromal tumors;
- to highlight some main issues in pathologic diagnosis of these tumors and their classification;
- to further elucidate the molecular features of endometrial stromal tumors;
- to collect data about the aromatase inhibitors and other medical therapies used in endometrial stromal tumors.

Study Design

This is an observational retrospective and prospective study on consecutive patients with endometrial stromal tumors seen at participating institutions.

All the patients with a diagnosis of Endometrial Stromal Tumor (EST) according to the WHO classification 2003 or 2014 will be included in this study (low grade endometrial stromal sarcoma, endometrial stromal nodule and undifferentiated stromal sarcomas according to the WHO 2003; endometrial stromal nodule (ESN), low-grade endometrial stromal sarcoma (LGESS), high-grade endometrial stromal sarcoma (HGESS) and undifferentiated uterine sarcoma (UUS) according to the WHO 2014).

The study is expected to close in 2022, but can be amended in order to prolong its duration.

Proper sharing of pathologic samples will be arranged: in all cases, diagnosis will be centralized and reviewed by an expert pathologist (Prof. Angelo Paolo Dei Tos University of Padoa)

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