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UTERINE SARCOMA – RECENT ADVANCES AND TREATMENT OPTIONS

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Abstract
Uterine sarcomas are very rare and diverse. Due to their rarity, pathological diagnosis, surgical treatment, and cure are difficult. They are medically and biologically heterogeneous diseases that are difficult to treat at advanced stages. Recent advances in understanding uterine sarcoma biology have improved diagnostic and clinical management. Promising strategies for treating patients with uterine leiomyosarcoma involve targeting the DNA damage repair pathways and suppressing the activity of the macrophage immune system. Endometrial stromal sarcomas often exhibit mutations in the Wnt, cyclin D-CDK4/6-Rb, and MDM2-p53 pathways. Translating these molecular discoveries into new clinical trials to benefit patients with these conditions is crucial.

Keywords: Uterine sarcoma, leiomyosarcoma, endometrial stromal sarcoma, undifferentiated uterine sarcoma, PEComa, targeted therapy

Introduction
Uterine sarcomas constitute around 1% of all malignant tumors in the female genital tract and about 3% to 7% of all uterine cancers. (1) The most common subtypes are leiomyosarcoma (uLMS), high-grade endometrial stromal sarcoma (HG-ESS), low-grade endometrial stromal sarcoma (LG-ESS), adenosarcoma, and uterine perivascular epithelioid cell tumors. Recently, advances in understanding molecular biological differences have prompted revisions in their classification. For example, uterine carcinosarcoma is now classified as a dedifferentiated carcinoma. (2)

Classification (3)
WHO Uterine Sarcoma Classification System: Categorization of Mesenchymal Tumors (2020)
- Leiomyoma (Subtypes: lipo leiomyoma, leiomyoma apoplectic, leiomyoma hydropic, dissecting leiomyoma, cellular leiomyoma, myxoid leiomyoma, epithelioid leiomyoma, symplastic leiomyoma, leiomyomatosis)
- Intravenous leiomyomatosis
- Smooth muscle tumor of uncertain malignant potential (Subtypes: Epithelioid, Myxoid, Spindle)
- Metastasizing leiomyoma
- Leiomyosarcoma
  - ✓ Spindle leiomyosarcoma
  - ✓ Epithelioid leiomyosarcoma
  - ✓ Myxoid leiomyosarcoma
- Endometrial stromal nodule
- Low-grade endometrial stromal sarcoma
- High-grade endometrial stromal sarcoma
- Undifferentiated uterine sarcoma
- Miscellaneous mesenchymal tumors

- ✓ Uterine tumor resembling ovarian sex cord tumor
- Perivascular epithelioid cell tumor
- Inflammatory myofibroblastic tumor

Mixed epithelial and mesenchymal tumors

- Adenomyoma
- Atypical polypoid adenomyoma
- Adenosarcoma

Diagnosis

Risk factors include age > 40, obesity (BMI > 30 kg/m2), Diabetes Mellitus, previous radiation therapy, and long-term tamoxifen use. Some genetic diseases, such as hereditary leiomyomatosis and retinoblastoma, have also been implicated. (4-6) Adenosarcoma may also result from endometriosis and adenomyosis. (7) T2 signal intensity and apparent diffusion coefficient maps on diffusion-weighted MRI showed 92.4% accuracy in distinguishing benign from malignant tumors. (8,9) Remember the acronym **BET^{1}T^{2}ER** Check! (**B**order- lobulated or irregular; **E**nhancement-heterogenous with irregular outline/invasion; **T1**WI SI- low with high SI in areas of hemorrhage; **T2**WI SI- intermediate and heterogenous; **E**ndometrial thickening- direct involvement/irregular; **R**estricted diffusion- present). (10)

Disease-specific chromosomal fusion transcripts, such as JAZF1, SUZ12, and PHF1, have been identified in endometrial stromal sarcomas (ESS). (11) The YWHAE-FAM22 rearrangement has been identified among undifferentiated sarcomas. (12) A prospective study found significant differences in the molecular profiles of uLMS and ESS in the expression of TP53, RB1, and ATRX genes. Although these three genes are frequently mutated in uLMS.(13)

Surgery

Surgical treatment includes total abdominal hysterectomy, bilateral salpingo-oophorectomy, and (if possible) metastasectomy, which are standard treatments. In the general population, many women are diagnosed with uterine fibroids, but 1 in 350 patients will be diagnosed with uterine LMS. Therefore, uterine morcellation should be avoided as this procedure can spread malignant cells into the abdominal cavity, causing local recurrence and reducing overall survival (OS). (14) To improve outcomes, uterine sarcomas should be removed en bloc, and oophorectomy should be individualized for patients of reproductive age. (15) Completion hysterectomy or trachelectomy with peritoneal and omental biopsies is recommended when occult uLMS is diagnosed, as the disease is upstaged in 15% of patients. (16) For LMS and ESS, the reported risk of lymph node metastasis is 3% and less than 10%, respectively (17). Hence, routine lymphadenectomy is not recommended for early-stage diseases. This was confirmed by a recent retrospective study that routine lymphadenectomy for early low-grade ESS does not improve survival. (18) The risk of ovarian metastasis in early uterine sarcomas is low and has been reported between 3.4% and 3.9%. (19) In cases of uterine leiomyosarcoma (uLMS), grossly normal-looking ovaries can be preserved in premenopausal women if there is no evidence of metastatic disease, as this does not seem to increase the risk of recurrence. (20) An important factor, however, is the presence of tumor estrogen and progesterone receptors. In such cases, the tumor is hormone-sensitive; therefore, there is a benefit to oophorectomy, as is seen in hormone-sensitive ESS. (19, 20) Performing a bilateral salpingo-oophorectomy during surgery for endometrial stromal sarcoma (ESS) has shown a survival benefit regardless of menopausal status, making it the standard of care. (20, 22) However, due to the relatively indolent nature of ESS, fertility-sparing surgery with both ovarian and uterine preservation is an option in select cases. After childbearing, hysterectomy and bilateral salpingo-oophorectomy can be performed. (21-23) A recent large retrospective series demonstrated that survival rates did not differ based on the type of surgery,

whether total hysterectomy with or without bilateral salpingo-oophorectomy, supracervical hysterectomy, or local tumor resection. (23)The NCCN guidelines recommend ER/PR testing for leiomyosarcoma (LMS), endometrial stromal sarcoma (ESS), and adenosarcoma to guide decisions regarding ovarian management, especially in young premenopausal patients. Generally, bilateral salpingo-oophorectomy (BSO) is favored for low-grade ESS or tumors expressing ER/PR, though ovarian management may be individualized for reproductive-age patients. (24)

Chemotherapy

Early stage: The risk of disease recurrence after surgery in ULMS has been reported to be 50% to 70% at two years. The Gynecologic Oncology Group (GOG) conducted a phase III study comparing doxorubicin versus observation in patients with ULMS or carcinosarcoma. Adjuvant pelvic radiation therapy was also allowed at the doctor's discretion. Chemotherapy has been shown to nonsignificantly reduce the relapse rate in the uterine leiomyosarcoma (ULMS) group, with a 44% relapse rate in the doxorubicin group compared to 61% in the observation group. Treatment with gemcitabine plus docetaxel resulted in 45% of patients remaining disease-free after two years and 59% of 18 women with the uterus-confined disease were progression-free at two years. The median progression-free survival (PFS) was over three years. Given the efficacy of doxorubicin in advanced LMS, a study was designed to provide four courses of gemcitabine plus docetaxel followed by four courses of doxorubicin. A total of 47 women with uterus-confined disease participated. With a median follow-up of 27.4 months, 78% of women remained progression-free after two years, with a median PFS of 39.3 months. This led to a GOG-EORTC phase III study comparing four cycles of gemcitabine and docetaxel followed by four cycles of doxorubicin versus observation in resected uterus-limited LMS. Unfortunately, the study was closed early due to poor accrual (National Clinical Trial identifier NCT01533207).

Advanced stage

Adriamycin/Ifosfamide: Anthracycline-based chemotherapy is the standard first-line treatment of uterine LMS. The response rate for these two drugs is approximately 17-25%. (27) Although no OS improvement was reported, combination therapy results in a greater response and more rapid control of symptoms. (28) Combining chemotherapy should be used in symptomatic patients with high-volume disease, whereas single-agent adriamycin can be used in asymptomatic, low-volume disease. The cardioprotective agent dexrazoxane may be considered early in doxorubicin therapy because systolic failure occurs in 25% of patients at doses >450 mg/m2 (29). In a randomized trial, the addition of dexrazoxane to doxorubicin did not affect chemotherapy efficacy but reduced the risk of systolic dysfunction. (30)

Gemcitabine/docetaxel: In the randomized phase III GeDDiS trial, doxorubicin/gemcitabine plus docetaxel showed equivalent efficacy as first-line treatment of soft tissue sarcoma, including uLMS.(31) Fixed dose-rate gemcitabine (900 mg/m2 79 over 90 minutes) on days 1 and 8 with docetaxel (100 mg/m2) on day 8 every 21 days showed efficacy as second-line therapy in metastatic uterine LMS.(32) Thirteen of 48 (27%) patients had objective tumor response with median duration of response being more than 9 months. However, the median PFS was only 5.6+ months. Another trial, but in the first-line setting, showed a higher response rate (36%). (33) The median PFS was 4.4 months, and the median response duration was only 6 months for the 15 responding patients. In a small randomized phase II study of advanced soft tissue sarcoma, gemcitabine (900 mg/m2 over 90 minutes on days 1 and 8) and docetaxel (100 mg/m2 on day 8) combination was superior to gemcitabine (1200 mg/m2 over 120 minutes on days 1 and 8). (34) The response rates were low in both arms (16% vs. 8%). However, the median OS was prolonged in the combination arm (17.9 mo vs. 11.5 mo). Patients with metastatic uterine leiomyosarcoma (LMS) often experience greater benefits from combining gemcitabine and docetaxel rather than single-agent gemcitabine, especially if their performance status is reasonably good.

Other chemotherapeutic agents:

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Dacarbazine: In a study involving 146 patients with uterine sarcoma, the combination of dacarbazine (250 mg/m² on days 1-5) and doxorubicin (60 mg/m²) achieved a response rate of 24%, compared to 16% for doxorubicin alone. However, this combination did not show a significant improvement in overall survival. (27)
Temozolomide, an oral prodrug that metabolizes dacarbazine, is also used in treating uterine leiomyosarcoma (LMS), with up to 20% response rates. (35)
Trabectedin: A large study indicated that median progression-free survival (PFS) was longer for LMS or liposarcoma (LPS) patients treated with trabectedin than those receiving dacarbazine. (36) In another study with 577 patients, 232 had uterine LMS. Of the 144 treated with trabectedin, the median PFS was 4 months, compared to 1.5 months for the 88 patients treated with dacarbazine (HR 0.57, P = 0.0012). (37) While response rates were similar (11% with trabectedin vs. 9% with dacarbazine), the clinical benefit rate was higher with trabectedin (31% vs. 18%). However, trabectedin can cause side effects such as transaminitis, cytopenias, and rhabdomyolysis. Due to the lack of overall survival benefit with trabectedin, dacarbazine might be preferred for patients with borderline performance status.

Eribulin: This non-taxane microtubule inhibitor is approved for treating previously treated LPS but has not shown PFS or overall survival advantages over dacarbazine for LMS in a large international study. (38)
HG-ESS (High-Grade Endometrial Stromal Sarcoma) and UUS (Undifferentiated Sarcoma): These tumors generally have poor responses to chemotherapy. Patients with these types should be considered for new drug trials. An ongoing EORTC study evaluates cabozantinib, an oral agent with anti-VEGFR and MET activity, in patients with HGUS responding to chemotherapy (NCT01979393).

Hormone Therapy
Hormonal Blockade in LG-ESS: Estrogen receptor (ER) and progesterone receptor (PgR) hormone receptors are frequently expressed in low-grade endometrial stromal sarcoma (LG-ESS) patients, making hormonal blockade an effective treatment option for advanced cases. (39-41) In a retrospective study of 48 LG-ESS patients treated with aromatase inhibitors as first-line therapy, the objective response rate was 8%, disease control at 12 months was 79%, and the median progression-free survival (PFS) was 161 months. (42) A phase II trial investigating fulvestrant in low-grade uterine sarcomas is ongoing in Europe (NCT03926936). Another randomized, multicenter phase II study is exploring the feasibility of interrupting aromatase inhibitor therapy for locally advanced or metastatic LG-ESS after stabilization or response to initial treatment (NCT03624244). Selective estrogen receptor modulators should be avoided due to their agonistic effects on endometrial stromal cells.

Trabectedin: Evidence supports the use of trabectedin after hormonal therapy failure. In one study, 14 out of 27 patients had stable disease, with a PFS at 12 weeks of 50% and a median treatment duration of 2.2 months. Trabectedin is better tolerated compared to chemotherapy, making it a suitable option for patients with both severe and less severe diseases. (43)

Hormonal Treatment in ULMS: A prospective phase II study of aromatase inhibitors in uterine leiomyosarcoma (ULMS) showed no objective responses. (44) However, 14 out of 27 patients had stable disease, with a PFS at 12 weeks of 50% and a median treatment duration of 2.2 months. Hormonal treatment is relatively well tolerated compared to chemotherapy and is recommended for patients with indolent and lower-burden disease. (45)

Radiation therapy
The EORTC/GCG randomized phase III trial compared external beam pelvic radiation therapy (RT) with observation in FIGO stage I and II uterine leiomyosarcoma (ULMS), endometrial stromal

sarcoma (ESS), and carcinosarcoma. (46) Results from the ULMS cohort indicated no benefit from adjuvant RT. Isolated local recurrences occurred in 4% of patients receiving radiotherapy compared to 24% in the observation group. However, 54% of patients who received RT developed metastases, while 33% of the control group developed metastases.
In a study by Sampath et al., involving 920 ULMS patients who received adjuvant RT (n = 230), the 5-year local disease-free survival rate increased from 84% to 98% in stage II and advanced disease ($P<0.01$). Although adjuvant pelvic RT does not improve overall survival in diseases with a high risk of metastasis, it may reduce pelvic recurrence, especially in FIGO stage II to IV disease. Thus, adjuvant RT may be considered in selected cases with higher local recurrence risk. (47)
The National Comprehensive Cancer Network (NCCN) consensus guidelines recommend observation alone for early-stage, low-grade ESS. Patients with oligometastatic disease may be considered for localized treatments such as surgery, RT, or radiofrequency ablation. (48)
High-grade undifferentiated sarcoma (HGUS) represents an aggressive subtype with poor outcomes regardless of the stage at presentation. The patterns of relapse into the abdominal cavity and distant metastases underscore the limited role of adjuvant RT to the pelvis and highlight the greater unmet need for evaluating systemic therapy.

Targeted therapy

Leiomyosarcoma:
DNA repair pathways: Multiple studies have shown that uLMS exhibit high genomic stress and often exhibit defects in the DNA damage repair pathway, specifically the HR DNA repair pathway. (49) A study of 211 LMS patients at Memorial Sloan Kettering Cancer Center found that abnormal mutations in HR pathway genes were more common in uLMS (18%) than in extrauterine LMS. (50) Among 22 patients with uLMS who received an average of 3 prior lines of treatments, the olaparib/temozolomide combination resulted in an objective response rate of 27%, median PFS of 6.9 months, and a median duration of response of 12 months. (51) An ongoing phase II study evaluates the combination of trabectedin/olaparib in ULMS (NCT04076579). (52)
ATX-101, a cell-penetrating peptide, is a novel therapy that blocks the interaction of proliferating cell nuclear antigens with other proteins involved in DNA damage responses. (53) A Phase II clinical trial evaluating ATX-101 monotherapy in LMS is ongoing and currently recruiting patients (NCT05116683).
Immunotherapy: ULMS has a low mutational burden; thus, mismatch repair deficiency is uncommon. (54,55) Clinical trials on immune checkpoint blockade have been disappointing. A phase II trial on nivolumab for uLMS did not show an objective response, and the median PFS was 1.8 months. (54) Another phase II trial evaluating nivolumab monotherapy and the ipilimumab/nivolumab combination did not show significant efficacy. (56)

A combination of eribulin and pembrolizumab failed to meet the endpoint of a 60% progression-free rate at 12 weeks in a phase II trial. (57) Ongoing studies include combining doxorubicin with pembrolizumab, evaluating anti-PD-1 plus gemcitabine (NCT03536780) and gemcitabine plus docetaxel (NCT04567014) in soft tissue sarcomas including uLMS. In a phase II trial testing pembrolizumab against axitinib, a small-molecule tyrosine kinase inhibitor that is very potent on VEGFR-1 to 3, there was no response in four uLMS patients. (58) Trial on combining cabozantinib, MET, and AXL with ipilimumab and nivolumab (NCT04551430) is ongoing. A phase II trial of rucaparib and nivolumab for LMS (NCT04624178) is also ongoing.

Uterine leiomyosarcoma (ULMS) is enriched in tumor-associated macrophages, contributing to cancer progression through paracrine signaling. (59) Combinations of avelumab with the colony-stimulating factor 1 receptor inhibitor DCC-3014 (NCT0424238) and of doxorubicin with the CD40

agonist APX005M (NCT03719430) are being evaluated. A clinical trial is ongoing combining doxorubicin with the novel immune checkpoint inhibitor TTI-621 (NCT04996004).

Tyrosine Kinases and Intracellular signaling pathways: Genomic profiling of uLMS could not demonstrate recurrent oncogenic alterations in receptor tyrosine kinases, thus hindering targeted therapy.

- Pazopanib is a multi-tyrosine kinase VEGF inhibitor. Of the 343 sarcoma patients treated with pazopanib in 2 studies (EORTC phase II and PALETTE phase III), 44 had uterine sarcoma (39 uterine LMS). (60-62) The median duration of response in uterine LMS patients was 3.9 months (1.8 months to 9.4 months, ORR 11%). Additionally, 57% of the patients had stable disease with a mean disease duration of 4.7 months. Regarding pazopanib, quality of life should be considered as it causes gastrointestinal symptoms, especially diarrhea. Dose modification should be considered early in treatment.
- Bevacizumab, a monoclonal antibody against VEGF, failed to improve clinical endpoints when added to first-line gemcitabine and docetaxel in a phase III trial enrolling patients with uLMS.(63) An ongoing study investigates temozolomide combined with cabozantinib for uLMS, HG-ESS, and adenosarcoma (NCT04200443). (64) Anlotinib, a multi-receptor tyrosine kinase inhibitor of vascular endothelial growth factor receptors 2 and 3, platelet-derived growth factor receptor A/B, fibroblast growth factor receptors 1 through 4, KIT, RET, FMS, and DDR1, significantly improved PFS when compared with placebo for patients with LMS in a phase II trial conducted in China. A randomized study comparing anlotinib and dacarbazine, including a leiomyosarcoma-specific arm, is ongoing in the United States and Europe (NCT03016819).
- It has been shown in studies that the PI3K/mTOR/AKT pathway is activated in uLMS through various mechanisms like an amplification of mTOR, RICTOR, AKT, or insulin-like growth factor 1, and loss of tumor suppressors such as PTEN.(65) however, mTOR inhibitor monotherapy has not shown efficacy in ULMS due to recurrent alterations that are not still targetable. Hence, more advanced approaches are required to gain results in targeted therapy.

  Low-Grade Endometrial Stromal Sarcoma: JAZF1-SUZ12 fusions are the most common in LG-ESS tumors. Gene expression profiling revealed that many derepressed genes are involved in the Wnt signaling pathway. Therefore, there is also an increase in β-catenin nuclear expression in LG-ESS. (66) Thus, efforts should be made to investigate inhibitors of the Wnt pathway for LG-ESS.

  High-Grade Endometrial Stromal Sarcoma: Gene expression profiles of HG-ESS showed increased expression of NTRK3, FGFR3, RET, BCOR, GLI1, and PTCH1, but decreased expression of ESR1.(67) This may suggest a role for tyrosine kinase inhibitors and sonic hedgehog pathway inhibitors in the treatment of HG-ESS. A clinical trial of cabozantinib/gemcitabine/docetaxel is currently in recruitment (NCT04200443). (68) Reduced ESR1 expression in HG-ESS may explain the limited activity of hormone blockers.
- The YWHAE–NUT2M fusions lead to the activation of CDK4 by cyclin D1, thus promoting the progression of the G1-S phase of the cell cycle and providing a therapeutic target for HG-ESS. In preclinical studies, the CDK4/6 inhibitor palbociclib and the mitogen-activated protein kinase inhibitor PD325901 provided 55% and 65% inhibition of cell viability in the HG-ESS model, respectively, and the combination inhibited 90% of the cells. (69)
- BCOR-rearranged uterine sarcomas are classified as high-grade endometrial stromal sarcomas (HG-ESS). (70) Genomic profiling of these tumors has revealed a low mutational burden and a lack of microsatellite instability. However, MDM2, CDK4, and FRS2 amplifications were detected in 45%, 38%, and 40% of cases, respectively, suggesting a potential role for CDK4/6 inhibitors in treating patients with HG-ESS. (71) Various MDM2 inhibitors are currently undergoing clinical trials. Less common alterations include amplifications in platelet-derived growth factor receptor A (PDGFRA), vascular endothelial growth factor receptor 2 (VEGFR2), ERBB3, and KIT (each in less than 10% of cases), as well as NF1 mutations. (72)

Perivascular epithelioid cell tumors of the uterus (PEComa): Perivascular epithelioid cell tumors are rare sarcomas that show smooth muscle and melanocyte features and are characterized by deletion of the tuberous sclerosis complex (TSC1/2) gene, which leads to mTOR Pathway activation. (73) These tumors have shown a response to hormone therapy and mTORC1 inhibition with oral drugs such as sirolimus, everolimus, and temsirolimus. (74,75) In a recent retrospective study of nab-sirolimus, a novel mTOR inhibitor in the AMPECT trial, 25% of participants had perivascular epithelioid tumors. These patients had an objective response rate of 39% and a median PFS of 10.6 months. (76)
Applicable genomic alterations: Fibrosarcomatoid uterine sarcomas are characterized by neurotrophic tyrosine receptor kinase fusions, usually TPM3-neurotrophic tyrosine receptor kinase 1, which tyrosine receptor kinase inhibitors can target. Another fusion, COL1A1-PDGFB, responds to the tyrosine kinase inhibitor imatinib. A subtype of undifferentiated uterine sarcoma is characterized by loss of SMARCA4 expression. These tumors may respond to the EZH2 inhibitor Tazemetostat.(77)

Conclusion

The primary treatment for uterine sarcomas remains surgery, with a strong emphasis on performing it correctly and avoiding morcellation. Adjuvant therapy has yet to demonstrate effectiveness. The most recent clinical trial by EORTC and GOG closed early due to insufficient participant accrual. There is optimism that a deeper understanding of tumor biology and intervention pathways, along with the development of new targeted therapies, will lead to improved outcomes in the future.

References

1. Major FJ, Blessing JA, Silverberg SG, et al. Prognostic factors in early-stage uterine sarcoma. A Gynecologic Oncology Group study. Cancer. 1993;71:1702–1709
2. McCluggage WG. Malignant biphasic uterine tumors: carcinosarcomas or metaplastic carcinomas? J Clin Pathol. 2002;55:321-325.
3. WHO Classification of Tumours Editorial Board (ed.). Female Genital Tumours: WHO Classification of Tumours. Lyon: International Agency for Research on Cancer; 2020.
4. Wysowski DK, Honig SF, Beitz J. Uterine sarcoma associated with tamoxifen use. N Engl J Med. 2002;346:1832-1833.
5. Wickerham DL, Fisher B, Wolmark N, et al. Association of tamoxifen and uterine sarcoma. J Clin Oncol. 2002;20:2758-2760.
6. Yu CL, Tucker MA, Abramson DH, et al. Cause-specific mortality in long-term survivors of retinoblastoma. J Natl Cancer Inst. 2009;101:581-591.
7. Lee SJ, Park JY: A rare case of intramural Müllerian adenosarcoma arising from adenomyosis of the uterus. J Pathol Transl Med 2017;51:433–440.
8. Thomassin-Naggara I, Dechoux S, Bonneau C, et al. How to differentiate benign from malignant myometrial tumors using MR imaging. Eur Radiol. 2013;23:2306-2314.
9. Abdel Wahab C, Jannot AS, Bonaffini PA, et al. Diagnostic algorithm to differentiate benign atypical leiomyomas from malignant uterine sarcomas with diffusionweighted MRI. Radiology. 2020;297:361-37
10. Smith J, Zawaideh JP, Sahin H, Freeman S, Bolton H, Addley HC. Differentiating uterine sarcoma from leiomyoma: BET1 T2ER Check! Br J Radiol 2021; 94: 20201332
11. Amant F, Coosemans A, Debiec-Rychter M, et al. Clinical management of uterine sarcomas. Lancet Oncol. 2009;10:1188-1198.
12. Kruse A-J, Croce S, Kruitwagen RFPM, et al. Aggressive behavior and poor prognosis of endometrial stromal sarcomas with YWHAE-FAM22 rearrangement indicate the clinical importance to recognize this subset. Int J Gynecol Cancer. 2014;24:1616-1622.
13. Hensley ML, Chavan SS, Solit DB, et al. Genomic landscape of uterine sarcomas defined through prospective clinical sequencing. Clin Cancer Res. 2020;26:3881-3888

14. George S, Barysauskas C, Serrano C, et al. Retrospective cohort study evaluating the impact of intraperitoneal morcellation on outcomes of localized uterine leiomyosarcoma. Cancer. 2014;120:3154–3158.
15. Koh W-J, Abu-Rustum NR, Bean S, et al. Uterine neoplasms, version 1.2018, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2018;16:170-199.
16. 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;18:1065-1070.
17. Benson C, Miah AB. Uterine sarcoma: current perspectives. Int J Womens Health. 2017;9:597-606.
18. Zhang Y, Li N, Wang W, et al. Long-term impact of lymphadenectomies in patients with low-grade, early-stage uterine endometrial stroma sarcoma. J Obstet Gynaecol Res. 2020;46:654-662.
19. Trope CG, Abeler VM, Kristensen GB. Diagnosis and treatment of sarcoma of the uterus: a review. Acta Oncol. 2012;51:694-705
20. Nasioudis D, Chapman-Davis E, Frey M, et al. Safety of ovarian preservation in premenopausal women with stage I uterine sarcoma. J Gynecol Oncol. 2017;28:e46.
21. Stewart LE, Beck TL, Giannakopoulos NV, et al. Impact of oophorectomy and hormone suppression in low grade endometrial stromal sarcoma: a multicenter review. Gynecol Oncol. 2018;149:297-300.
22. Bai H, Yang J, Cao D, et al. Ovary and uterus-sparing procedures for low-grade endometrial stromal sarcoma: a retrospective study of 153 cases. Gynecol Oncol. 2014;132:654-660.
23. Zheng Y, Yin Q, Yang X, et al. Fertility-sparing management of low-grade endometrial stromal sarcoma: analysis of an institutional series, a population-based analysis and review of the literature. Ann Transl Med. 2020;8:1358.
24. Dondi G, Porcu E, De Palma A, et al. Uterine Preservation Treatments in Sarcomas: Oncological Problems and Reproductive Results: A Systematic Review. Cancers (Basel) 2021;13.
25. Omura GA, Blessing JA, Major F, et al. A randomized clinical trial of adjuvant adriamycin in uterine sarcomas: a gynecologic oncology group study. J Clin Oncol. 1985;3(9):1240.
26. Hensley ML, Wathen JK, Maki RG, et al. Adjuvant therapy for high-grade, uterus-limited leiomyosarcoma: results of a phase 2 trial (SARC 005). Cancer. 2013;119(8):1555–1561.
27. Omura GA, Major FJ, Blessing JA, et al. A randomized study of adriamycin with and without dimethyl triazenoimidazole carboxamide in advanced uterine sarcomas. Cancer. 1983;52:626–632
28. Judson I, Verweij J, Gelderblom H, et al. European organization and treatment of cancer soft tissue and bone sarcoma group. Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomized controlled phase 3 trial. Lancet Oncol. 2014;15:415–423
29. Brown TR, Vijarnsorn C, Potts J. Anthracycline induced cardiac toxicity in pediatric Ewing sarcoma: a longitudinal study. Pediatr Blood Cancer. 2013;60:2–848.
30. Schwartz CL, Wexler LH, Krailo MD, et al. Intensified chemotherapy with dexrazoxane cardioprotection in newly diagnosed nonmetastatic osteosarcoma: a report from the children's oncology group. Pediatr Blood Cancer. 2016;63:54– 61
31. Seddon B, Strauss SJ, Whelan J, et al. Gemcitabine and docetaxel versus doxorubicin as first-line treatment in previously untreated advanced unresectable or metastatic soft-tissue sarcomas (GeDDiS): a randomised controlled phase 3 trial. Lancet Oncol. 2017;18:1397-1410.
32. 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;109:323–328.

33. Hensley ML, Blessing JA, Mannel R, et al. Fixed-dose rate gemcitabine plus docetaxel as first-line therapy for metastatic uterine leiomyosarcoma: a gynecologic oncology group phase II trial. Gynecol Oncol. 2008;109:329–334.
34. Maki RG, Wathen JK, Patel SR, et al. 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;25:2755–2763
35. Talbot SM, Keohan ML, Hesdorffer M, et al. A phase II trial of temozolomide in patients with unresectable or metastatic soft tissue sarcoma. Cancer. 2003;98:1942–1946.
36. Demetri GD, von Mehren M, Jones RL, et al. Efficacy and safety of trabectedin or dacarbazine for metastatic liposarcoma or leiomyosarcoma after failure of conventional chemotherapy: results of phase III randomized multicenter clinical trial. J Clin Oncol. 2016;34:786–793
37. Hensley ML, Patel SR, von Mehren M, et al. Efficacy and safety of trabectedin or dacarbazine in patients with advanced uterine leiomyosarcoma after failure of anthracycline-based chemotherapy: subgroup analysis of a phase 3, randomized clinical trial. Gynecol Oncol. 2017;146:531–537
38. Schöffski P, Chawla S, Maki RG, et al. Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: a randomized, open-label, multicentre, phase 3 trial. Lancet. 2016;387:1629–1637
39. Nakayama K, Ishikawa M, Nagai Y, et al. Prolonged long-term survival of low-grade endometrial stromal sarcoma patients with lung metastasis following treatment with medroxyprogesterone acetate. Int J Clin Oncol. 2010;15:179-183.
40. Altman AD, Nelson GS, Chu P, et al. Uterine sarcoma and aromatase inhibitors: Tom Baker Cancer Centre experience and review of the literature. Int J Gynecol Cancer. 2012;22:1006-1012.
41. Burke C, Hickey K. Treatment of endometrial stromal sarcoma with a gonadotropin-releasing hormone analogue. Obstet Gynecol. 2004;104:1182-1184
42. Crowley F, Cadoo KA, Chiang S, et al. Evaluating the role of aromatase inhibitors (AIs) in the treatment of endometrial stromal sarcomas (ESS). J Clin Oncol. 2021;39:15s (suppl; abstr 5575).
43. Pink D, Lindner T, Mrozek A, et al. Harm or benefit of hormonal treatment in metastatic low-grade endometrial stromal sarcoma: single center experience with 10 cases and review of the literature. Gynecol Oncol. 2006;101:464-469
44. Le Cesne A, Cresta S, Maki RG, et al. A retrospective analysis of antitumor activity with trabectedin in translocation-related sarcomas. Eur J Cancer. 2012;48(16):3036–3044.
45. George S, Feng Y, Manola J, et al. Phase 2 trial of aromatase inhibition with letrozole in patients with uterine leiomyosarcomas expressing estrogen and/or progesterone receptors. Cancer. 2014;120(5):738–74
46. Reed NS, Mangioni C, Malmstrom H, et al. European Organisation for Research and Treatment of Cancer Gynaecological Cancer Group. 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(6):808–818.
47. Sampath S, Schultheiss TE, Ryu JK, Wong JY. The role of adjuvant radiation in uterine sarcomas. Int J Radiat Oncol Biol Phys. 2010;76(3): 728–734
48. National Comprehensive Cancer Network (NCCN) [webpage on the Internet]. NCCN Clinical Practice Guidelines in Oncology. 2017
49. Oza J, Doshi SD, Hao L, et al. Homologous recombination repair deficiency as a therapeutic target in sarcoma. Semin Oncol. 2020;47:380-389
50. Rosenbaum E, Jonsson P, Seier K, et al. DNA damage response pathway alterations and clinical outcome in leiomyosarcoma. J Clin Oncol. 2019;37:15s (suppl; abstr 11048)

51. Ingham M, Allred JB, Gano K, et al. NCI protocol 10250: a phase II study of temozolomide and olaparib for the treatment of advanced uterine leiomyosarcoma. J Clin Oncol. 2021;39:15s (suppl; abstr 11506)
52. Grignani G, D'Ambrosio Llll;;;;;;;, Pignochino Y, et al. Trabectedin and olaparib in patients with advanced and non-resectable bone and soft-tissue sarcomas (TOMAS): an open-label, phase 1b study from the Italian Sarcoma Group. Lancet Oncol. 2018;19:1360-1371.
53. Choe KN, Moldovan GL. Forging ahead through darkness: PCNA is still the principal conductor at the replication fork. Mol Cell. 2017;65:380-392.
54. Ben-Ami E, Barysauskas CM, Solomon S, et al. Immunotherapy with single-agent nivolumab for advanced leiomyosarcoma of the uterus: results of a phase 2 study. Cancer. 2017;123:3285-3290.
55. Tawbi HA, Burgess M, Bolejack V, et al. Pembrolizumab in advanced soft-tissue sarcoma and bone sarcoma (SARC028): a multicentre, two-cohort, single-arm, open-label, phase 2 trial. Lancet Oncol. 2017;18:1493-1501.
56. D'Angelo SP, Mahoney MR, Van Tine BA, et al. Nivolumab with or without ipilimumab treatment for metastatic sarcoma (Alliance A091401): two open-label, non-comparative, randomized, phase 2 trials. Lancet Oncol. 2018;19:416-426.
57. Nathenson MJ, Choy E, Carr N, et al. Phase II study of eribulin and pembrolizumab in patients (pts) with metastatic soft tissue sarcomas (STS): report of LMS cohort. J Clin Oncol. 2020;38:15s (suppl; abstr 11559).
58. Wilky BA, Trucco MM, Subhawong TK, et al. Axitinib plus pembrolizumab in patients with advanced sarcomas including alveolar soft-part sarcoma: a singlecentre, single-arm, phase 2 trial. Lancet Oncol. 2019;20:837-848.
59. Lee CH, Espinosa I, Vrijaldenhoven S, et al. Prognostic significance of macrophage infiltration in leiomyosarcomas. Clin Cancer Res. 2008;14:1423-1430.
60. Sleijfer S, Ray-Coquard I, Papai Z, et al. Pazopanib, a multikinase angiogenesis inhibitor, in patients with relapsed or refractory advanced soft tissue sarcoma: a phase II study from the european organisation for research and treatment of cancer-soft tissue and bone sarcoma group (EORTC study 62043). J Clin Oncol. 2009;27:3126–3132.
61. Van der Graaf WT, Blay JY, Chawla SP, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomized, double-blind, placebo-controlled phase 3 trial. Lancet. 2012;379:1879–1886.
62. Benson C, Ray-Coquard I, Sleijfer S, et al. Outcome of uterine sarcoma patients treated with pazopanib: a retrospective analysis based on two european organisation for research and treatment of cancer (EORTC) soft tissue and bone sarcoma group (STBSG) clinical trials 62043 and 62072. Gynecol Oncol. 2016;142:89–94
63. Hensley ML, Miller A, O'Malley DM, et al. Randomized phase III trial of gemcitabine plus docetaxel plus bevacizumab or placebo as first-line treatment for metastatic uterine leiomyosarcoma: an NRG Oncology/Gynecologic Oncology Group study. J Clin Oncol. 2015;33:1180-1185.
64. Ray-Coquard I, Hatcher H, Bompas E, et al. A randomized double-blind phase II study evaluating the role of maintenance therapy with cabozantinib in high grade uterine sarcoma after stabilization or response to doxorubicin ± ifosfamide following surgery or in metastatic first line treatment (EORTC62113). Int J Gynecol Cancer. 2020;30:1633-1637
65. Kawaguchi K, Oda Y, Saito T, et al. Mechanisms of inactivation of the p16INK4a gene in leiomyosarcoma of soft tissue: decreased p16 expression correlates with promoter methylation and poor prognosis. J Pathol. 2003;201:487-495.
66. Przybyl J, Kidzinski L, Hastie T, et al. Gene expression profiling of low-grade endometrial stromal sarcoma indicates fusion protein-mediated activation of the Wnt signaling pathway. Gynecol Oncol. 2018;149:388-393

67. Momeni-Boroujeni A, Mohammad N, Wolber R, et al. Targeted RNA expression profiling identifies high-grade endometrial stromal sarcoma as a clinically relevant molecular subtype of uterine sarcoma. Mod Pathol. 2021;34:1008-1016.
68. Sminu Bose, Gary K. Schwartz, Matthew Ingham. Novel Therapeutics in the Treatment of Uterine Sarcoma. 2022 ASCO EDUCATIONAL BOOK, DOI https://doi.org/ 10.1200/ EDBK_350541
69. Ou WB, Lundberg MZ, Zhu S, et al. YWHAE-NUTM2 oncoprotein regulates proliferation and cyclin D1 via RAF/MAPK and Hippo pathways. Oncogenesis. 2021;10:37
70. Kommoss FKF, Stichel D, Schrimpf D, et al. DNA methylation-based profiling of uterine neoplasms: a novel tool to improve gynecologic cancer diagnostics. J Cancer Res Clin Oncol. 2020;146:97-104.
71. Lin DI, Hemmerich A, Edgerly C, et al. Genomic profiling of BCOR-rearranged uterine sarcomas reveals novel gene fusion partners, frequent CDK4 amplification and CDKN2A loss. Gynecol Oncol. 2020;157:357-366.
72. Kommoss FK, Chang KT, Stichel D, et al. Endometrial stromal sarcomas with BCOR-rearrangement harbor MDM2 amplifications. J Pathol Clin Res. 2020;6:178-184.
73. Bennett JA, Braga AC, Pinto A, et al. Uterine PEComas: a morphologic, immunohistochemical, and molecular analysis of 32 tumors. Am J Surg Pathol. 2018;42:1370-1383.
74. Chiang S, Vasudevaraja V, Serrano J, et al. TSC2-mutant uterine sarcomas with JAZF1-SUZ12 fusions demonstrate hybrid features of endometrial stromal sarcoma and PEComa and are responsive to mTOR inhibition. Mod Pathol. 2022;35:117-127.
75. Dickson MA, Schwartz GK, Antonescu CR, et al. Extrarenal perivascular epithelioid cell tumors (PEComas) respond to mTOR inhibition: clinical and molecular correlates. Int J Cancer. 2013;132:1711-1717
76. Wagner AJ, Ravi V, Riedel RF, et al. nab-Sirolimus for patients with malignant perivascular epithelioid cell tumors. J Clin Oncol. 2021;39:3660-3670.
77. Kolin DL, Dong F, Baltay M, et al. SMARCA4-deficient undifferentiated uterine sarcoma (malignant rhabdoid tumor of the uterus): a clinicopathologic entity distinct from undifferentiated carcinoma. Mod Pathol. 2018;31:1442-1456.