LATEST 2024 MARROW NEET-SS NOTES

UPDATED OBSGYNE RESIDENCY NOTES

GYNECOLOGIC ONCOLOGY

UTERINE SARCOMA

Introduction

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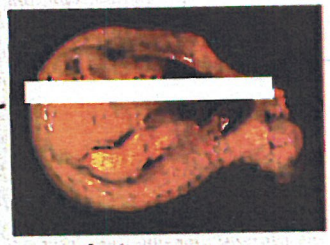
Sarcoma arising from stromal cells → Stromal sarcoma.
Sarcoma arising from muscle → Leiomyoma sarcoma.



Uterine sarcoma.

WHO classification of uterine sarcomas :

- Leiomyosarcoma (LMS).
- Low-grade endometrial stromal sarcoma (LG-ESS).
- High-grade endometrial stromal sarcoma (HG-ESS).
- Undifferentiated uterine sarcoma (UUS).
- Adenosarcoma (AS).
- PEComa (perivascular epithelioid cell tumor), malignant variant → TSC gene mutation.

Histologic type of uterine sarcoma :

- Leiomyosarcoma.
  i. Not otherwise specified.
  ii. Spindle (Conventional).
  iii. Epitheloid.
  iv. Myxoid.
- Endometrial stromal sarcoma, low grade.
- Endometrial stromal sarcoma, high grade.
- Undifferentiated sarcoma.
- Adenosarcoma.
  i. Not otherwise specified.
  ii. With sarcomatous overgrowth.
- Rhabdomyosarcoma.
- Malignant perivascular epitheloid cell tumour.
- Other (Specify).

FIGO/TNM staging :

LMS & ESS :

FIGO/TNM stage.		Definition.
I/T1.		Tumor limited to the uterus.
	IA/T1a.	Tumor ≤ 5cm in greatest dimension.
	IB/T1b.	Tumor > 5cm in greatest dimension.
II/T2.		Tumor extends beyond the uterus, within the pelvis.
	IIA/T2a.	Involvement of the adnexa (unilateral/bilateral).
	IIB/T2b.	Tumor has spread into extrauterine pelvic tissue excluding the adnexa.
III/T3.		Tumor has infiltrated abdominal tissue.
N.	IIIA/T3a.	One site.
	IIIB/T3b.	more than one site.
	IIIC.	metastasis of pelvic and/or paraaortic lymph nodes.
IV/T4.	IVA/T4.	Tumor has infiltrated bladder and/or rectum.
	IVB.	Distant metastasis.

Adenosarcoma :

FIGO/TNM Stage.		Definition.
I/T1.		Tumor limited to the uterus.
	IA/T1a.	Tumor limited to the endometrium/endocervix without myometrial infiltration.
	IB/T1b.	Tumor has infiltrated less than half of the myometrium.
	IC/T1c.	Tumor has infiltrated ≥ 50% of the myometrium.
II/T2.		Tumor has spread to the pelvis.
	IIA/T2a.	Involvement of the adnexa (unilateral/bilateral).
	IIB/T2b.	Tumor has spread to extrauterine pelvic tissue excluding the adnexa.
III/T3.		Intraabdominal tumor spread.
N.	IIIA/T3a.	One site.
	IIIB/T3b.	more than one site.
	IIIC.	metastasis in pelvic and/or paraaortic lymph nodes.
IV/T4.	IVA/T4.	Tumor has infiltrated bladder and/or rectal mucosa.
	IVB.	Distant metastasis.

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General treatment :

- Standard treatment for all localised uterine sarcomas is total hysterectomy and bilateral salpingectomy.

- Lymphadenectomy for staging purposes is not indicated.
- Low grade ESS → No post op HRT → Use of adjuvant anti-oestrogen therapy is not routinely indicated.
- Adjuvant pelvic radiotherapy has not been shown to improve local control or survival and is not routinely indicated in FIGO stage I and II uterine sarcoma → It could be considered for selected high-risk cases.

Leiomyosarcoma 00:23:27

Incidence :

Constitutes 1 - 2% of uterine malignancies.

Around 1 in every 800 smooth muscle tumors of the uterus.

Incidence → 3 - 7 /1 lakh people.

Median age → 50 - 70 years of age.

Risk factors :

- Increase age /postmenopausal → Average age of 60 years.
- Suspicion if uterine mass is enlarging in postmenopausal patients.
- Tamoxifen use for ≥ 5 years → Risk is 17/1 lakh.
- Pelvic irradiation.
- H/o childhood Rb/HLRCC syndrome.

Symptoms :

- Abnormal bleeding (56 %).
- Palpable pelvic mass (54 %).
- Pelvic pain (22 %).

Causes :

- Arise de novo.
- < 5 % arise from malignant transformation of existing leiomyoma.
- Large uterine size and rapid growth is not associated with increased risk of leiomyosarcoma.

Diagnostic criteria :

Conventional (Spindle cell) LMS :

- Moderate to high grade cellular atypia (2+/3+ nuclear atypia).
- Confirmed tumor cell necrosis.
- > 4 mitosis/mm^2 (Corresponds to > 10 mitotic figures/10 hpf with a diameter

of field of view of 0.55 mm and a field of view surface of 0.24 mm^2.

Atleast 2 criteria must be met.

Epitheloid LMS :

- Moderate to high grade cellular atypia (2+/3+ nuclear atypia).
- Confirmed tumor cell necrosis.
- > 1.6 mitosis/mm^2 (Corresponds to > 4 mitotic figures/10 hpf with a diameter of field of view of 0.55 mm and a field of view surface of 0.24 mm^2.

Atleast 1 criteria must be met.

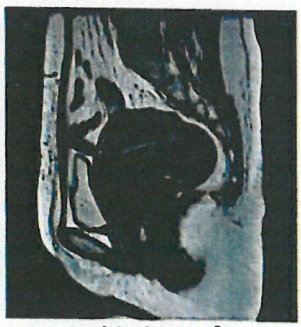
Myxoid LMS :

- Moderate to high grade cellular atypia (2+/3+ nuclear atypia).
- Confirmed tumor cell necrosis.
- > 0.4 mitoses/mm^2 (Corresponds to > 1 mitotic figure/10 hpf with a diameter of field of view of 0.55 mm and a field of view surface of 0.24 mm^2.
- Infiltrative tumor borders or irregular lesion border.

Atleast 1 criteria must be met.

Leiomyosarcoma.

Leiomyoma.



T2 weighted MRI of leiomyosarcoma.

Other features :

- Recurrence rates → 53 to 71 %.
- 5 year survival rate → 40 to 50 %.
- Ovarian mets are rare.
- LMS has less ER/PR +ve.
- LND → Lymph node metastasis is rare → If lymph node metastasis present → Hematogenous/distant mets is probable → No role for LND.

Pathological features :

- Typically large (>10 cm), yellow or tan solitary masses with soft, fleshy cut surfaces with areas of hemorrhage and necrosis.
- Epicenter in myometrium, lacks the prominent whorled appearance of leio-

myomas.

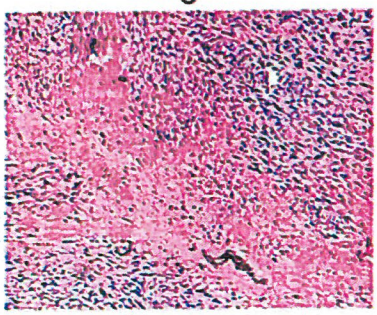
- Leiomyomas originate from the myometrium but can extend upto the endometrium → Such cases present with abdominal bleeding.

Leiomyosarcoma.

Histopathologic diagnosis :

- Constellation of hypercellularity.
- Severe nuclear atypia.
- High mitotic rate generally exceeding 10 mitotic figures per 10 high-power-fields (MF/10 hpf).

Diagnosis → Requires 2 of 3 histologic features.



HPE of leiomyosarcoma.

Differential diagnosis :

Leiomyoma variants that mimic malignancy :

- Mitotically active leiomyoma (mitosis > 10/10 hpf) → mitosis > 15/10 hpf → STUMP → Necrosis → Poor prognosis.
- Cellular leiomyoma
- Hemorrhagic leiomyoma and hormone-induced changes.
- Leiomyoma with bizarre nuclei (Atypical leiomyoma).
- Myxoid leiomyoma.
- Epithelioid leiomyoma.
- Leiomyoma with massive lymphoid infiltration.

Smooth muscle proliferation with unusual growth patterns :

- Disseminated peritoneal leiomyomatosis.
- Benign metastasizing leiomyoma.
- Intravenous leiomyomatosis.
- Lymphangioleiomyomatosis.

Atypical smooth muscle tumors (STUMP) :

- Tumor cell necrosis in a typical leiomyoma.
- Necrosis of uncertain type with ≥10 MF/10 HPFs, or marked diffuse atypia.
- Marked diffuse or focal atypia with borderline mitotic counts.
- Necrosis difficult to classify.

IHC:

- Usually express smooth muscle markers such as desmin, h-caldesmon, SMA, and histone deacetylase 8 (HDAC8).
- Often immunoreactive for CD10 and epithelial markers including Keratin and EMA
- Estrogen receptors, progesterone receptors, and androgen receptors → 30%–40%.
- Overexpression of p16 has been described and Ki67.

Prognosis:

- Associated with poor prognosis even when confined to the uterus.
- Recurrence rate → 53 % to 71 %.
- 5 year survival → 41.9 %, in advanced uLMS → < 15 %.
- First recurrences occur in lungs in 40% patients, pelvis in only 13%.
- Tumors ≥ 10 cm in diameter, with ≥ 20 MF/10 HPF, ≥ 10% immunoreactive nuclei for Ki67, and negative for Bcl-2 had worse prognosis than smaller leiomyosarcomas with ≤ 20 MF/10 HPF, ≤ 10% immunoreactive nuclei for Ki67, and positive or negative for Bcl-2.

Preop diagnosis:

There is no single test to differentiate with 100 % sensitivity to differentiate leiomyoma and leiomyosarcoma.

US FDA has issued blackbox warning in 2014 → Not to do morcellators while doing myomectomy in peri/postmenopausal women.

Investigations used for pre op diagnosis are:

- USG.
- MRI.
- Endometrial biopsy.
- LDH.

USG:

- Difficult to distinguish from leiomyomas.
- Both show focal masses within uterus and can have central necrosis.
- Features suggestive of sarcomas (may be also seen in leiomyoma):
  i. Mixed echogenic and poor echogenic parts.
  ii. Central necrosis.
  iii. Color doppler → Irregular vessel distribution.
  iv. Low impedance to flow.
  v. High peak systolic velocity.

MRI:

MRI findings of uterine sarcomas:

	Leiomyoma.	Leiomyosarcoma.
Age.	Premenopausal.	Peri/postmenopausal.
Borders.	Well delineated.	Often nodular.
DWI.	Variable.	Restricted diffusion, low ADC.
Invasiveness.	No.	Adjacent tissues.
Number.	Commonly multiple.	Solitary.
Size.	Variable.	Large (> 10cm).
T2WI.	mostly low, high in degeneration, whorled pattern.	Inhomogenous with areas of hemorrhage, intralesional vessels, T2 dark areas.
Vascularity.	Variable; often parallels myometrium, cellular types with avid enhancement.	Hypervascularisation; peripheral early enhancement, central necrosis.

Summary of typical MRI imaging features for leiomyosarcomas and sarcoma: BETTER Check.						
	Typical leiomyoma.	Hyaline & cystic degeneration.	Red degeneration.	Lipoleiomyoma.	Cellular leiomyoma.	Sarcoma.
Border.	Well defined.	Well defined.	Well defined.	Well defined.	Well defined.	Lobulated or irregular.
Enhancement.	Heterogenous.	Heterogenous with no enhancement in degeneration.	Heterogenous with no enhancement in degeneration.	Heterogenous.	Homogenous.	Heterogenous with irregular outline/ invasion.
T1WISI.	Low.	Low.	Hemorrhage high.	Fat high with saturation on fat saturated T1WI.	Low.	Low with high SI in areas of hemorrhage.
T2WISI.	Low.	High in cystic areas.	Variable depending on age of hemorrhage.	Variable given the fat containing component.	Intermediate.	Intermediate and heterogenous.
Endometrial thickening.	None.	None.	None.	None.	None.	Direct involvement/ irregular or thickened.
Restricted diffusion.	No.	No.	No.	No.	Yes.	Yes.

Endometrial biopsy :

- Yields a preoperative diagnosis in 33 - 68 % of patients with uterine sarcomas .
- The method of endometrial sampling (office endometrial biopsy or dilation and curettage) does not impact the sensitivity.

Management :

- Surgery → mainstay treatment, avoiding intraoperative rupture, morcellation or spillage.
- Total hysterectomy & BSO are recommended for patients with LMS grossly confined to the uterus.
- The recommendation for BSO in premenopausal women with LMS should be individualized.
- Reported risk of ovarian metastases → 4 %.
- Ovarian preservation may be considered without compromising survival outcome when there is documented negative endocrine receptor-status.
- The incidence of retroperitoneal lymph node metastases is low (< 5 %).
- Pelvic and para-aortic lymph node dissection not routinely recommended.
- Lymphadenectomy (Debulking) can be performed as part of a cytoreductive effort.

Adjuvant treatment :

Adjuvant treatment with CT/RT/HT → Controversial

It is usually given only in the advanced stages

Chemotherapy :

- First line agents.
- Doxorubicin (19 % response rate).
- Doxorubicin plus ifosfamide (17 % response for Ifosfamide alone, 30% of response rate for combination).
- Gemcitabine (20 % response rate)
- Gemcitabine plus docetaxel (36 % response rate)
- Observation following completely resected uLMS remains the standard approach (NCCN, ESMO).
- Postresection chemotherapy may be offered in patients with advanced disease, rather than observation, although whether treatment improves survival has not been established.

Author.	N.	FIGO.	Study type.	Chemo.	Results.	Conclusion.
Omura et al JCO 1985.	156.	I-II.	Randomised.	Doxorubicin vs observation.	Relapse 31/75 dox 43/81 obs.	No significance.
Hensley et al Gyn onco 2009.	25.	I-IV.	Non randomised.	Gemcitabine, Docetaxel x4.	PFS 2 yr 59 %.	Improved results than historical controls.
Hensleyet al cancer 2013 SARC 005.	47.	I-III.	Non randomised.	Gemcitabine Docetaxel x 4 → Doxorubicin x 4.	PFS 2yr 78 % PFS 3 yr 57 %	Improved results than historical controls.
Pautrieret al Ann oncol 2013.	81.	I-III.	Randomised.	Doxo, ifosf, Cisf/b RT vs RT.	PFS 3 YR 55 % VS 41 % OS at 3 - 5 yr N.S.	Improved PFS at 3 year N.S. OS ↑Toxicity.

Phase III NRG oncology/gynaecologic oncology group study :

- Randomised phase III trial.
- Adjuvant gemcitabine + Docetaxel followed by Doxorubicin vs observation of high grade uterine leiomyosarcoma.
- Asses whether adjuvant chemotherapy improves survival in women with uterine leiomyosarcoma + uterus confined disease.
- Observed OS & RFS data do not show superior outcomes with adjuvant chemo.

European organisation for research and treatment of cancer gynaecological group study :

- Phase III randomised study.
- Evaluates the role of adjuvant pelvic radiotherapy in the treatment of uterine sarcomas stages I and II.
- Only prospective randomised trial
- Post operative RT or observation → 103 patients with uterine leiomyosarcomas → Post operative RT did not improve local or distant progression/survival.

The choice of adjuvant RT in uLMS should be determined on a case by- case basis, balancing between the risk of relapse, patient performance status and side effects, considering the absence of a proven benefit.