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Review

# Systemic therapy for advanced uterine sarcoma: A systematic review of the literature

Sindu Kanjeekal[a,*], Alexandra Chambers[b], Michael Fung Kee Fung[a], Shailendra Verma[a]

on behalf of the Cancer Care Ontario Practice Guidelines Initiative Gynecology Cancer Disease Site Group

Program in Evidence-based Care, Cancer Care Ontario, Canada

[a]*University of Ottawa, Ottawa, Ontario, Canada*
[b]*McMaster University, Hamilton, Ontario, Canada*

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**Abstract**

*Objective.* To conduct a systematic review of the literature regarding the systemic treatment of advanced uterine sarcoma and provide an evidence-based summary of the available literature.

*Methods.* MEDLINE, EMBASE, and the Cochrane Library databases were searched. "Uterine sarcoma," "leiomyosarcoma," "mixed mesodermal tumor," "chemotherapy," and "systemic therapy" were combined with the search terms for study designs.

*Results.* Three randomized controlled trials and 24 prospective phase II trials were included in the systematic review. In a randomized trial of doxorubicin versus doxorubicin plus cyclophosphamide for advanced or recurrent uterine sarcoma, doxorubicin produced an overall response rate (RR) of 19% and median survival of 11.6 months, which was similar to the response with combination chemotherapy (RR 19%, median survival 10.9 months). A randomized trial comparing ifosfamide plus cisplatin versus ifosfamide alone in mixed mesodermal tumors showed a significant improvement in RR and progression-free survival with the combination compared with ifosfamide alone, however, the combination was associated with increased toxicity including death. A randomized trial comparing doxorubicin to doxorubicin with dacarbazine in women with advanced or recurrent uterine sarcoma demonstrated a significantly higher RR with the combination ($P < 0.05$), but no significant difference in survival.

*Conclusions.* Offering palliative chemotherapy to patients with advanced, unresectable uterine sarcoma who are symptomatic from this disease is a reasonable decision. Doxorubicin is an option for women with advanced uterine sarcoma. The combination of cisplatinum and ifosfamide is also an option for women with metastatic mixed mesodermal tumors; however, this combination is associated with significant toxicity when compared to ifosfamide alone.


*Keywords:* Uterine sarcoma; Leiomyosarcoma; Mesodermal tumors; Endometrial stromal sarcoma

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* Corresponding author. Program in Evidence-based Care, McMaster University, 1280 Main Street West, T27, 3rd Floor, Hamilton, Ontario, Canada L8S 4L8. Fax: +1 905 522 7681.
*E-mail address:* ccopgi@mcmaster.ca (S. Kanjeekal).

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## Introduction

Uterine sarcomas are a rare group of neoplasms with a worldwide annual incidence of between 0.5 and 3.3 cases per 100,000 women. The annual incidence of uterine sarcoma in a large cancer registry in the United Kingdom was 1/100,000 women; 87% (367/423) of these were mixed mesodermal tumors or leiomyosarcoma (LMS) [1]. According to an analysis of the Surveillance, Epidemiology, and End Results (SEER) Program data, mixed mesodermal tumors (carcinosarcoma) were the most common uterine sarcoma (0.82/100,000) followed by LMS (0.64/100,000) and endometrial stromal sarcoma (0.19/100,000). There are a number of other pathological subtypes, but these are so rare that they account for a very small proportion of cases (0.05/100,000) and are not usually identified separately in clinical trials [2]. Uterine sarcomas account for less than 4% of all malignancies of the uterine corpus. They are a heterogeneous group of tumors with many pathologic subtypes that present with a varying natural history from a benign course to aggressive disease [3].

In recent years, the pathological classification of MMT has been challenged. Evidence has emerged that many MMTs are actually monoclonal, as they are derived from a single stem cell. The carcinomatous element appears to be the central force while the sarcomatous element is a result of dedifferentiation [4]. Therefore, these tumors may be better described as carcinomas with sarcomatous metaplasia, rather than true mixed tumors. This pathological distinction has important clinical implications since it has been suggested that these tumors should be treated as endometrial adenocarcinomas rather than as sarcomas [5].

Low-grade sarcomas often have an indolent natural history, and long-term survival has been reported after surgical resection. Disease usually recurs locally with a long disease-free interval [4]. Studies have shown the presence of estrogen and progesterone receptors in low-grade endometrial sarcomas [6,7]. Treatment of low-grade endometrial stromal sarcoma with hormonal therapy has shown objective responses [8,9]. Two recent case reports of recurrent low-grade endometrial stromal sarcoma treated with the aromatase inhibitor letrozole have been published. One reported a PR of 9 months after previous treatment with surgery, radiation, megestrol acetate, and tamoxifen. The second case report described a significant PR >50% after first-line hormonal therapy with letrozole [10,11]. There are no reported phase II or phase III trials.

MMT, high-grade LMS, and high-grade endometrial stromal sarcoma behave in an aggressive fashion. The interval from the onset of symptoms to the diagnosis of early-stage disease ranges from 2 to 5 months. Patients who present with early-stage disease confined to the uterus have a 2- to 5-year overall survival of approximately 50% [12]. In a prospective, multicenter surgical staging trial from the GOG (Gynecologic Oncology Group), 71% of the patients with LMS and 53% of the patients with MMT recurred [13].

In general, the median survival for metastatic MMT is less than 1 year. There are a few cases of long-term survivors after resection of lung metastases [14]. Patients with LMS that has spread beyond the uterus and is judged unresectable rarely attain long-term survival, unless the tumor is very low-grade [15]. Typically, management of metastatic uterine sarcoma conforms to treatment practice for metastatic soft tissue sarcomas. The principles of management include surgical resection of isolated metastases, radiation to sites of local recurrence for optimal disease control, and palliative hormonal or systemic chemotherapy for advanced disease.

This systematic review evaluates the current available evidence for the systemic therapy of advanced, recurrent, or metastatic uterine sarcoma. This systematic review, developed by Cancer Care Ontario's Program in Evidence-based