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GCIG Consensus Review: Uterine and Ovarian Leiomyosarcomas

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Abstract

Objective—The GCIG aimed to provide an overview of uterine and ovarian leiomyosarcoma management.

Methods—Published articles and author experience were used to draft management overview. The draft manuscript was circulated to international members of the GCIG for review and comment, and appropriate revisions were made.

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Results—The approach to management of uterine and ovarian leiomyosarcoma management is reviewed.

Conclusions—Uterine and ovarian leiomyosarcomas are rare, aggressive cancers that require specialized expertise for optimal management.

Keywords

uterine leiomyosarcoma; ovarian leiomyosarcoma; Gynecologic Cancer Intergroup

Introduction

Uterine sarcomas represent about 8% of uterine cancers, with an incidence of about 0.4 per 100,000 women[1]. Leiomyosarcomas are the most common subtype; most are high grade malignancies with a high risk for recurrence and progression. Overall survival is dependent on stage with 5-year survival estimates of stage I: 76%, stage II: 60%, stage III: 45%, and stage IV: disease 29%[2]. Uterine leiomyosarcomas are staged using the FIGO 2009 uterine sarcoma staging system, although anatomic staging systems perform poorly in terms of survival prognostication[3]. Other factors that have been evaluated for their potential prognostic impact include tumor morcellation[4], mitotic index[5,6], and tumor grade. A nomogram that includes additional non-anatomic prognostic factors such as patient age, tumor grade, and mitotic rate provides better estimates of overall survival[7,8].

Epidemiology

Most patients with uterine leiomyosarcoma have no identifiable risk factors. Patients who carry a germline p53 gene mutation (Li Fraumeni syndrome) have an increased risk of soft tissue sarcoma, including uterine LMS, as well as other cancers[9]. Patients with Rb mutations who are survivors of childhood retinoblastoma, and survivors of childhood rhabdomyosarcoma, or other childhood cancers whose treatment involves radiation, have an increased risk secondary cancers, including uterine LMS[10]. The familial syndrome hereditary leiomyomatosis with renal cell carcinoma (HLRCC), in which there are germline mutations in fumarate hydratase, has also been associated with an increased risk of uterine LMS[11]. Some studies have suggested an increased risk for uterine sarcoma among women with a history of obesity and diabetes[12], and among women exposed to tamoxifen[13].

Pathology

Stanford criteria are commonly used to diagnosis uterine LMS, incorporating histologic atypia, tumor cell necrosis, and mitotic rate[14]. There is incomplete consensus regarding the grading of uterine leiomyosarcomas[15]. Immunohistochemistry for smooth muscle differentiation markers such as SMA and caldesmon may be used to support the diagnosis. Histologic subtypes of uterine LMS such as epithelioid and myxoid LMS may have different histologic criteria. Because of the nuances of the histologic diagnosis of uterine LMS, expert review by gynecologic pathologists and/or sarcoma pathologists is recommended.

Molecular biology and genetics

No single driving mutation has been identified in uterine LMS. Most tumors show multiple somatic chromosomal abnormalities. Genetic profiling is investigational in LMS, but could potentially elucidate treatment targets[16,17]. Genetic profiling may be able to improve prognostication by identifying gene signatures that differentiate indolent uterine LMS tumors from clinically aggressive tumors[18].

Diagnosis

Presenting symptoms may include pelvic pain or pressure, or abnormal vaginal bleeding. Sonogram, CT, or MRI imaging may reveal a uterine mass. No single imaging criterion can reliably distinguish a benign uterine tumor from a malignant one. One small study of pre-operative MRI for patients with uterine mesenchymal neoplasms showed poor accuracy in distinguishing leiomyomas with atypical features from malignant mesenchymal neoplasms[19]. A separate study (19 patients with uterine mesenchymal lesions, 3 of which were LMS) suggested that MRI may be able to distinguish benign from malignant disease[20]. Intrauterine tumors that continue to increase in size after menopause should raise suspicion for malignancy. In most patients the diagnosis of uterine LMS is made at the time of myomectomy or hysterectomy for presumed benign disease[21,22].

Staging

Uterine sarcomas are staged using the FIGO 2009 staging system.

LEIOMYOSARCOMAS

Stage		Definition
I		Tumor limited to uterus
	IA	≤5 cm
	IB	>5 cm
II		Tumor extends beyond the uterus, within the pelvis
	IIA	Adnexal involvement
	IIB	Involvement of other pelvic tissues
III		Tumor invades abdominal tissues (not just protruding into the abdomen).
	IIIA	One site
	IIIB	>one site
	IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
IV	IVA	Tumor invades bladder and/or rectum
	IVB	Distant metastases

Initial treatment

Surgery

For patients whose disease appears limited to the uterus, hysterectomy is recommended. If there is suspicion of malignancy prior to surgery, we recommend against morcellation

hysterectomy because of concern for intra-operative spread of malignant tissue[23]. Morcellation of malignant tumors are associated with poorer survival outcomes[24]. Routine lymph node dissection is not generally required; however, it is recommended that lymph nodes that appear enlarged/suspicious for malignant involvement should be resected[25]. Bilateral salpingo-oophorectomy (BSO) is reasonable in peri-menopausal and post-menopausal women, although there are no data to show that oophorectomy improves survival outcomes[26]. Estrogen receptors and/or progesterone receptors have been reported to be positive in 40 to 70% of uterine leiomyosarcomas[27],[28], and may have prognostic significance[29], suggesting that oophorectomy may be reasonable even in pre-menopausal women. However, retrospective data have not shown survival differences among women under age 50 with uterus-limited disease who did or did not undergo BSO[30].

For disease that appears locally advanced but potentially completely resectable, an attempt to resect all disease is reasonable. Retrospective data have shown longer overall survival among women whose disease is completely resected compared to those with residual disease at end of the resection attempt[31].

For women who present with multi-site metastatic, unresectable disease, there is not generally a role for hysterectomy. Palliative hysterectomy may be appropriate for patients with metastatic disease who have poorly controlled uterine bleeding.

Laparoscopic re-evaluation of the pelvis after morcellation hysterectomy should be considered to evaluate for, and resect, any residual malignant tissue. Resection of the cervix, and consideration of BSO if not yet performed, is reasonable for patients who had only a supracervical hysterectomy.

Post-resection management of uterus-limited disease

Although it is recognized that the risk for recurrence after resection of uterus-limited high grade LMS exceeds 50%[32], no adjuvant intervention has been shown to improve progression-free or overall survival outcomes. Standard management after complete resection of uterus-limited disease is observation. Nearly one-third of patients who are found at time of hysterectomy to have uterine LMS will have evidence of metastatic disease on post-resection imaging[33] ; therefore CT and/or PET/CT and/or MRI is recommended to rule out distant metastases. PET imaging has not been shown to be superior to CT or MRI for detection of recurrent disease[34]. PET imaging may not detect small volume lung metastases[35].

Adjuvant pelvic radiation was evaluated in a prospective randomized trial for women with uterine carcinosarcoma, leiomyosarcoma, or endometrial stromal sarcoma. Survival outcomes were not improved by adjuvant radiation. Among the patients with uterine LMS, there was no difference in local recurrence rates between patients assigned to adjuvant pelvic RT and those assigned to observation[36].

A small prospective randomized trial of adjuvant doxorubicin versus observation for uterine LMS and carcinosarcoma did not show a survival benefit for doxorubicin. A prospective phase II study of adjuvant gemcitabine-docetaxel, followed by doxorubicin, demonstrated a

2-year progression-free survival rate of 78%; however at 3 years only 58% remained progression-free[37]. In a small study of 81 patients with a variety of uterine sarcoma histologies and stages (52 stage I, 16 stage II, 13 stage III; 53 leiomyosarcomas, 9 undifferentiated sarcomas, 19 carcinosarcomas) chemotherapy with doxorubicin plus ifosfamide plus cisplatin followed by radiation was superior to radiation alone at 3 years for disease-free survival (55% v. 41%) but not for overall survival[38]. These data cannot be used to support a recommendation for adjuvant chemotherapy as standard treatment given the heterogeneity of the tumor types and stages and the very small sample size and no overall survival benefit. An international randomized, phase III trial of observation versus adjuvant chemotherapy (gemcitabine-docetaxel for four cycles followed by doxorubicin for four cycles) is ongoing (GOG 0277/IRCI study 001).

For patients with locally advanced, completely resected uterine LMS, there are no prospective data upon which to base management recommendations. Choices may include observation, adjuvant radiation, adjuvant hormone blockade, or adjuvant chemotherapy. The location of the disease, histologic grade, estrogen receptor and progesterone receptor status, patient preferences, organ function, and comorbidities would be incorporated into the decision.

Metastatic disease

Patients found to have metastatic disease should be evaluated to determine whether resection of metastases may be appropriate.

Potentially resectable metastatic disease

Retrospective data show that survival may be prolonged among patients who undergo resection of metastatic disease. These data have inherent patient selection bias, but nevertheless support consideration of metastasectomy for selected patients. Outcomes are more favorable for those patients who have had a long disease-free interval, have a paucity of metastatic sites, and for whom the resection is likely to render them measurably disease-free[39],[40],[41],[42]. Radiofrequency ablation and other non-surgical, interventional radiology techniques may be appropriate for certain patients[43]. There are no prospective studies of these interventions, nor randomized trials comparing ablation outcomes with surgical outcomes. There are no data evaluating adjuvant systemic treatment after metastasectomy. The standard approach is surveillance.

Systemic treatment options for unresectable metastatic disease

Objective response rates can be achieved with systemic treatment for metastatic uterine LMS; in patients with symptomatic disease, chemotherapy may provide palliation of symptoms. There is no established superior first line chemotherapy regimen. Treatment recommendations for an individual patient should take into consideration the patient’s preferences for the treatment schedule, drug side effects, venous access, co-morbidities, disease burden, and organ function. Reasonable regimens to consider for first-line therapy include doxorubicin, doxorubicin plus ifosfamide, gemcitabine, gemcitabine plus docetaxel.

Other treatment options, used as second-line therapy or after, include pazopanib, trabectedin, dacarbazine or temozolomide. Enrollment on clinical trials is highly recommended.

Doxorubicin 60 mg/m2 every 3 weeks achieved objective response in 19% of patients with uterine sarcoma whether given as a single agent or combined with cyclophosphamide. Median overall survival was 12 months[44].

Doxorubicin plus ifosfamide achieved objective response in 30% of patients with uterine LMS[45]. The choice between single agent doxorubicin versus doxorubicin plus ifosfamide should incorporate the disease burden and the patient's risk for toxicity from dual-agent treatment.

Gemcitabine 1000 mg/m^2 IV over 30 minutes on a three-week on/one-week off schedule achieved objective response in 20% of patients with uterine LMS in a phase II trial[46].

Fixed dose-rate gemcitabine plus docetaxel achieved objective response in 27% of patients with uterine LMS when given as second-line therapy (90% of patients had progressed on or after doxorubicin) in a phase II trial[47]. The objective response rate was 36% in the phase II trial as first-line therapy[48]. A randomized trial in patients with metastatic soft tissue sarcoma showed superior objective response rates, progression-free, and overall survival among patients treated with gemcitabine plus docetaxel compared to those assigned to gemcitabine alone[49]. Another randomized trial did not find a difference between gemcitabine v. gemcitabine-docetaxel but the very small sample size, and the imbalance in the treatment arms for important variables make these data difficult to interpret[50]. The toxicity of gemcitabine plus docetaxel is greater than that of single agent gemcitabine.

Ifosfamide 1.5 g/m^2 IV for five days with Mesna, every three weeks achieved objective response in 17% of patients with uterine LMS[51].

Pazopanib 800 mg oral daily achieved objective response in about 6% of patients with metastatic soft tissue sarcoma in a phase III trial. The PFS was 20 weeks with pazopanib versus 7 weeks with placebo. There was no difference in overall survival[52].

Trabectedin 1.5 mg/m^2 IV over 24 hours every three weeks achieved objective response in 10% of patients with uterine LMS as first line therapy[53]. The study was closed for failure to meet the objective response rate goal. Among the 20 patients treated, the median PFS was 5.8 months. In a retrospective study, among patients with uterine LMS who had had prior treatment, trabectedin was associated with a 16% response rate but only a 3 month PFS[54].

Trabectedin by three hour infusion plus doxorubicin yielded an objective response in 57% of patients with leiomyosarcoma of either uterine or soft tissue origin.[55]

Dacarbazine and Temozolomide have modest activity in soft tissue sarcomas, and in uterine LMS, although prospective data are limited for these agents in the uterine LMS population[56,57,58].

Special considerations for patients with small volume and indolently paced uterine LMS

Although there are no specifically established histologic criteria by which to recognize them, clinically, there are patients whose uterine LMS disease pace is indolent[59] and/or in whom the disease burden is very low. Such patients may not need systemic cytotoxic chemotherapy. Observation may be appropriate in order to keep the toxicity of the treatment from being worse than the burden of the disease.

Hormonal blockade may be considered for these low-disease-burden/indolent disease-pace patients, if their tumors are ER and/or PR positive. In a retrospective study, aromatase inhibition treatment was associated with objective response in fewer than 10% of patients. The relatively prolonged PFS that was observed could be attributed to the inherent biology of the uterine LMS in these cases rather than to the hormonal intervention[60]. A small prospective study of letrozole in ER and/or PR positive uterine LMS patients showed a 12-week progression-free survival rate of 50% with median duration of treatment being 2.2 months[61].

Ovarian Leiomyosarcomas

Ovarian leiomyosarcomas arise from the smooth muscle component of the ovary or are of vascular origin[62]. These are generally considered to be high-risk cancers[63]. There are no prospective studies upon which to base management recommendations for ovarian leiomyosarcomas. In the absence of data specific to ovarian LMS, it is reasonable to adapt recommendations from data that exist for uterine LMS.

Surgery for disease limited to the ovary

Total hysterectomy and BSO is recommended. For patients who have not had lymph node dissection or omentectomy, a second operation is not considered necessary since the probability of occult metastatic disease is likely low.

Post-resection management

For disease that is limited to the ovary, there are no prospective data to support the routine use of adjuvant chemotherapy[64]. For locally advanced, completely resected disease, post resection therapy may be considered; however there are no data to show that treatment will improve survival outcomes.

Management of metastatic disease

Extrapolation of data for treatment of uterine LMS to the ovarian LMS setting is reasonable. Agents with demonstrated activity in uterine LMS and in soft tissue sarcoma are reasonable to consider as treatment options for metastatic ovarian LMS.

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References

1. Koivisto-Korander R, Martinsen JI, Weiderpass E, Leminen A, Pukkala E. Incidence of uterine leiomyosarcoma and endometrial stromal sarcoma in Nordic countries: results from NORDCAN and NOCCA databases. Maturitas. 2012 May.72:56–60. [PubMed: 22377186]
2. Kapp DS, Shin JY, Chan JK. Prognostic factors and survival in 1396 patients with uterine leiomyosarcomas: emphasis on impact of lymphadenectomy and oophorectomy. Cancer. 2008; 112:820. [PubMed: 18189292]
3. Zivanovic O, Leitao MM, Iasonos A, Jacks LM, Zhou Q, Abu-Rustum NR, Soslow RA, Juretzka MM, Chi DS, Barakat RR, Brennan MF, Hensley ML. Stage specific outcomes of patients with

uterine leiomyosarcoma: a comparison of the FIGO and AJCC staging systems. J Clin Oncol. 2009; 27:2066–2072. [PubMed: 19255317]

4. Serrano C, Oduyebo T, Manola J, Feng Y, Muto M, George S. Impact of tumor morcellation on the natural history of uterine leiomyosarcoma. Connective Tissue Oncology Society. 2013 Abstract 011.
5. Pautier P, Genestie C, Rey A, Morice P, Roche B, Lhommé C, Haie-Meder C, Duvillard P. Analysis of clinicopathologic prognostic factors for 157 uterine sarcomas and evaluation of a grading score validated for soft tissue sarcoma. Cancer. 2000; 88(6):1425–1431. [PubMed: 10717626]
6. Pelmus M, Penault-Llorca F, Guillou L, Collin F, Bertrand G, Trassard M, Leroux A, Floquet A, Stoeckle E, Thomas L, MacGrogan G. Prognostic factors in early-stage leiomyosarcoma of the uterus. Int J Gynecol Cancer. 2009; 19:385–390. [PubMed: 19407564]
7. Zivanovic O, Jacks LM, Iasonos A, Leitao MM, Soslow RA, Veras E, Chi DS, Abu-Rustum NR, Barakat RR, Brennan MF, Hensley ML. A Nomogram to Predict 5-Year Overall Survival for Patients with Uterine Leiomyosarcoma. Cancer. 2012; 118:660–669. [PubMed: 21751199]
8. Iasonos A, Keung E, Zivanovic O, Mancari R, Peiretti M, Nucci M, George S, Colombo N, Carinelli S, Hensley ML, Raut CP. External validation of a nomogram predicting overall survival of women with uterine leiomyosarcoma. Cancer. 2013 In press.
9. Gonzalez KD, Noltner KA, Busin CH, Gu D, Wen-Fong CY, Nguyen VQ, Han JH, Lowstuter K, Longmate J, Sommer SS, Weitzel JN. Beyond Li Fraumeni syndrome: clinical characteristics of families with p53 germline mustations. J Clin Oncol. 2009; 8:1250–1256. [PubMed: 19204208]
10. Kleinerman RA, Tucker MA, Tarone RE, Abramson DH, Seddon JM, Stovall M, Li FP, Fraumeni JF. Risk of new cancers after radiotherapy in long-term survivors of retinoblastoma: an extended follow-up. J Clin Oncol. 2005; 23:2272–2279. [PubMed: 15800318]
11. Ylisaukko-oja SK, Kiuru M, Lehtonen HJ, Lehtonen R, Pukkala E, Arola J, Launonen V, Aaltonen LA. Analysis of fumarate hydratase mutations in a population-based series of early onset uterine leiomyosarcoma patients. Int J Cancer. 2006; 119:283–287. [PubMed: 16477632]
12. Felix AS, Cook LS, Gaudet MM, Rohan TE, Schouten LJ, Setiawan VW, Wise LA, Anderson KE, Bernstein L, De Vivo I, Friedenreich CM, Gapstur SM, Goldbohm RA, Henderson B, Horn-Ross PL, Kolonel L, Lacey JV, Liang X, Lissowska J, Magliocco A, McCullough ML, Miller AB, Olson SH, Palmer JR, Park Y, Patel AV, Prescott J, Rastogi R, Robien K, Rosenberg L, Schairer C, Ou Shu X, van den Brandt PA, Virkus RA, Wentzensen N, Xiang YB, Xu WH, Yang HP, Brinton LA. The etiology of uterine sarcomas: a pooled analysis of the epidemiology of endometrial cancer consortium. Br J Cancer. 2013; 108:727–734. [PubMed: 23348519]
13. Lavie O, Barnett-Griness O, Narod SA, Rennert G. The risk of developing uterine sarcoma after tamoxifen use. Int J Gynecol Cancer. 2008 Mar-Apr;18(2):352–356. [PubMed: 18334013]
14. Bell SW, Kempson RL, Hendrickson MR. Problematic uterine smooth muscle neoplasms: a clinicopathologic study of 213 cases. Am J Surg Path. 1994; 6:535–538. [PubMed: 8179071]
15. Giuntoli RL 2nd, Gostout BS, DiMarco CS, Metzinger DS, Keeney GL. Diagnostic criteria for uterine smooth muscle tumors: leiomyoma variants associated with malignant behavior. J Reprod Med. 2007; 52:1001–1010. [PubMed: 18161397]
16. Davidson B, Abeler VM, Hellesylt E, Holth A, Shih IeM, Skeie-Jensen T, Chen L, Yang Y, Wang TL. Gene expression signatures differentiate uterine endometrial stromal sarcoma from leiomyosarcoma. Gynecol Oncol. 2013; 2:349–355. [PubMed: 23178314]
17. Chaing S, Oliva E. Recent developments in uterine mesenchymal neoplasms. Histopathology. 2013; 1:124–137.
18. Barlin J, Hensley ML, Levine D.
19. Cornfeld D, Israel G, Martel M, Weinreb J, Schwartz P, McCarthy S. MRI appearance of mesenchymal tumors of the uterus. Eur J Radiol. 2010; 74:241–249. [PubMed: 19349135]
20. Thomassin-Naggara I, Dechoux S, Bonneau C, Morel A, Rouzier R, Carette MF, Daraï E, Bazot M. How to differentiate benign from malignant myometrial tumours using MR imaging. Eur Radiol. 2013 Aug; 23(8):2306–2314. [PubMed: 23563602]
21. D'Angelo E, Prat J. Uterine sarcomas: a review. Gynecol Oncol. 2010; 116:131. [PubMed: 19853898]
22. Sagae S, Yamashita K, Ishioka S, et al. Preoperative diagnosis and treatment results in 106 patients with uterine sarcoma in Hokkaido, Japan. Oncology. 2004; 67:33. [PubMed: 15459493]

23. Einstein MH, Barakat RR, Chi DS, et al. Management of uterine malignancy found incidentally after supracervical hysterectomy or uterine morcellation for presumed benign disease. Int J Gynecol Cancer. 2008; 18:1065. [PubMed: 17986239]
24. Park JY, Park SK, Kim DY, Kim JH, Kim YM, Kim YT, Nam JH. The impact of tumor morcellation during surgery on the prognosis of patients with apparently early uterine leiomyosarcoma. Gynecol Oncol. 2011; 122:255–259. [PubMed: 21565389]
25. Leitao MM, Sonoda Y, Brennan MF, Barakat RR, Chi DS. Incidence of lymph node and ovarian metastases in leiomyosarcoma of the uterus. Gynecol Oncol. 2003 Oct; 91(1):209–212. [PubMed: 14529683]
26. Goff BA, Rice LW, Fleischhacker D, et al. Uterine leiomyosarcoma and endometrial stromal sarcoma: lymph node metastases and sites of recurrence. Gynecol Oncol. 1993; 50:105. [PubMed: 8349151]
27. Kelley TW, Borden EC, Goldblum JR. Estrogen and progesterone receptor expression in uterine and extrauterine leiomyosarcomas: an immunohistochemical study. Appl Immunohistochem Mol Morphol. 2004; 12:338. [PubMed: 15536333]
28. Leitao MM, Soslow RA, Nonaka D, et al. Tissue microarray immunohistochemical expression of estrogen, progesterone, and androgen receptors in uterine leiomyomata and leiomyosarcoma. Cancer. 2004; 101:1455. [PubMed: 15316901]
29. Leitao MM Jr, Hensley ML, Barakat RR, Aghajanian C, Gardner GJ, Jewell EL, O'Cearbhaill R, Soslow RA. Immunohistochemical expression of estrogen and progesterone receptors and outcomes in patients with newly diagnosed uterine leiomyosarcoma. Gynecol Oncol. 2012 Mar; 124(3):558–562. [PubMed: 22085894]
30. Kapp DS, Shin JY, Chan JK. Prognostic factors and survival in 1396 patients with uterine leiomyosarcomas: emphasis on impact of lymphadenectomy and oophorectomy. Cancer. 2008; 112:820. [PubMed: 18189292]
31. Leitao MM Jr, Zivanovic O, Chi DS, Hensley ML, O'Cearbhaill R, Soslow RA, Barakat RR. Surgical cytoreduction in patients with metastatic uterine leiomyosarcoma at the time of initial diagnosis. Gynecol Oncol. 2012 May; 125(2):409–413. [PubMed: 22366592]
32. Wang WL, Soslow R, Hensley M, Asad H, Zannoni GF, de Nictolis M, Branton P, Muzikansky A, Oliva E. Histopathologic prognostic factors in stage I leiomyosarcoma of the uterus: a detailed analysis of 27 cases. Am J Surg Pathol. 2011 Apr; 35(4):522–529. [PubMed: 21383611]
33. Dinh TA, Oliva EA, Fuller AF Jr, et al. The treatment of uterine leiomyosarcoma. Results from a 10-year experience (1990–1999) at the Massachusetts General Hospital. Gynecol Oncol. 2004; 92:648. [PubMed: 14766261]
34. Sharma P, Kumar R, Singh H, Jeph S, Sharma JB, Jain SK, Sharma DN, Bal C, Malhotra A. Role of FDG PET-CT in detecting recurrence in patients with uterine sarcoma: comparison with conventional imaging. Nucl Med Commun. 2012 Feb; 33(2):185–190. [PubMed: 22107993]
35. Kao YH, Saad U, Tan AE, Magsombol BM, Padhy AK. Fluorine-18-fluorodeoxyglucose PET/CT for the evaluation of suspected recurrent uterine leiomyosarcomas. Acta Radiol. 2011 May 1; 52(4):463–466. [PubMed: 21498277]
36. Reed NS, Mangioni C, Malmström H, et al. Phase III randomised study to evaluate the role of adjuvant pelvic radiotherapy in the treatment of uterine sarcomas stages I and II: an European Organisation for Research and Treatment of Cancer Gynaecological Cancer Group Study (protocol 55874). Eur J Cancer. 2008; 44:808. [PubMed: 18378136]
37. Hensley ML, Wathen JK, Maki RG, Araujo DM, Sutton G, Priebat DA, George S, Soslow RA, Baker LH. Adjuvant therapy for high-grade, uterus-limited leiomyosarcoma: Results of a phase 2 trial (SARC 005). Cancer. 2013 Jan 18.
38. Pautier P, Floquet A, Gladieff L, Bompas E, Ray-Coquard I, Piperno-Neumann S, Selle F, Guillemet C, Weber B, Largillier R, Bertucci F, Opinel P, Duffaud F, Reynaud-Bougnoux A, Delcambre C, Isambert N, Kerbrat P, Netter-Pinon G, Pinto N, Duvillard P, Haie-Meder C, Lhommé C, Rey A. A randomized clinical trial of adjuvant chemotherapy with doxorubicin, ifosfamide, and cisplatin followed by radiotherapy versus radiotherapy alone in patients with localized uterine sarcomas (SARCGYN study). A study of the French Sarcoma Group. Ann Oncol. 2013; 24:1099–1104. [PubMed: 23139262]

39. Anraku M, Yokoi K, Nakagawa K, et al. Pulmonary metastases from uterine malignancies: results of surgical resection in 133 patients. J Thorac Cardiovasc Surg. 2004; 127:1107. [PubMed: 15052209]
40. Burt BM, Ocejo S, Mery CM, et al. Repeated and aggressive pulmonary resections for leiomyosarcoma metastases extends survival. Ann Thorac Surg. 2011; 92:1202. [PubMed: 21867989]
41. Clavero JM, Deschamps C, Cassivi SD, et al. Gynecologic cancers: factors affecting survival after pulmonary metastasectomy. Ann Thorac Surg. 2006; 81:2004. [PubMed: 16731120]
42. Leitao MM, Brennan MF, Hensley M, Sonoda Y, Hummer A, Bhaskaran D, Venkatraman E, Alektiar K, Barakat RR. Surgical resection of pulmonary and extrapulmonary recurrences of uterine leiomyosarcoma. Gynecol Oncol. 2002 Dec; 87(3):287–294. [PubMed: 12468327]
43. O'Cearbhaill, RE.; Maki, RG.; Zheng, J., et al. Evaluation of the role of thermal ablation in the treatment of soft tissue sarcomas. Connective Tissue Oncology Society Meeting; Miami, FL. 2009. #39259
44. Muss HB, Bundy B, DiSaia PJ, et al. Treatment of recurrent or advanced uterine sarcoma. A randomized trial of doxorubicin versus doxorubicin and cyclophosphamide (a phase III trial of the Gynecologic Oncology Group). Cancer. 1985; 55:1648. [PubMed: 3884128]
45. Sutton G, Blessing JA, Malfetano JH. Ifosfamide and doxorubicin in the treatment of advanced leiomyosarcomas of the uterus: a Gynecologic Oncology Group study. Gynecol Oncol. 1996; 62:226. [PubMed: 8751554]
46. Look KY, Sandler A, Blessing JA, et al. Phase II trial of gemcitabine as second-line chemotherapy of uterine leiomyosarcoma: a Gynecologic Oncology Group (GOG) Study. Gynecol Oncol. 2004; 92:644. [PubMed: 14766260]
47. Hensley ML, Blessing JA, Degeest K, et al. Fixed-dose rate gemcitabine plus docetaxel as second-line therapy for metastatic uterine leiomyosarcoma: a Gynecologic Oncology Group phase II study. Gynecol Oncol. 2008; 109:323. [PubMed: 18394689]
48. Hensley ML, Blessing JA, Mannel R, Rose PG. Fixed-dose rate gemcitabine plus docetaxel as first-line therapy for metastatic uterine leiomyosarcoma: a Gynecologic Oncology Group phase II trial. Gynecol Oncol. 2008; 109:329. [PubMed: 18534250]
49. Maki RG, Wathen JK, Patel SR, Priebat DA, Okuno SH, Samuels B, Fanucchi M, Harmon DC, Schuetze SM, Reinke D, Thall PF, Benjamin RS, Baker LH, Hensley ML. Randomized phase II study of gemcitabine and docetaxel compared with gemcitabine alone in patients with metastatic soft tissue sarcomas: results of Sarcoma Alliance for Research through Collaboration study 002. J Clin Oncol. 2007 Jul 1; 25(19):2755–2763. [PubMed: 17602081]
50. Pautier, et al. Randomized Multicenter and Stratified Phase II Study of Gemcitabine Alone Versus Gemcitabine and Docetaxel in Patients with Metastatic or Relapsed Leiomyosarcomas: A Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) French Sarcoma Group Study (TAXOGEM study). The Oncologist. 2012 Sep 1.:1213–1220. [PubMed: 22907974]
51. Sutton GP, Blessing JA, Barrett RJ, McGehee R. Phase II trial of ifosfamide and mesna in leiomyosarcoma of the uterus: a Gynecologic Oncology Group study. Am J Obstet Gynecol. 1992; 166:556. [PubMed: 1536229]
52. van der Graaf WT, Blay JY, Chawla SP, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2012; 379:1879. [PubMed: 22595799]
53. Monk BJ, Blessing JA, Street DG, et al. A phase II evaluation of trabectedin in the treatment of advanced, persistent, or recurrent uterine leiomyosarcoma: a gynecologic oncology group study. Gynecol Oncol. 2012; 124:48. [PubMed: 21996263]
54. Sanfilippo R, Grosso F, Jones RL, et al. Trabectedin in advanced uterine leiomyosarcomas: a retrospective case series analysis from two reference centers. Gynecol Oncol. 2011; 123:553. [PubMed: 21917307]
55. Duffaud F, Chevreau C, Penel N, Le Cesne A, Guillemet C, Delcambre C, Floquet A, Cupissol D, Rey A, Pautier P. LMS-02: A phase II single-arm multicenter study of trabectedin in combination with doxorubicin as first line treatment of metastatic and/or locally advanced leiomyosarcoma of

uterine or soft tissue origin. Results from both cohorts, for the French Sarcoma Group. Connective Tissue Oncology Society. 2013 abstract 012.

56. García-Del-Muro X, López-Pousa A, Maurel J, et al. Randomized phase II study comparing gemcitabine plus dacarbazine versus dacarbazine alone in patients with previously treated soft tissue sarcoma: a Spanish Group for Research on Sarcomas study. J Clin Oncol. 2011; 29:2528. [PubMed: 21606430]
57. Anderson S, Aghajanian C. Temozolomide in uterine leiomyosarcomas. Gynecol Oncol. 2005; 98:99. [PubMed: 15916799]
58. Garcia del Muro X, Lopez-Pousa A, Martin J, et al. A phase II trial of temozolomide as a 6-week, continuous, oral schedule in patients with advanced soft tissue sarcoma: a study by the Spanish Group for Research on Sarcomas. Cancer. 2005; 104:1706. [PubMed: 16134177]
59. Veras E, Zivanovic O, Jacks L, Chiappetta D, Hensley M, Soslow R. "Low-grade leiomyosarcoma" and late-recurring smooth muscle tumors of the uterus: a heterogeneous collection of frequently misdiagnosed tumors associated with an overall favorable prognosis relative to conventional uterine leiomyosarcomas. Am J Surg Pathol. 2011 Nov; 35(11):1626–1637. [PubMed: 21921786]
60. O'Cearbhaill R, Zhou Q, Iasonos A, et al. Treatment of advanced uterine leiomyosarcoma with aromatase inhibitors. Gynecol Oncol. 2010; 116:424. [PubMed: 19932916]
61. George S, Feng Y, Manola J, Nucci MR, Butrynski JE, Morgan JA, Ramaiya N, Quek R, Penson RT, Wagner AJ, Harmon D, Demetri GD, Krasner C. Phase 2 trial of aromatase inhibition with letrozole in patients with uterine leiomyosarcomas expressing estrogen and/or progesterone receptors. Cancer. 2013 Nov 12. Epub ahead of print.
62. Tsuyoshi H, Yoshida Y, Kurokawa T, Kotsuji F. Diagnosis and management of leiomyosarcoma arising from ovarian vein: case report and literature review. J Obstet Gynaecol Res. 2012; 38:466–470. [PubMed: 22229846]
63. Taskin S, Taskin EA, Uzum N, Ataoglu O, Ortac F. Primary ovarian leiomyosarcoma: a review of the clinical and immunohistochemical features of the rare tumors. Obstet Gynecol Surv. 2007; 62:480–486. [PubMed: 17572920]
64. Arslan OS, Sumer C, Cihangiroglu G, Kanat-Pektas M, Gungor T. A rare tumor of the female genital tract: primary ovarian leiomyosarcoma. Arch Gynecol Obstet. 2011; 283(Suppl 1):83–85. [PubMed: 21061129]