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Review Article

Uterine sarcoma Part II—Uterine endometrial stromal sarcoma: The TAG systematic review

Huann-Cheng Horng [a, b, 1], Kuo-Chang Wen [a, b, 1], Peng-Hui Wang [a, b, c, *], Yi-Jen Chen [a, b], Ming-Shyen Yen [a, b], Heung-Tat Ng [a, d], The Taiwan Association of Gynecology Systematic Review Group[e, 2]

[a] Department of Obstetrics and Gynecology, Taipei Veterans General Hospital, Taipei, Taiwan
[b] Department of Obstetrics and Gynecology, National Yang-Ming University School of Medicine, Taipei, Taiwan
[c] Department of Medical Research, China Medical University Hospital, Taichung, Taiwan
[d] Foundation of Female Cancer, Taipei, Taiwan
[e] The Taiwan Society of Gynecology Systematic Review Group at the Taipei Veterans General Hospital, Taipei, Taiwan

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ABSTRACT

Endometrial stromal tumors are rare uterine tumors (<1%). Four main categories include endometrial stromal nodule, low-grade endometrial stromal sarcoma (LG-ESS), high-grade endometrial stromal sarcoma (HG-ESS), and uterine undifferentiated sarcoma (UUS). This review is a series of articles discussing the uterine sarcomas. LG-ESS, a hormone-dependent tumor harboring chromosomal rearrangement, is an indolent tumor with a favorable prognosis, but characterized by late recurrences even in patients with Stage I disease, suggesting the requirement of a long-term follow-up. Patients with HG-ESS,

* Corresponding author. Department of Obstetrics and Gynecology, Taipei Veterans General Hospital, 201, Section 2, Shih-Pai Road, Taipei, Taiwan.
E-mail addresses: phwang@vghtpe.gov.tw, phwang@ym.edu.tw, pongpongwang@gmail.com (P.-H. Wang).

[1] Both authors contributed equally.

[2] The Taiwan Society of Gynecology Systematic Review Group includes the following members: Yen-Hou Chang, Yi Chang, Hsiang-Tai Chao, Kuan-Chong Chao, Chi-Mu Chuang, Chi-Hong Ho, Chen-Yu Huang, Zhi-Chen Hung, Ling-Yu Jiang, Hei-Yu Lau, Hsin-Yang Li, Chi-Yao Lin, Chia-Hao Liu, Pi-Lin Sun, Nae-Fang Twu, Hua-Hsi Wu, and Hann-Chin Yu, Department of Obstetrics and Gynecology, Taipei Veterans General Hospital and National Yang-Ming University, Taipei, Taiwan. Dr. Fong-Yuan Ju, Department of Family Medicine, Taipei Veterans General Hospital, Taipei, Taiwan. Dr. Chih-Ping Tsai, Emergency Department, Taipei Veterans General Hospital, Taipei, Taiwan. Ms. Wen-Hsun Chang, Yen-Mei Hsu, Na-Rong Lee, Department of Obstetrics and Gynecology, and Department of Nursing, Taipei Veterans General Hospital and National Yang-Ming University, Taipei, Taiwan. Dr. Chih-Yao Chen, Dianthus MFM Center Minquan, Dianthus MFM Group, and National Yang-Ming University, Taipei, Taiwan. Drs. Ting-Chen Chang, Wen-Chun Chang, Chii-Hou Chen, Ruey-Jian Chen, Song-Nan Chow, Yih-Ron Lien, Bor-Ching Sheu, Pao-Ling Torng, and Men-Luh Yen, Department of Obstetrics and Gynecology, National Taiwan University Hospital and National Taiwan University, Taipei, Taiwan. Dr. Wen-Ling Lee, Department of Medicine, Cheng-Hsin General Hospital, Taipei and Department of Nursing, Oriental Institute of Technology, New Taipei City, Taiwan. Dr. Kuan-Chin Wang, Department of Nursing, Oriental Institute of Technology, New Taipei City, Taiwan. Drs. Chih-Long Chang, Chih-Ping Chen, Jen-Ruei Chen, Tze-Chien Chen, Jian-Pei Huang, Ming-Chao Huang, and Yeou-Lih Wang, Department of Obstetrics and Gynecology, Mackay Memorial Hospital, Taipei, Taiwan. Drs. Cheng-Chang Chang, Jah-Yao Liu, Her-Young Su, Yu-Chi Wang, and Mu-Hsien Yu, Department of Obstetrics and Gynecology, Tri-Service General Hospital and National Defense Medical Center, Taipei, Taiwan. Dr. Lee-Wen Huang and Kok-Min Seow, Department of Obstetrics and Gynecology, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan. Drs. Tsung-Hsuan Lai, and Fa-Kung Lee, Department of Obstetrics and Gynecology, Cathay General Hospital, Taipei, Taiwan. Dr. Ching-Hui Chen, Department of Obstetrics and Gynecology, Taipei Medical University Hospital and Taipei Medical University, Taipei, Taiwan. Dr. Ben-Shian Huang, Department of Obstetrics and Gynecology, National Yang-Ming University Hospital, Ilan, Taiwan. Drs. Sheng-Mou Hsiao, Hsu-Dong Sun, and Wen-Yih Wu, Department of Obstetrics and Gynecology, Far Eastern Memorial Hospital, New Taipei City, Taiwan. Dr. Sen-Wen Teng, Department of Obstetrics and Gynecology, Cardinal Tien Hospital-Hsintien and Fu Jen Catholic University, New Taipei City, Taiwan. Drs. Kuo-Hu Chen, and Jeng-Hsiu Hung, Department of Obstetrics and Gynecology, Taipei Buddhist Tzu Chi General Hospital, New Taipei City, Taiwan. Drs. Hung-Cheng Lai, and Chiou-Chung Yuan, Department of Obstetrics and Gynecology, Taipei Medical University-Shuang Ho Hospital, New Taipei City, Taiwan. Dr. Ching-Hung Hsieh, Department of Obstetrics and Gynecology, Clinic of Fu Jen Catholic University, New Taipei City, Taiwan. Dr. Chin-Jung Wang, Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital, and Chang Gung University, Taoyuan, Taiwan. Dr. Shing-Jyh Chang, Department of Obstetrics and Gynecology, Mackay Memorial Hospital, Hsinchu, Taiwan. Drs. Man-Jung Hung, Shih-Tien Hsu, Yu-Min Ke, Chien-Hsing Lu, and Lou Sun, Department of Obstetrics and Gynecology, Taichung Veterans General Hospital, Taichung, Taiwan. Drs. Wei-Chun Chang, Yao-Ching Hung, and Wu-Chou Lin, Department of Obstetrics and Gynecology, China Medical University Hospital and China Medical University, Taichung, Taiwan. Dr. Po-Hui Wang, Department of Obstetrics and Gynecology, Chung-Shang General Hospital and Chung-Shang Medical University, Taichung, Taiwan. Drs. Tze-Ho Chen, Department of Obstetrics and Gynecology, Changhua Christian Hospital, Changhua, Taiwan. Dr. Yiu-Tai Li, Department of Obstetrics and Gynecology, Kuo General Hospital, Tainan, Taiwan. Dr. Meng-Hsing Wu, Department of Obstetrics and Gynecology, National Cheng Kung University Hospital and National Cheng Kung University, Tainan, Taiwan. Dr. Kuo-Feng Huang, Department of Obstetrics and Gynecology, Chi-Mei Medical Center, Tainan, Taiwan. Dr. Hung-Chun Fu, Department of Obstetrics and Gynecology, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, and Chang Gung University, Taoyuan, Taiwan. Drs. San-Nung Chen, An-Jen Chiang, Ju-Yueh Li, Li-Te Lin, Hsiao-Wen Tsai, and Kuan-Hao Tsui, Department of Obstetrics and Gynecology, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan.

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undifferentiated sarcoma
uterine sarcoma
uterus

based on the identification of *YWHAE-NUTM2A/B* (*YWHAE-FAM22A/B*) gene fusion, typically present with advanced stage diseases and frequently have recurrences, usually within a few years after initial surgery. UUS is, a high-grade sarcoma, extremely rare, lacking a specific line of differentiation, which is a diagnosis of exclusion (the wastebasket category, which fails to fulfill the morphological and immunohistochemical criteria of translocation-positive ESS). Surgery is the main strategy in the management of uterine sarcoma. Due to rarity, complex biological characteristics, and unknown etiology and risk factors of uterine sarcomas, the role of adjuvant therapy is not clear. Only LG-ESS might respond to progestins or aromatase inhibitors.

Introduction

Endometrial stromal tumors (EST) account for less than 1% of all uterine tumors [1], which can be divided into four main categories, currently recognized by the World Health Organization, including endometrial stromal nodule (ESN); endometrial stromal sarcoma (ESS), low-grade (LG-ESS); endometrial stromal sarcoma, high-grade (HG-ESS); and uterine undifferentiated sarcoma (UUS) [2]. Endometrial stromal tumors, especially LG-ESS, represent the second most common category of mesenchymal uterine tumors (second to uterine leiomyosarcoma [uLMS]) [3]. A stage system, similar to the uLMS, has been introduced in the previous issue of the Taiwanese Journal of Obstetrics and Gynecology [3]. In brief, a tumor limited to the uterus is Federation International Gynecology and Obstetrics (FIGO) I [<5 cm in diameter (IA) and ≥5 cm (IB)]; a tumor limited to pelvic cavity but extended beyond the uterus is II [an adnexal involvement (IIA) and other pelvic cavity invasion (IIB)]; tumor outside the pelvic cavity is III [positive retroperitoneal lymph node metastases (IIIC)]; tumor invaded to bladder and rectum is IVA, and distant metastases is IVB [3].

To distinguish benign and malignant is based on the type of tumor margin, although it is sometimes not easy to define the category. The following key points may help to define the benign and malignant ESS (Table 1). In general, a well-circumscribed tumor is diagnosed as benign stromal nodules, whereas those exhibiting myometrial invasion and lymphovascular space (LVS) invasion are malignant [3]. Occasionally, benign ESN might have focal irregularity of the border and form finger-like or nodular projections. However, these unusual presentations should not extend >3 mm from the main tumor mass. As shown above, total absence of LVS invasion of these tumors (ESN) is considered a benign tumor [2].

Table 1
Useful key factors to distinguish benign and malignant endometrial stromal neoplasms.

Identify benign ESN
(1) Adequate sampling of the border/surrounding myometrium (tumor −myometrial interface)
(2) The projections into the adjacent myometrium <3 mm from the main tumor mass
(3) The projections into the adjacent myometrium <3 in number
(4) Absence of vascular invasion
Identify HG-ESS
(1) In a tumor with marked mitotic activity (>20−30 mitoses/10 high-power fields)
(2) Loss of hormone receptors
(3) Additional sampling to exclude the possibility of HG-ESS for fibrous or myxoid appearance
(4) Negative for smooth muscle markers
(5) Diffusely positive for c-kit but negative for DOG1
(6) Diffusely positive for cyclin D1 but negative for EMA and/or broad spectrum cytokeratin
Identify UUS
(1) Lacking smooth muscle or endometrial stromal differentiation
(2) Destructive myomatrial infiltration, a fascicular or patternless growth pattern, highly pleomorphic cells (nondescript cells)
(3) Positive CD10 immunoactivity
(4) Lacking the defining genetic rearrangement (complex karyotypes and genomic gains and losses without specific translocations)

CD10 = cluster of differentiation 10; DOG1 = Discovered On Gastrointestinal stromal tumors protein 1; EMA = Epithelial Membrane Antigen; ESN = endometrial stromal nodule; HG-ESS = high-grade endometrial stromal sarcoma; UUS = uterine undifferentiated sarcoma.

ESN

ESN is benign. The tumor is usually presented with abnormal vaginal bleeding or as an incidental finding in a hysterectomy specimen performed for other reasons [4]. Grossly, ESN is a well-circumscribed tumor with a fleshy and soft yellow to tan cut surface and can be found as an intramural mass or as a polypoid tumor protruding into the endometrial cavity [4]. Microscopically, ESN is expansible in nature without myometrial invasion and absence of LVS invasion. An immunohistochemical profile did not help to distinguish ESN and LG-ESS, suggesting that conventional morphological and histological features are important for the diagnosis of ESN [4].

LG-ESS

Overview

LG-ESS affects women primarily in the perimenopausal age group and more than half of patients were diagnosed premenopausally [1,2]. The most commonly presented symptoms or signs were abnormal uterine bleeding, pelvic pain, and dysmenorrhea [1,2]. Nearly one-third of patients present with symptoms or signs related to extrauterine spread and one-fourth of patients are asymptomatic [1,2]. The most frequent site of extrauterine pelvic extension is the ovary [1]. Extrauterine pelvic extension of LG-ESS is also frequently associated with endometriosis [4]. LG-ESS might manifest as an endometrial polyp, such that endometrial biopsy is more likely to be diagnostic [5]. Obesity, diabetes, younger age at menarche, and tamoxifen intake are associated with increased risk of LG-ESS [5].

Pathology

Grossly, LG-ESS may be submucosal or intramural, usually with ill-defined borders and wormlike permeation within the myometrium and parametrial tissue [6]. LG-ESS can form multiple poorly defined, frequently coalescent, fleshly tan to yellow, soft nodules within the endometrium and myometrium. LG-ESS appears paler, firmer and gray if the tumor underwent smooth muscle differentiation. Microscopically, LG-ESS shows extensive permeation of the myometrium as irregular islands with frequent LVS invasion [5], and the “tongue-like” patterns of myometrial and LVS invasion are

classical histological features, which can distinguish LG-ESS from ESN [6]. LG-ESS cells have bland nuclear features with monotonous oval to spindle nuclei that resemble proliferative phase endometrial stroma, with low mitotic activity (<5/10 high power fields), and without necrosis [2].

Immunohistochemically, LG-ESS is a typical positive cluster of differentiation 10 (CD10), vimentin, actins, WT-1, IFITM1, estrogen receptor [(ER), only alpha isoform], androgen receptor, and progesterone receptor (PR) [2]. In fact, it is occasionally hard to make an accurate diagnosis of LG-ESS. The differential diagnosis should include gland-poor adenomyosis, cellular leiomyoma, intravascular leiomyomatosis, uLMS with extensive intravascular component, HG-ESS, uterine tumor resembling ovarian sex-cord tumor, perivascular epithelioid cell tumor and gastrointestinal stromal tumor [6]. A recent article was conducted to evaluate an immunohistochemical panel differentiating ESS from uLMS and leiomyoma and found that the combination of ER(+)/PR(+)/CD10(+)/GEM(−)/h-caldesmon(−)/transgelin(−) could predict ESS versus uLMS with an area under the curve predictive value of 0.872 (95% confidence interval [CI] 0.784–0.961, $p < 0.0001$) and the combination of ER(+)/PR(+)/CD10(+)/h-caldesmon(−)/transgelin(−) could predict LG-ESS from low-grade uLMS with an area under the curve predictive value of 0.914 (95% CI 0.832–0.995, $p < 0.0001$) [6], suggesting that it is important to use a panel of immune-stains that includes CD10 and at least two smooth muscle markers (for example, desmin, h-caldesmon, smooth muscle heavy chain myosin, HDAC8) as there is no single marker that is specific for ESS [5,7].

The majority of LG-ESS harbors chromosomal rearrangement [2,6]. The most common genetic abnormality is t(7;17)(p15;q21), resulting in the fusion of *JAZF1* (juxtaposed with another zinc finger gene 1) and *SUZ12*(*JJAZ*1) genes (polycomb repressive Complex 2 subunit) at 7p15 and 17q21, respectively [2,6]. The reported frequency of *JAZF1-JJAZ*1 fusion is nearly 50% in LG-ESS cases [6]. The second most frequent abnormality is t(6;7)(p21;p15), resulting in the fusion of *JAZF1* and *PHF1* genes (Cys4-His-Cys3 motif in the plant homeodomain (PHD) finger Protein 1) at 7p15 and 6p21, respectively [2,6]. Much less common genetic abnormality, including that the *PHF1* gene at 6p21 could also fuse with *EPC1* (enhancer of polycomb 1) at 10p11 and *MEAF6* at 1p34 [2,6], or *ZC3H7-BCOR* and *MBTD1-CXorf67* have been also reported [8,9]. *PHF1* genetic rearrangement might result in sex cord-like differentiation in LG-ESS [2], which might make a pitfall to distinguish LG-ESS from a uterine tumor resembling an ovarian sex-cord tumor. Table 2 shows the summary of common genetic abnormalities of LG-ESS.

Table 2
Common genetic alterations in ESS.

LG-ESS
t(7;17)(p15;q21) → the fusion of JAZF1 and SUZ12(JJAZ1) genes at 7p15 and 17q21, respectively
t(6;7)(p21;p15) → the JAZF1–PHF1 fusion gene at 7p15 and 6p21, respectively
t(6;10)(p21;p11) → the PHF1–EPC1 fusion gene at 6p21 and 10p11, respectively
t(1;6)(p34;p21) → the PHF1–MEAF6 fusion gene at 6p21 and 1p34, respectively
t(X;22)(p11;q13) → the ZC3H7B–BCOR fusion gene at Xp11 and 22q13, respectively
t(X ;17) (p11.2;q21.33) → the MBTD1-CXorf67 fusion gene at Xp11.2 and 17q21.33, respectively
HG-ESS
t(10;17)(q22;p13) → the YWHAE-FAM22 (NUTM2AB) fusion gene at 10q22 and 17 p13, respectively

ESS = endometrial stromal sarcoma; HG-ESS = high-grade endometrial stromal sarcoma; LG-ESS = low-grade endometrial stromal sarcoma.

Image

The prediction of malignancy is of utmost importance; however, uterine sarcoma could be predicted by clinical characteristics [10–12]. In addition, data on the prediction of uterine sarcoma by ultrasound examination are scare and only limited information on their ultrasound features has been reported to date. Based on investigating 10 patients with LG-ESS, ultrasound findings of LG-ESS are variable with regard to the location, margin, and configuration of the lesion [13]. Among these ultrasound findings, multiseptated cystic areas and multiple small areas of cystic degeneration are most common [13]. Magnetic resonance image may have a developing role in the assessment of uterine masses. LG-ESS may appear as a polypoid endometrial mass, with low signal on T1-weighted images and heterogeneously increased high T2 signal [11]. These malignant tumors (LG-ESS, HG-ESS, and UUS) typically have myometrial invasion, either sharply demarcated or in a more diffuse and destructive manner (especially for UUS) [11]. ESS has a tendency for lymphovascular invasion, showing worm-like extension bands of low signal intensity within areas of myometrial involvement on T2-weighted image, similar to a bag of worms, corresponding to preserved bundles of myometrium [11]. Contrast-enhancement is moderate and often heterogeneous [11]. However, these features are neither specific nor sensitive for the diagnosis of malignant or benign lesions. Sumi et al [14] used contrast ratio of signal intensity in T2-weighted images for the areas of lowest, highest, and main signal intensity of each tumor as well as contrast-enhanced ratio for the main solid part of each tumor in contrast-enhanced T1-weighted images to perform quantitative assessment for distinguishing benign and malignant uterine tumors, and found that the contrast-enhanced ratio for ESS showed the most homogeneous enhancement; however, the reproducibility needs further confirmation.

Treatment

LG-ESS is an indolent tumor with a favorable prognosis, but characterized by late recurrences even in patients with Stage I disease, suggesting the requirement of a long-term follow-up [1,15,16]. In addition, in the literature review, recurrent LG-ESS can occur 10–20 years after the initial diagnosis [17]. Stage is the most significant prognostic factor, and 5-year overall survival (OS) rate for Stage I patients is more than 90%, but decreased to 50% for Stage III and IV [1,16]. The most common sites for recurrence are pelvis and abdomen [1].

Surgery is the most important procedure in the management of patients with LG-ESS. Hysterectomy and bilateral salpingo-oophorectomy (BSO) is a preferred procedure. LG-ESS is often sensitive to hormones, therefore, BSO may play an important role to cease the hormone production. The benefits of BSO for women with LG-ESS can be further supported indirectly by the following observation: (1) withdrawing estrogen replacement therapy and tamoxifen can result in stable disease of women with LG-ESS [17,18]; (2) aromatase inhibitors (AIs) might have partial responses and even achieve complete responses in these women with LG-ESS [18–20]; high-dose progestins and antiprogestin agents were the key component in the management of these LG-ESS patients [17,20]. Therefore, hormone replacement therapy for menopausal syndrome is contraindicated, and progestins (megestrol and medroxyprogesterone acetate) or AIs are the therapeutic choice in the management of women with LG-ESS, especially acting as post-operative adjuvant therapy for residual or recurrent diseases [20].

A Phase II study showed that single-agent mifepristone (RU-486) in the management of LG-ESS could result in a stable disease rate of 50% [17]. There are two categories of AIs available in the market, based on their chemical structure [21]. Type I AIs are

steroidal inhibitors and bind aromatase irreversibly by covalent bonds, while Type II AIs are nonsteroidal inhibitors that bind reversibly and covalently with aromatase [21]. Exemestane is a Type I AI whereas letrozole and anastrozole are Type II AIs [22]. One retrospective study evaluated the effect of AIs in the management of 16 ESS patients, and found an overall response rate of 67% (60% partial response rate, 7% complete response rate) and a 20% stable disease rate in these patients [23].

Not all patients can receive completely destructive surgery, such as hysterectomy and BSO, even though the procedure is highly recommended as the therapeutic choice in the management of women with LG-ESS. These women might be young, and might not have completed their family. Therefore, conservative treatment to maintain the reproductive function is the aim of these women [24–27]. The question is raised—is it possible to preserve the reproductive function for these women with LG-ESS? In fact, a similar concept has been well-accepted in the management of endometrial cancer [28–30], which fulfills the following criteria: (1) younger than 40 years; (2) having a strong desire to preserve fertility; (3) having a need to give birth; (4) having the ability to give birth; (5) having to get pregnant immediately after tumor regression; (6) pathologically-confirmed LG-ESS; (7) limited to 2009 FIGO IA stage or highly selected IB; (8) having a good compliance; (9) no contraindication for high-dose progestin or other hormone therapies.

Due to similar response to progestin treatment in both Type I-Grade I endometrial endometrioid carcinoma and LG-ESS, it is reasonable to maintain part or total reproductive function [30], such as ovary and/or uterus for these relatively indolent diseases [31]. Two small series reported in China evaluated 5 and 19 patients with LG-ESS, who received conservative surgeries of local resection of the tumors with uterine reconstruction [26] or myomectomy [32], respectively. The patients then received megestrol acetate (160–320 mg/day) or gonadotropin-releasing hormone agonist for 5–6 months [26], or no treatment (due to pathological misdiagnosis) [32]. During the follow-up, three uterine reconstruction patients and five myomectomy patients finally had a successful birth [26,32]; suggesting that fertility-sparing treatment might be suitable in highly selected younger women with LG-ESS, especially for those whose lesion showed a clear border and could be removed by complete *en bloc* resection. Of course, adjuvant endocrine therapy, especially the use of high-dose progestins, is highly recommended for 6 months after the operation. Although the above-mentioned report is promising [26], one report in Japan showed the fatal case of ESS 10 years after fertility-sparing management [27]. In addition, all 19 patients who underwent myomectomy for LG-ESS did have recurrence [32], suggesting that hysterectomy and BSO may be still a better choice for women who have completed their families; and a delayed hysterectomy and BSO for women who have been treated with fertility-sparing therapy but subsequently finish their families might be needed.

Secondary to the indolent nature of the LG-ESS and the effectiveness of hormonal treatment, complete cytoreduction, even if considered radical cytoreduction, is recommended in LG-ESS [32–34]. In regard to surgical staging in patients with LG-ESS, several studies have investigated the utility of lymph node dissection in these LG-ESS patients. The reported lymphatic involvement of ESS ranged from 7% to 9% [16,35,36]. Although removal of enlarged lymph nodes may be one of a completely cytoreductive procedure, a survival benefit has not been proven in the literature [37]. Two studies evaluated 831 and 384 patients, respectively, and found that lymphadenectomy did not provide the survival benefits for these patients with LG-ESS [16,35]. In addition, one Chinese study showed that no benefit was found for lymphadenectomy regarding either recurrence-free survival or overall survival [32]. Furthermore, one study further found that there was no statistically significant differences of 5-year survival rate between node-positive LG-ESS and node-negative LG-ESS (86% vs. 95%) [35]. All may make interpretation of the value of lymphadenectomy difficult in LG-ESS. Therefore, some suggested that distant resection must be considered individually in the setting of metastatic diseases of women with LG-ESS [38].

Recurrence

Although LG-ESS is an indolent tumor with a favorable prognosis, recurrence rates might be higher, up to the range between 36% and 56% [36]. Recurrence occurs even in early-stage LG-ESS with a median time to recurrence of 65 months [39]. The most common sites for recurrence are abdomen and pelvis in 40–50% of cases; however, 25% of current cases are found in the lung [40]. Because of relatively limited and focused areas of recurrence, it is possible to consider the role of aggressive and intensive *en-bloc* metastatectomy, similar to the treatment for other gynecological malignancies [41,42]. For example, Thomas et al [34] reported that two of three patients with recurrent LG-ESS had successfully managed by complete surgical resection and postoperative adjuvant therapy and these two patients had a long-term survival. Other reports also showed four of six patients with recurrent LG-ESS who underwent secondary cytoreduction had a mean follow-up of 16-year survival [33]. However, the reported cases are too rare; therefore, it is difficult to ascertain the benefit of such therapy [38].

HG-ESS

One of the main highlights of the 2014 World Health Organization classification of uterine mesenchymal tumors is the reintroduction of HG-ESS as a distinct entity, based on the identification of *YWHAE-NUTM2A/B* (*YWHAE-FAM22A/B*) gene (tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, epsilon isoform- family with sequence similarity 22) fusion (Table 2), which gives rise to a 14-3-3 *oncoprotein*, as a recurrent event in this more malignant subgroup of tumors (Table 1), which is intermediate between LG-ESS and UUS [2,4,43–47]. Unlike LG-ESS, patients with HG-ESS have earlier and more frequent recurrences (often <1 year) and are more likely to die of disease [46].

Pathology

Grossly, HG-ESS may be a polypoid intracavitary mass, or intramural mass, poorly circumscribed with myometrial invasion [1,2]. On sectioning of HG-ESS, the tumor is fleshy with extensive areas of hemorrhage and necrosis [1,2]. HG-ESS often contains both morphologically low- and high-grade areas appreciable on low power examination as hyper- and hypocellular areas (biphasic) [2,4]. Microscopically, the tumor consists predominantly of high-grade round, epithelioid cells with scant to moderate amounts of eosinophilic cytoplasm, containing round to oval vesicular nuclei (4–6 times the size of a lymphocyte) with irregular nuclear contours and nucleoli. HG-ESS has an extensive permeative growth finger-like or tongue-like myometrial and vascular invasion, and forms nested and corded growth with delicate curvilinear vasculature [2,4]. Mitotic activity is strikingly apparent and often greater than 10 per 10 high-power fields. Necrosis is usually present.

Immunohistochemically, HG-ESS is typical negative CD10, ER, and PR, but shows strong diffuse cyclin D1 immunoreactivity (>70% nuclei) and typically c-kit positive immunoactivity but Discovered On Gastrointestinal stromal tumors protein 1 (DOG1) negative staining [1,4]. CD 117 is often positive in HG-ESS [2]. However, the

above-mentioned immunoactivity might be absent in the "hypocellular" areas in the HG-ESS; careful evaluation is critical. Nucci [2] emphasized the following key points to hint the possibility of diagnosed HG-ESS, including (1) in a tumor with marked mitotic activity (>20–30 mitoses/10 high-power fields); (2) loss of hormone receptors; (3) additional sampling to exclude the possibility of HG-ESS for fibrous or myxoid appearance; (4) negative for smooth muscle markers; (5) diffusely positive for c-kit but negative for DOG1; (6) diffusely positive for cyclin D1 but negative for Epithelial Membrane Antigen (EMA) and/or broad spectrum cytokeratin (Table 1).

Treatment

Little is known about the natural course, prognostic factors and optimal treatment of HG-ESS [47]. In addition, most reports described the patients without further differentiating LG-ESS, HG-ESS, and UUS. Furthermore, patients with HG-ESS typically present with advanced stage diseases (FIGO II–IV) and frequently have recurrences, usually within a few years after initial surgery [1]. Median progression-free survival (PFS) and OS ranged from 7 to 11 months and 11 to 23 months, respectively [47]. Data from the Surveillance, Epidemiology, and End Results database between 1988 and 2005 evaluated 464 patients with ESS who were treated with at least a hysterectomy and information on tumor size, and identified 96 patients with HG-ESS [48]. The results showed that more than three-fourths of patients had a tumor size more than 5 cm (FIGO IB); two-thirds of patients had myometrial invasion; and 18.7% of patients had cervical invasion (worst prognosis), contributing to 51.4% and 43.5% of a 5-year OS rate for FIGO Stage IA and FIGO Stage IB, respectively [48]. By contrast, for 368 patients with LG-ESS, the prognosis is very good, with 5-year OS rates of 100% for FIGO IA and 93.5% for FIGO IB, respectively [48]. Finally, due to the rarity of the disease, there are no prospective, randomized trials which have been completed yet. Therefore, the following suggestions need further confirmation.

The treatment of choice consists of hysterectomy and BSO. Unlike LG-ESS, it is not clear whether the adnexa could be preserved in premenopausal women with HG-ESS. Because stage is an important prognostic factor, therefore, the metastases of pelvic and/or para-aortic lymph nodes are associated with a poorer prognosis. There is no indication that surgical removal will improve this limited prognosis, because most recurrences occur in visceral sites [49]. However, in the case of extensive disease, abdominal debulking surgery, including extensive lymphadenectomy is recommended if feasible. The results of the Taiwan Gynecology Oncology Group 2005 (TGOG-2005) showed the adequate debulking surgery, including dissection of both pelvic and para-aortic lymph nodes might provide a better rate of survival in FIGO III–IV pure endometrioid-type endometrial cancer [42], which might also be applicable to the management of patients with an extensive HG-ESS. In fact, residual disease has a negative prognostic impact, and metastatectomy should be considered as for other sarcoma [50].

Adjuvant therapy with external pelvic irradiation

Due to the poor prognosis in patients with HG-ESS, postoperative adjuvant therapy might provide a better chance for survival. One prospective randomized study conducted by the European Organization for Research and Treatment of Cancer (EORTC) Gynecological Cancer Group study (protocol 55874) showed that adjuvant external pelvic radiation did not improve PFS and OS among women with FIGO I–II stage HG-ESS [51]. However, it is interesting that it is believed that external pelvic irradiation may decrease loco-regional recurrence in the patients with HG-ESS; therefore, to date, this approach has been widely used as adjuvant treatment for these patients [50]. Our comment is that external pelvic irradiation could be considered in those HG-ESS patients without residual tumors, although the survival benefits are not confirmed.

Adjuvant chemotherapy with and without external pelvic irradiation

Because the recurrence pattern of patients with HG-ESS is often distant and visceral, it is reasonable to use an adjuvant chemotherapy (CT) in the management of this particularly aggressive disease. A study of the French Sarcoma Group (SARCGYN study) enrolled 81 patients with FIGO Stage I–III uterine sarcoma (nine patients with HG-ESS), who were randomly allocated to adjuvant CT (doxorubicin, ifosphamide and cisplatin) followed by external pelvic irradiation or external pelvic irradiation alone [52]. The results showed that the addition of CT to radiotherapy increased the 3-year disease-free survival rate (55% vs. 41%, $p = 0.048$) [52]. There was a trend toward an improvement in 3-year OS (81% vs. 69%), although it did not reach statistical significance [52]. Although the data of the SARCGYN study seemed to favor the benefits of CT and the following external pelvic irradiation, based on the limited data available to date, the benefits of this approach deserves further investigation.

Cytotoxic CT in the form of doxorubicin and ifosfamide or gemcitabine plus docetaxel and doxorubicin has been noted to show activity in HG-ESS [36,53–56]. The effect of treatment on persistent and/or recurrent HG-ESS is poor, particularly for patients who have the recurrence after the first line CT. Furthermore, when these patients received the second-line CT, reusing single agent or multiagent CT, such as doxorubicin, ifosfamide, cisplatin, topotecan, paclitaxel, docetaxel, gemcitabine, trabectedin and gemcitabine combined with docetaxel), the effectiveness of these regimen is only 5–27% [53,57–60]. A general treatment algorithm for ESS is presented in Figure 1.

UUS

UUS is, a high-grade sarcoma, extremely rare, lacking a specific line of differentiation, which is a diagnosis of exclusion (the wastebasket category, which fails to fulfill the morphological and immunohistochemical criteria of translocation-positive ESS) [2,4]. Patients with UUS often have postmenopausal bleeding or symptoms/signs secondary to extrauterine spread; therefore, more than 60% of patients are far-advanced stage diseases (FIGO Stage III–IV) and associated with a very poor prognosis (<2-year survival) [1].

Grossly, UUS is a relatively large fleshy tumor demonstrating destructive infiltrative growth into the uterine wall, associated with extensive necrosis and/or hemorrhage [4]. Microscopically, the tumors show sheets or fascicles of highly atypical nondescript cells, with a brisk mitotic activity. Lymphovascular invasion is common. Table 1 shows the key factors used to diagnose UUS.

Despite limited evidence, recommended surgical treatment for UUS is total hysterectomy and BSO. It is unclear whether lymphadenectomy provides survival benefits for UUS [55]. Due to complex biological characteristics and unknown etiology, the value and better choices of adjuvant therapy are still under investigation. Therefore, there is no conclusive data available yet. The main risk is hematogenous spread and distant metastases, suggesting that CT might be an option. Similar to treatment of HG-ESS, doxorubicin and/or ifosfamide are frequently used in clinical practice. The available regimens include trabectedin, gemcitabine, and docetaxel. Of course, the other choices identical to the management of

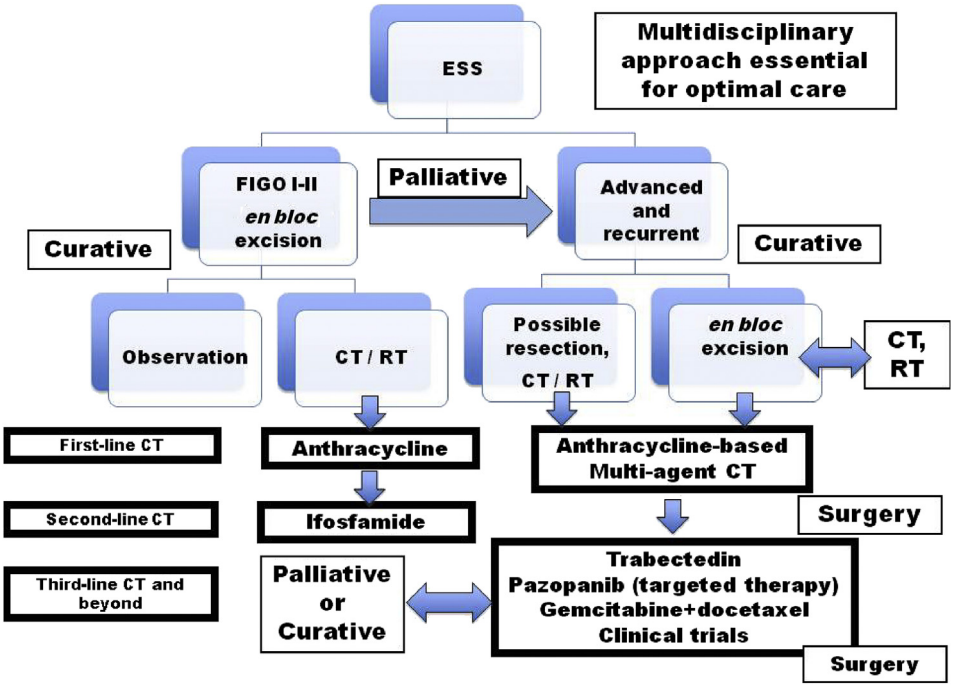

Figure 1. A flow chart for clinical practice in the management of women with a diagnosed uterine ESS. CT = chemotherapy; ESS = endometrial stromal sarcoma; FIGO = Federation International Gynecology and Obstetrics; RT = radiation therapy.

soft tissue sarcoma at other sites might be also appropriate for the women with UUS. Because there is no data supported by randomized trials, the treatment for persistent and recurrent UUS can be similar to soft tissue sarcomas at other sites.

Adenosarcoma

Adenosarcoma is a mixed tumor of benign glandular epithelium and low-grade sarcoma, usually of endometrial stromal type [1]. The stage system of the adenosarcoma differs from that of uLMS and ESS (Table 3) [3]. Grossly, adenosarcoma is a polypoid tumor, typically filling and distending the uterine cavity. Sometimes, a sarcomatous component might overgrow, resulting in a larger size with a fleshy, hemorrhagic and necrotic cut surface. Microscopically, the stroma typically concentrates around the glands forming periglandular cuffs [1]. The prognosis of adenosarcoma is favorable, although one-fourth of patients might finally die of their disease. The golden standard therapy is total hysterectomy and BSO. It is not clear whether BSO and/or lymphadenectomy should be included in the management of women with adenosarcoma [49]. The role of adjuvant therapy has not been established. In addition, for metastatic and recurrent patients with adenosarcoma, the proposed approach is also unavailable. The possible strategy might be individualized, including complete resection for operable disease, palliative radiotherapy for local nonresectable recurrence or postoperative adjuvant therapy for isolated tumor after metastatectomy, CT containing ifosfamide or doxorubicin-based combination for disseminated disease [49]. The management algorithm is shown in Figure 1.

Future perspectives

The scope of the clinical problems of uterine sarcomas includes rare malignancy, heterogeneous, complex biological characteristics, unknown etiology, and unknown risk factors; therefore, a multidisciplinary approach might be essential for optimal care. There are many ongoing clinical trials to evaluate the effectiveness of different approaches in the management of advanced soft tissue

Table 3
2014 FIGO and 010 American Joint Committee on Cancer system-TNM staging for uterine adenosarcoma.

FIGO	TNM	Definition
I	T1N0M0	Tumor limited to uterus
IA	T1aN0M0	Tumor limited to endometrium/endocervix without myometrial invasion
IB	T1bN0M0	Less than or equal to half myometrial invasion
IC	T1cN0M0	More than half myometrial invasion
II	T2N0M0	Tumor extends beyond the uterus but limited within the pelvic cavity
IIA	T2aN0M0	Adnexal involvement
IIB	T2bN0M0	Involvement of other pelvic tissues
III		Tumor invades abdominal tissues (not just protruding into the abdominal cavity)
IIIA	T3aN0M0	One site
IIIB	T3bN0M0	More than one site
IIIC	T1-T3N1M0	Pelvic and/or para-aortic lymph node metastases
IV		
IVA	T4N0-N1M0	Tumor invades bladder and/or rectum
IVB	T1-T4N0-N1M1	Distant metastasis

FIGO = Federation International Gynecology and Obstetrics; TNM = tumor, lymph node and metastases.

sarcomas, including uterine sarcomas. One collaborative study conducted by European Organization for Research and Treatment of Cancer (EORTC) (EORTC 62012) enrolled 455 patients at 38 hospitals in 10 countries (age ≤60 years) to compare doxorubicin and intensified doxorubin plus ifosfamide for advanced soft tissue sarcomas (locally advanced, unresectable, or metastatic high-grade soft-tissue sarcoma) [61]. During the median follow-up of 56 and 59 months, median PFS was significantly higher for the multiagent group than for the doxorubicin group (7.4 months. 95% CI 6.6–8.3 months vs. 4.6 months, 95% CI 2.9–5.6 months, stratified log-rank test $p = 0.003$) [61]. In addition, more patients in the multiagent group than in the doxorubicin group had an overall response [60 (26%) of 227 patients vs. 31 (14%) of 228, $p < 0.006$] [61]. However, there was no significant difference in OS between the two groups (median OS 14.3 months, 95% CI 12.5–16.5 months in the multiagent group vs. 12.8 months, 95% CI 10.5–14.3 months in the doxorubicin group; hazard ratio 0.83, 95% CI 0.67–1.03), suggesting that the use of intensified doxorubicin and ifosfamide for palliation of advanced soft-tissue sarcoma might not provide a better chance of survival [61].

In addition to conventional CT, target therapy might be another choice in the management of these highly lethal diseases. Many Phase III studies with pazopanib, regorafenib, muramyl tripeptide, and ridaforolimus are still ongoing [62]. Other promising agents that are still in earlier stages of development such as CDK4 and MDM2 inhibitors, cedirabnib, eribulin, and crizotinib, are also being tested [62–65]. We hope that the results of these studies will provide a better chance of survival in patients with sarcoma in the near future.

Conclusion

Standard treatment for early- and far-advanced ESS is hysterectomy plus BSO and complete cytoreduction of the tumor *en bloc* with adherent structures, respectively, even if not overtly infiltrated. Similar to the management for patients with uLMS [3], for early-stage (uterus-limited) ESS diseases, an *en bloc* and intact resection of tumor (no morcellation) might be of paramount importance [66,67], even though the uterus was removed by minimally invasive surgery and the diagnosis of ESS was accidental. For far-advanced ESS, adequate cytoreduction and metastatectomy might provide a better chance for survival. Adjuvant radiotherapy and chemotherapy are not administered routinely because the survival benefits are doubtful, especially for those patients with totally eradicated tumors. Treatment outcomes in HG-ESS and UUS are still disappointing, especially in patients with inoperable, locally advanced, recurrent and/or metastatic diseases. Available evidence showed the following regimens could be tried, including the single agent of doxorubicin, ifosfamide, trabectedin, and gemcitabine, and the combination of therapy, such as doxorubicin plus ifosfamide. Doxorubicin plus ifosfamide can be used for rapid palliation, stopping rapidly progressing disease, or to facilitate patients to become surgical candidates [68,69]. This is a concept of neoadjuvant therapy for relatively bulky-sized tumors [70,71]. In addition to further information provided by randomized clinical trials, future efforts could focus on better defining the molecular etiology of ESS in order to provide better care for patients with uterine sarcomas.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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