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Uterine leiomyosarcoma: Epidemiology, contemporary treatment strategies and the impact of uterine morcellation☆,☆☆

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HIGHLIGHTS

- Leiomyosarcoma contributes to a significant proportion of uterine cancer deaths.
- Surgery is the mainstay of treatment for uterine leiomyosarcoma (LMS).
- Uterine LMS is challenging to diagnose and can mimic the appearance of leiomyomas.
- Cytotoxic chemotherapy regimens remain inadequate in the treatment of this disease.
- Novel early detection strategies and targeted drugs are a focus of recent studies.

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ABSTRACT

Leiomyosarcoma, a rare tumor subtype, accounts for 1% of all uterine malignancies, but contributes to a significant proportion of uterine cancer deaths. Surgery is considered the mainstay of treatment for all soft tissue sarcomas, including uterine variants. However, uterine leiomyosarcoma is challenging to diagnose preoperatively and can mimic the appearance of benign uterine leiomyomas. Recently, concerns have grown in this regard, as surgeons have utilized uterine morcellation and myomectomy procedures unknowingly in the setting of occult uterine sarcoma. Because of aggressive tumor biology and relative chemotherapy and radiotherapy resistance, efficacious therapies to achieve prolonged survival or cure in those with both early and advanced-stage uterine leiomyosarcoma have been elusive. The strongest determinant of survival remains stage at diagnosis, though prediction models may provide a more accurate prognosis. Given the aggressive nature of this sarcoma subtype, novel early detection strategies and targeted therapies are the focus of several recently published and ongoing studies. While gemcitabine/docetaxel and doxorubicin remain the most active regimens in the treatment of advanced or recurrent disease, currently available cytotoxic regimens remain inadequate, with 5-year disease-specific survival of <30%. Pazopanib, trabectedin and olaratumab, are FDA-approved, targeted therapies with activity in uterine and other leiomyosarcomas, while aromatase inhibitors and immunotherapies are under active investigation. This review provides a critical appraisal of the literature regarding the contemporary surgical and medical management of uterine leiomyosarcoma, the role of targeted therapies, and the implications of uterine morcellation on gynecologic surgical practice.

1. Introduction

Leiomyosarcoma (LMS) is a rare tumor subtype that accounts for approximately 1% of all uterine malignancies. However, it contributes to nearly 70% of all uterine sarcomas and a significant proportion of uterine cancer deaths [1–12]. Because of aggressive tumor biology and relatively chemoresistant disease, efficacious therapies to achieve prolonged survival or cure in those with both early and advanced-stage disease has been elusive. Surgery remains the standard of care in the management of all soft tissue sarcomas, including uterine LMS [2–31]. In spite of this, uterine LMS is challenging to diagnose preoperatively, as it can mimic the appearance of benign uterine leiomyomas. Recently, concerns have grown in this regard, as surgeons have utilized uterine morcellation and myomectomy procedures unknowingly in the setting of occult uterine sarcoma [32–46].

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In the last two decades, an increase in the use of both post-operative chemotherapy and radiation therapy has been observed in the treatment of uterine LMS, with chemotherapy incurring a small survival advantage [2]. The strongest predictor of survival remains stage at diagnosis, though prediction models may provide a more precise prognosis [3]. Given the aggressive nature of this sarcoma subtype, novel early detection strategies and targeted therapies are the focus of several recently published and ongoing studies [2]. Herein, this review summarizes our contemporary understanding of uterine LMS, the role of surgery and other therapies in the treatment of all disease stages, the dilemma of differentiating uterine sarcoma from leiomyomas, and how uterine morcellation has complicated this diagnostic problem, and updates on innovative uterine sarcoma clinical trials.

2. Epidemiology

The incidence of uterine LMS is 0.36 per 100,000 woman-years [5]; most occur in women over 40 years of age, with incidence increasing rapidly after age 50 [9]. Black women have a 2-fold higher incidence than white women. LMS may be associated with obesity and diabetes [6]. Tamoxifen use for >5 years may also increase LMS risk to 17 per 100,000 woman-years [7]. Additionally, studies in soft tissue sarcoma have attributed an increased risk of LMS with p53 gene mutations, radiation treatment for childhood cancers, and germ line mutations in fumarate hydratase (hereditary leiomyomatosis with renal cell carcinoma) [4]. Most uterine LMS is unassociated with pre-existing leiomyomas and no biologic evidence exists to link LMS with their benign, smooth muscle uterine tumors [6].

3. Pathology/leiomyosarcoma subtypes

In those with uterine-confined disease, LMS presents as a solitary, often palpable and large, intramural mass in >50% of cases [9]. Like uterine leiomyomas, uterine LMS express estrogen, progesterone and androgen receptors in a substantial proportion of cases (40–50%) [8]. However, the similarities end there. Unlike leiomyomas, uterine LMS tumors are softer in consistency, do not have a distinct whorled appearance, and microscopically, contain extensive areas of hemorrhage and necrosis as well as severely atypical nuclei with multiple mitotic figures in excess of 15 per 10 high power field [9]. Additionally, LMS often expresses smooth muscle markers, including desmin, h-caldesmon, histone deacetylase 8 (HDCA8) and smooth muscle actin [10]. LMS is further differentiated from uterine leiomyomas by the presence of strong staining with p53, Ki67, and nuclear p16, and are often immunoreactive for CD10 and epithelial markers including keratin and EMA.

Uterine LMS and their variants exist on a spectrum of biologic aggressiveness and are distinguished by a complicated set of pathologic features. As a general matter, the presence of certain pathologic features including infiltrative borders, coagulative necrosis and nuclear atypia differentiate a uterine leiomysarcoma from a benign leiomyoma. A more nuanced pathologic interpretation of the various leiomyosarcoma subtypes and variants can be challenging and is beyond the scope of this manuscript. Thus, review by expert gynecologic pathologists in the setting of a multidisciplinary tumor board is recommended to insure the most accurate diagnosis and avoid under or overtreatment [11–12].

4. Molecular characteristics

The molecular basis of LMS is poorly understood, as no single contributing gene mutation has been identified. Most uterine LMS is sporadic. Recent studies have elucidated the importance of cell cycle regulatory genes (30 genes) as potential therapeutic targets [14–15]. One study in particular which was externally validated found an 84% overexpression in cell cycle regulatory genes such as *CDC7*, *CDC20*, *GTSE1*, *CCNA2*, *CCNB1* and *CCNB2* [16]. When correlating molecular profile with clinical outcome, improved survival was observed among women with tumors over-expressing genes involved in histidine metabolism (5-year OS 22.2% vs. 57.8%, $p = 0.04$) [16]. Though these findings are preliminary and limited by small sample size, they are promising not only for potential molecular targets, but also for patient stratification with regard to clinical trials.

5. Diagnosis

Because uterine LMS lacks presenting characteristics or symptoms that are distinct from uterine leiomyomas, it is challenging to diagnose preoperatively. Nevertheless, the vast majority of uterine LMS are diagnosed in menopausal women and malignancy should be strongly suspected in the presence of fibroid-like tumor growth that occurs in this setting [5]. Symptoms of both uterine entities may be vague and include uterine bleeding (56%), an increase in abdominal girth or palpable uterine mass (52%) and pelvic pain and/or pressure (22%) [10]. Historically, a woman with a rapidly growing uterine mass (defined as an increase of 6 cm in 6–12 months) was thought to be at increased risk of a sarcoma [72]. Subsequent research has demonstrated that both uterine leiomyomas and LMS have the propensity to grow rapidly, and neither tumor size, nor increase of a pre-existing uterine mass, is necessarily a risk factor for malignancy [73,74].

Additionally, unlike epithelial endometrial carcinoma, which is almost always heralded by abnormal uterine or postmenopausal bleeding and which can be detected with >90–95% sensitivity by endometrial biopsy (EMB) or dilation and curettage (D&C), there are no preoperative diagnostic tests to reliably diagnose a uterine sarcoma [17]. Nevertheless, endometrial biopsy or curettage may detect uterine LMS in a substantial proportion of cases (Table 1). A retrospective study identified 72 women with uterine sarcoma who underwent preoperative endometrial sampling; an invasive tumor was correctly diagnosed in 86% (62/72) and predicted the correct histologic diagnosis in 64% (46/72) [17]. Interestingly, the rate of detection of an invasive cancer by preoperative sampling was not statistically different among sarcomas and epithelial tumors (86% vs. 84%, $p = 0.76$) and did not differ by sampling method (EMB vs. D&C, $p = 0.84$). Endometrial sampling, therefore, detects uterine LMS with considerable reliability when involving or encroaching on the endometrium and is strongly recommended prior to hysterectomy when considering uterine tissue extraction [41].

Magnetic resonance imaging (MRI) may be more diagnostic of uterine sarcoma than ultrasound or computed tomography (CT) scan, but studies are small with low reproducibility [13,18–19]. Diagnostic accuracy is increased (0.94, specificity 0.96) with contrast-enhanced MRI when compared with diffusion-weighted MRI in differentiating LMS and smooth muscle tumors of uncertain significance (STUMP) tumors to uterine leiomyomas [19]. In addition, studies investigating the usefulness of Gd-DTPA contrast-enhanced dynamic MRI in conjunction with serum LDH isoenzyme type 3 levels reported the specificity, positive predictive value, negative predictive value and diagnostic accuracy to be 100% in differentiating uterine LMS from degenerated leiomyomas [21]. Although these results are promising, only 10 women out of 227 analyzed had a LMS diagnosis, and select radiologists were used to read all study MRIs, which may not be generalizable. Furthermore, utilization of diffusion-weighted techniques with a diffusion coefficient may also provide more precision in LMS diagnosis, but this technique will require further validation [12,40].

There are few studies regarding the role of PET imaging in LMS diagnosis. A small study comparing PET with MRI and ultrasound in 5 women reported 100% sensitivity for PET compared with 80% and 40% for MRI and ultrasound, respectively [22]. Nonetheless, more data is needed, and the current best modality to preoperatively assess uterine masses and their malignancy potential remains MRI.

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