Uterine Sarcomas & their Management

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Introduction

- Rare & varied group of neoplasms of mesenchymal origin
- Incidence – 3-7% of all uterine malignancies, 1% of female tract malignancies
- Behave more aggressively than EC
- Poor prognosis as compared to endometrial cancer
- Higher incidence in patients >50 years of age
- Twice incidence in women of Afro-Caribbean descent than Caucasians’

Classification- Mesenchymal tumours

Smooth muscle tumours

1.Leiomyoma
2.I/V Leiomyomatosis
3. Smooth muscle tumour of uncertain malignant potential(STUMP)
4.Metastasizing leiomyoma
5.LMS

Endometrial stromal tumours

1.Endometrial stromal nodule (ESN)
2. Low grade Endometrial stromal sarcoma LGESS
3.HGESS
4. Undiff uterine sarcoma USS

Mixed epith/ mesenchymal tumours

1.Adenomyoma
2. Atypical polypoidal adenomyosis
3. Adenosarcoma
4. Carcinosarcoma

Aetiology

- Poorly understood
- Raised/ unopposed estrogen levels
- Tamoxifen- Long term use >5yrs, Absolute risk 17/100,000 personyrs
- Obesity
- Diabetes
- Prev H/O RT -esp carcinosarcoma

Hereditary conditions

- **Hereditary leiomyomatosis & RCC syndrome**- Rare autosomal disorder
- Caused by mutation in fumarate hydrase enzyme in the Kreb’s cycle
- Multiple cutaneous & uterine leiomymoma & aggressive papillary RCC
- Long term survivors of **hereditary type of retinoblastoma**

General Features

- Different for each group of tumours

	Incidence	Age at diagnosis	
CS	45%	57.4 yrs	
LMS	40%	53.5 yrs	
ESS	15%	41 yrs	

Clinical features

- Usually diagnosed after myomectomy/ hysterectomy for a leiomyoma
- Abnormal uterine bleed - premenopausal - 27-34%, post-31-46%
- Pelvic pain/ pressure- 4-13%
- Abdominal distension - 8-17%
- Urinary S/S- 1-2%
- Rarely sarcoma prolapses through the cervix
- Asymptomatic- 1-2%

Discharge P/V

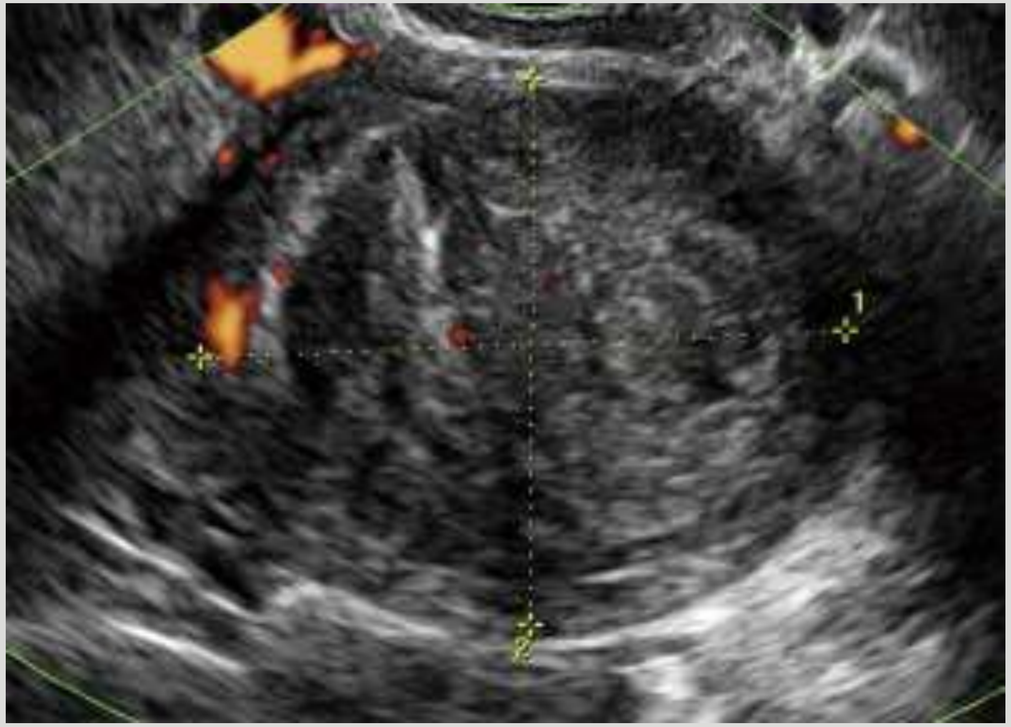
Constipation

Examination

- Size of uterus large
- Ca125, LDH raised
- Suspect sarcoma in premenopausal women if bleeding disproportionate to uterine size
- Doubling in size over 3-6 mths or increase by 6 wk gestational size within a year
- Endometrial Biopsy can correctly identify sarcoma in 63% cases

Ultrasound exam

- Both leiomyoma & sarcoma are focal masses in the uterus
- Sarcomas- Mixed echogenic & poor echogenic parts
- Central necrosis
- Colour Doppler- Irregular vessel distribution
- Low impedence to flow
- High peak systolic velocity



Imaging differences

Histology	Ultrasound findings	MRI findings
LMS	Large heterogenous mass, distorting architecture, contains areas of necrosis & haemorrhage, Increased vascularity on Doppler	Large mass with irregular margins , int to high signal intensity on T2 , hyperintense areas on T1, Central nonenhancement
ESS	Heterogenous hypoechoic mass with extensive myometrial involvement	Low intensity rim on T2 wted image ass with intratumoral haemorrhage , soft polypoid tumours with worm like tumour plugs in the myomet vessels & lymphatics
Undiff US	Unreliable, can lead to incorrect diagnosis of adenomyosis/ uterine leiomyoma	Voluminous polypoid masses with heterogenous appearance & marked vascular & lymphatic invasion, bag of worms appearance, Feather like enhancement
Adenosarcoma	Large polypoidal mass, wihin endometrial cavity	Endometrial based, multiseptate cystic mass with low signal intensity solid areas on T2

Diagnosis

- Based on HPE
- Examination of multiple sites in the mass
- Gross- colour, consistency, variegation of incised surface
- May help guide sites for sampling
- Microscopic- Mitotic index, cellularity, type (myxoid/ epitheloid)

Stage	Definition
(1) Leiomyosarcomas and endometrial stromal sarcomas[a]	
I	Tumor limited to uterus
IA	Less than or equal to 5 cm
IB	More than 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	More than one site
IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
IV	
IVA	Tumor invades bladder and/or rectum
IVB	Distant metastasis
(2) Adenosarcomas	
I	Tumor limited to uterus
IA	Tumor limited to endometrium/endocervix with no myometrial invasion
IB	Less than or equal to half myometrial invasion
IC	More than half myometrial invasion
II	Tumor extends beyond the uterus, within the pelvis
IIA	Adnexal involvement
IIB	Tumor extends to extrauterine pelvic tissue
III	Tumor invades abdominal tissues (not just protruding into the abdomen).
IIIA	One site
IIIB	More than one site
IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
IV	
IVA	Tumor invades bladder and/or rectum
IVB	Distant metastasis
(3) Carcinosarcomas	
Carcinosarcomas should be staged as carcinomas of the endometrium.	

[a] Note: Simultaneous endometrial stromal sarcomas of the uterine corpus and ovary/pelvis in association with ovarian/pelvic endometriosis should be classified as independent primary tumors.

ESS

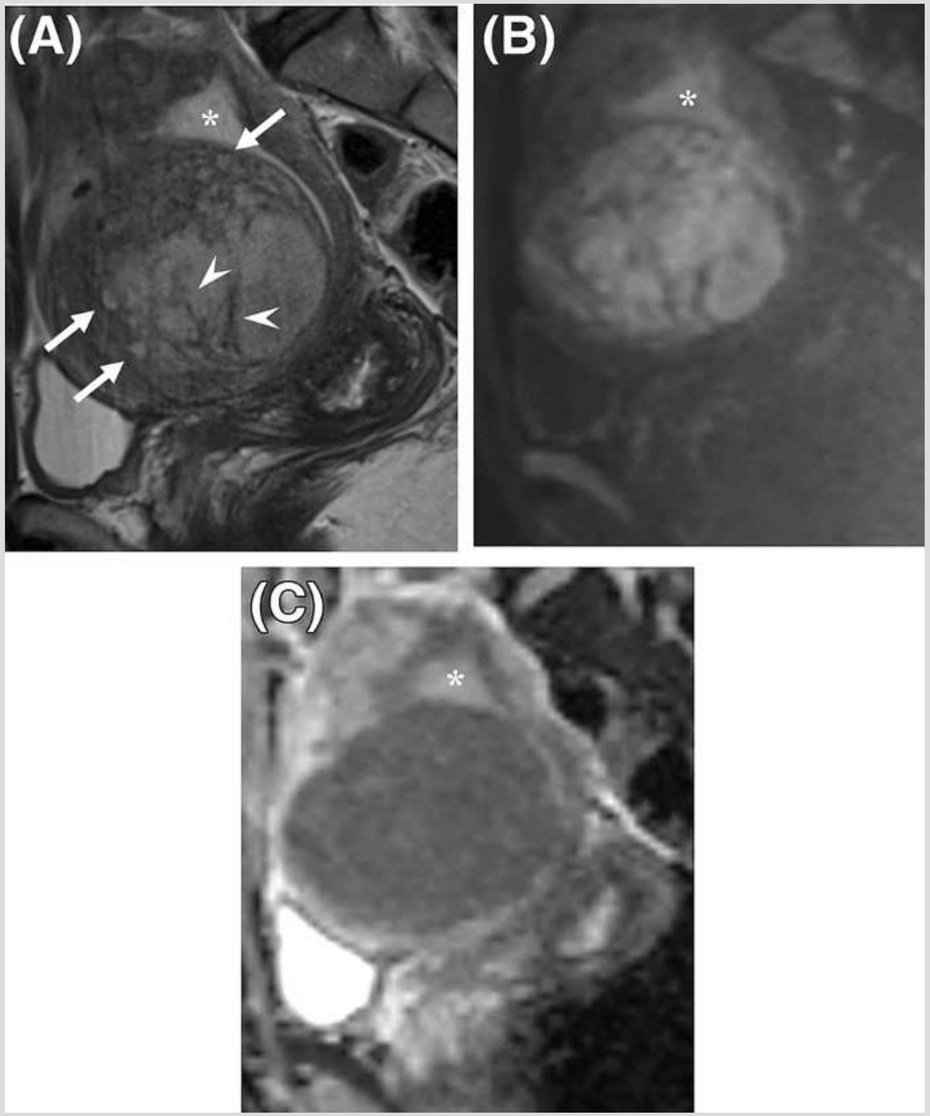
- Uterine mesenchymal tumours with malignant potential
- Gross- Polypoid mass that can invade through blood vessels/ lymphatics
- ESN/ LGESS/HGESS/Undiff
- Classified by
- 1. Invasion into myometrium 2. Degree of differentiation
- Can have heterogenous morphology- Fibrous, mixed, epitheloid, rhabdoid , smooth muscle differentiation

ESS

Type	Clinical behaviour	HPE	Others	Molecular markers
LGESS	low grade with metastatic potential	Myometrial & vascular invasion +	Dense uniform stromal cells, min cellular pleomorphism, mild nuclear atypia, variable mitotic figures	ER+ PR +, Strongle positive CD 10, actin+ h caldesmon & histone e deacytalase 8(HDAC 8) negative
HGESS	Endostromal diff , high grade nuclear atypia	More destructive growth pattern, extensive myometrial invasion, necrosis, LVI&MI>10/10HPF	More frequent recurrences , Higher mortality than LG, worse prognosis	CD10, ER PR negative Strong diffuse cyclin D positive High C Kit expression- poor prognosis
UUS	Marked cytologic atypia, nuclear pleomorphism, High MI, extensive invasion	Lack features of endometrial stromal diff, Exhibit haemorrhge & necrosis	Destructive myometrial invasion	CD10, ER , PR variable Cyclin D1 - can be diffusely positive, ass with CD 10 positivity

Imaging ESS

- Heterogenous ,hypoechoic endometrial mass , can show extensive myometrial involvement
- LG ESS- worm like projections in vessels/ along ligaments, best visualised on MRI/DWI
- PETCT- Distinguish between benign & malignant masses



Diagnosis

- Made on HPE
- Metastatic work up - CECT Chest, abd, Pelvis
- Extrauterine disease - 32% (mostly in ovary)

Poor prognostic factors

- Older pts
- Black race
- Advanced stage
- Higher grade
- Lack of primary surgery
- Nodal mets

Treatment

Confined to uterus

TAH +/- BSO Morcellation should not be attempted
Decreases 5 yr DFS - 55% vs 84%

Extending outside uterus

TAH + BSO & surgical cytoreduction of intra abdominal & retroperitoneal disease
Optimal<2cm residual disease
Signly longer median survival (52 vs 2 mths)
If not fit- NACT

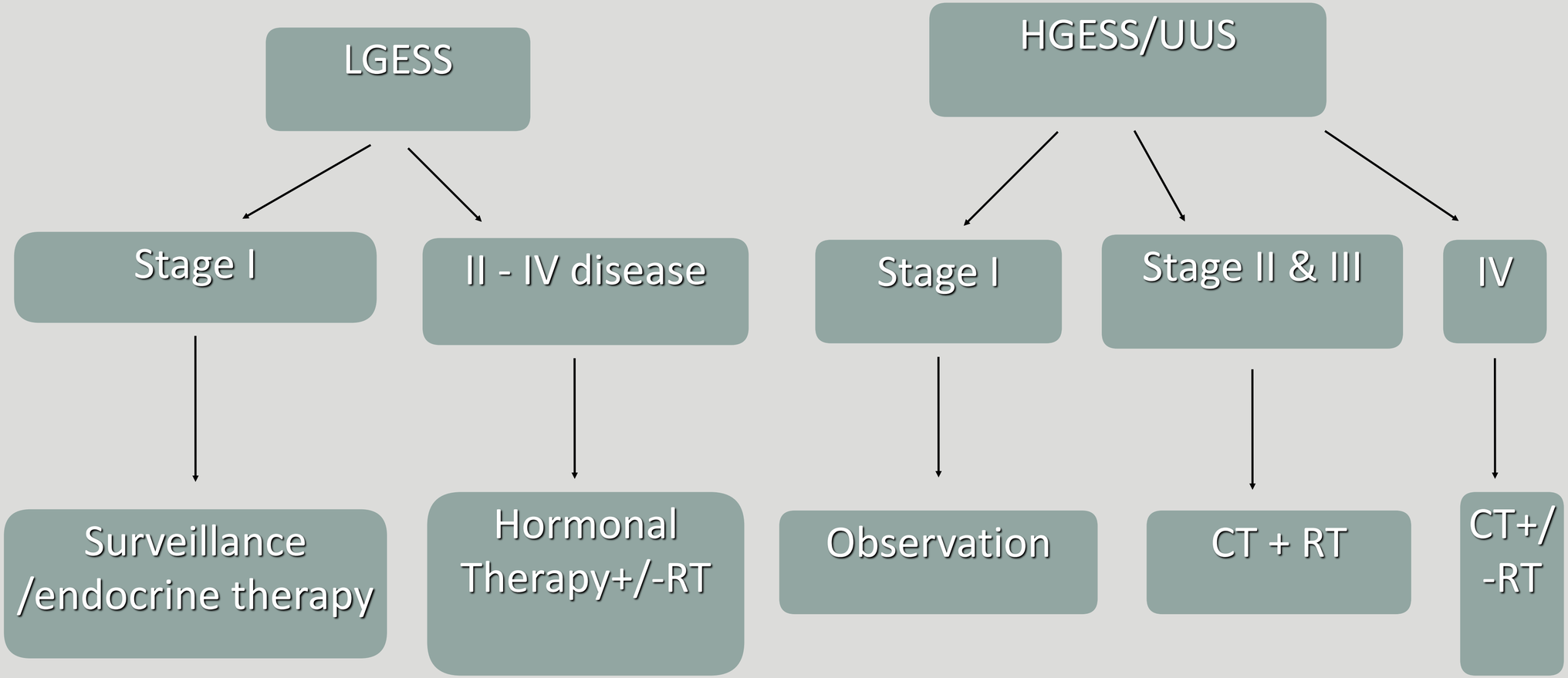
Lymphadenectomy

- Benefit of routine LNE controversial
- Performed only if preop evidence of enlarged nodes (on imaging or intraop)
- Esp in pts without extrauterine disease
- Early stage LGESS- risk of nodal involvement-5%(Major et al,1992)
- Routine LNE does not improve outcome in these pts

Fertility Preservation

- TAH with BSO recommended
- Ovary & uterine sparing procedures- reasonable in premenopausal women who desire fertilty preservation
- Ass with higher risk of relapse at 5yrs, vs those with TAH BSO alone

Adjuvant Therapy



Recurrent disease

- Abdomen/pelvis-40-50%
- Lung -25%
- Rare- spine
- Treatment naive - hormonal therapy
- Post Treatment- Cytotoxic CT

Hormonal therapy

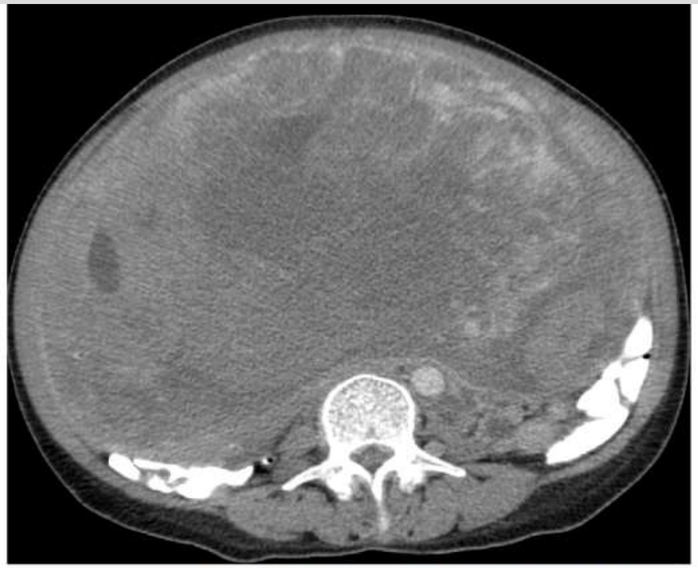
- **Progestins**-Antiestrogenic activity after binding to PR receptors
- Megestrol acetate 160 mg OD/ Medroxy progesterone 250 mg OD
- **Aromatase inhibitors** -Reduce estrogen levels by inhibiting estrogen synthesis in peripheral sites & tumour tissues
- Leads to reduced receptor mediated growth stimulation
- Letrozole/ Anastrazole

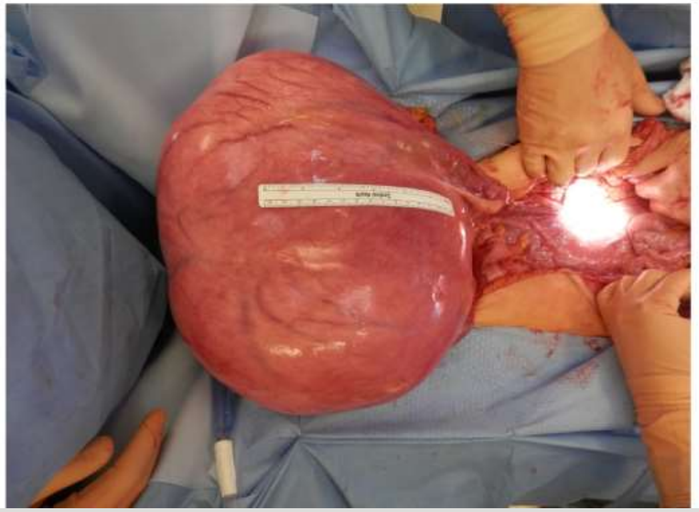
Hormonal therapy

- GnRH analogues- Suppress ovarian estrogen production
- Addtnl growth inhibitory effect via intratumoral modulation of mitogenic signalling of growth factor receptors
- Leuprolide, Goserilin, Triptorelin
- Tamoxifen & HRT containing estrogens contraindicated in pts after treatment of ESS

LMS

- Large>10cm, yellow/tan solitary masses with soft, fleshy cut surfaces with areas of haemorrhage & necrosis
- May bulge into uterine cavity , but epicenter is myometrium
- 1.Prominent cellular atypia, 2.abundant mitoses≥10/10HPF & 3.areas of coagulative necrosis -STANFORD CRITERIA
- 2/3 features indicative of risk of metastatic spread > 10%



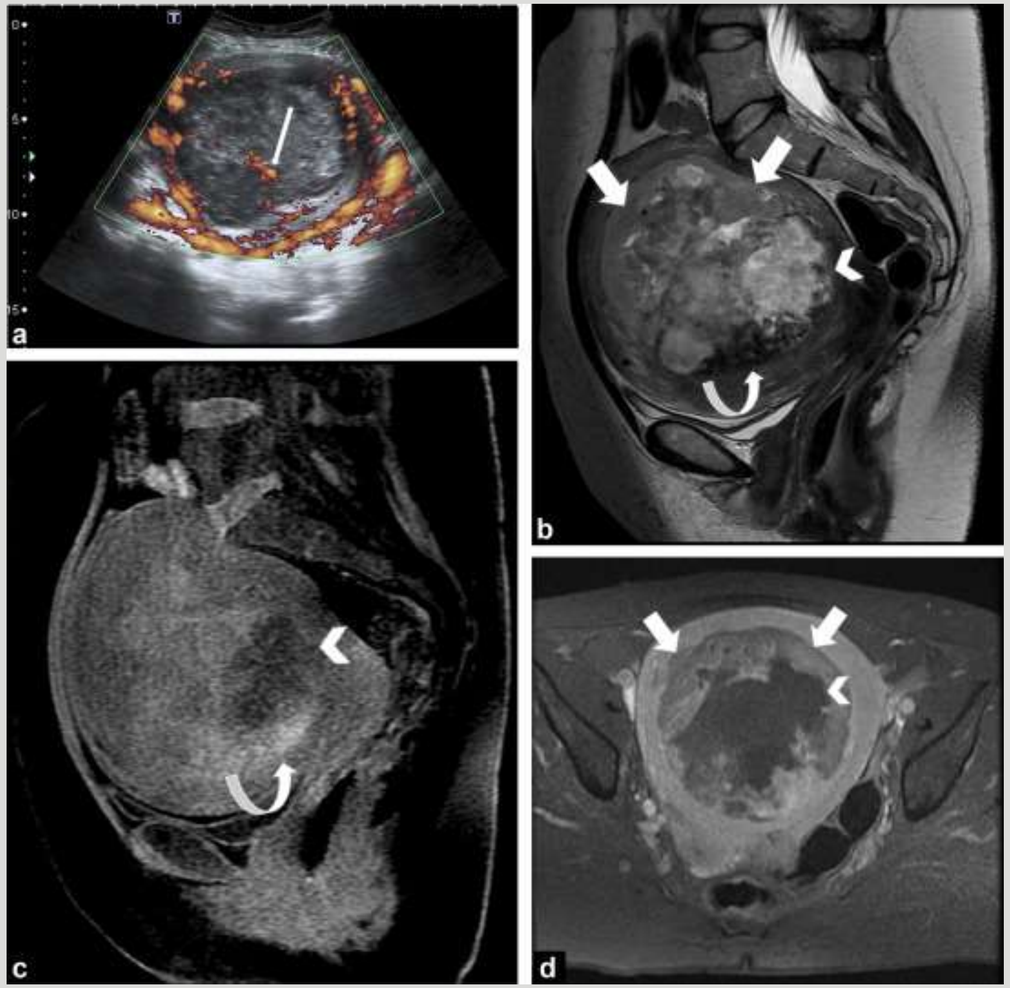


MRI

- a : High vascularity within the mass

- b: T2 wted- intermediate /high signal -Single heterogenous intramural mass with nodular borders with peripheral enhancing components with areas of tongue like projections within rt ant edges of adj myometrium

- c: T1 wted- Low signal intensity large central nonenhancing lesion within mass- necrotic changes/ haemorrhagic components



Subtypes of LMS

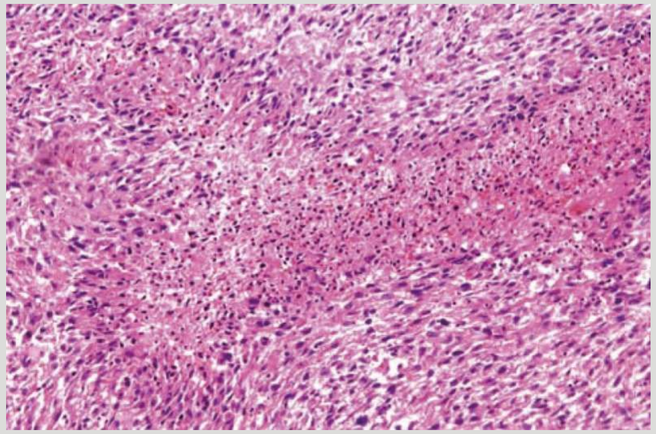
Spindle cell LMS

Conventional

Char by 2/more of

1. Tumour cell necrosis
2. ≥10/10HPF mitoses
3. Marked cytological atypia

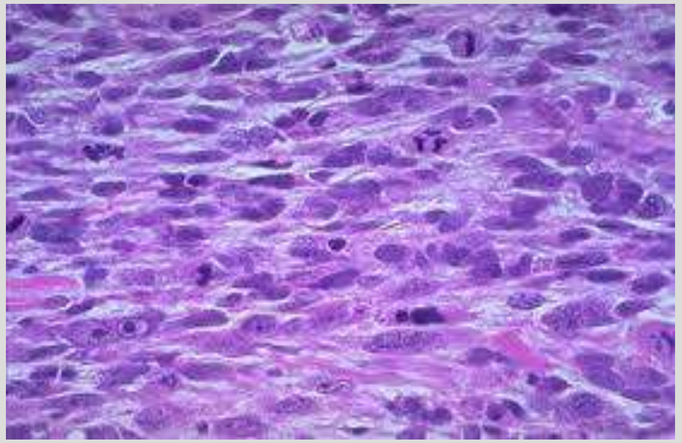
May arise from a background of leiomyoma



Epitheloid LMS

Round to polygonal cells with abundant eosinophillic / clear cytoplasm

Epitheloid leiomyoma with≥5 mitoses/ 10HPF

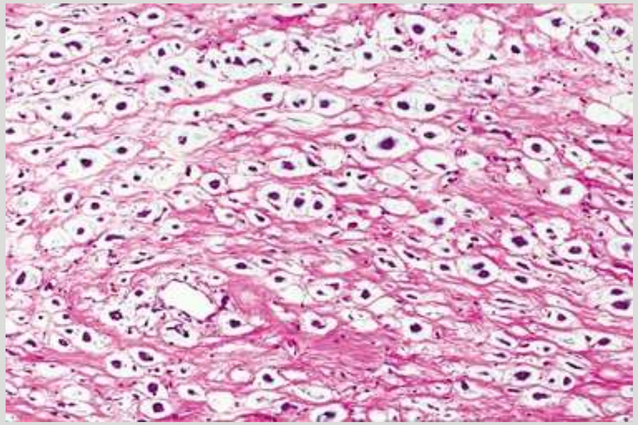


Myxoid LMS

Classified separately

Myxoid appearance may obscure smooth muscle diff , extent of nuclear pleomorphism & true no of mitotic figures

Highly malignant tumours

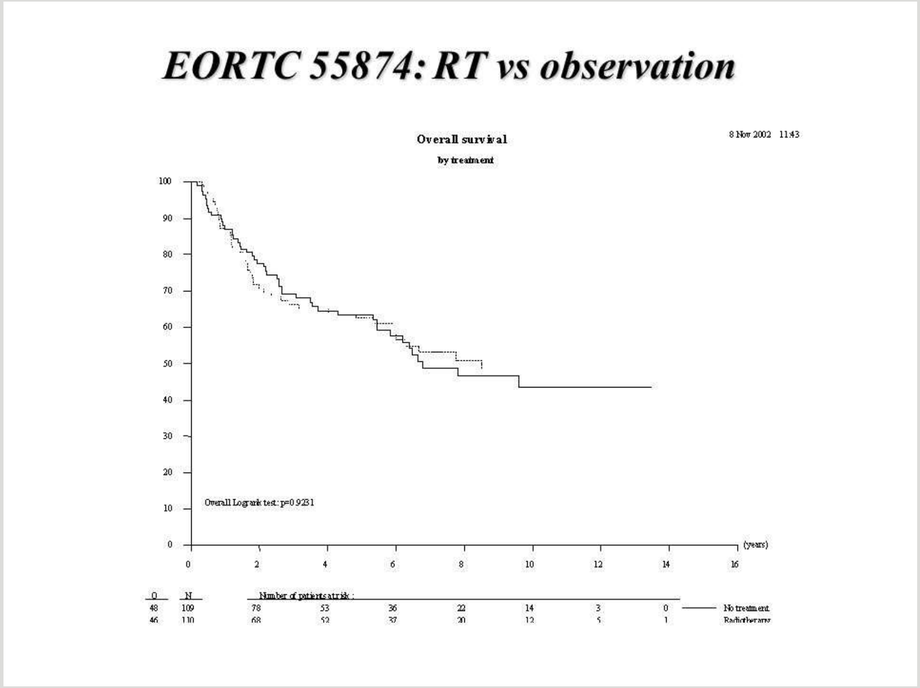


IHC

- Positive for smooth muscle markers
- desmin, H -Caldeson, Actin, Histone deacetylase 8
- Epitheloid & myxoid variants less immunoreactive
- Epitheloid- keratin , EMA positive
- ER+ PR+, androgen receptor positive- 30-40% cases
- Ki 67 increased,
- P16 overexpression - differentiate benign from malignant

Adjuvant treatment

- Chemotherapy/ Pelvic RT
- Whether any adjuvant therapy improves survival compared to observation, not known
- Early stage disease(stage I & II)- observation preferred
- GOG277 38 pts , stage I- CT + Surgery vs surgery alone
- No statistically sign improvement in PFS & worse OS in CT arm
- No benefit of adjuvant RT in stage I & II LMS pts (EORTC 55874) so not recommended.



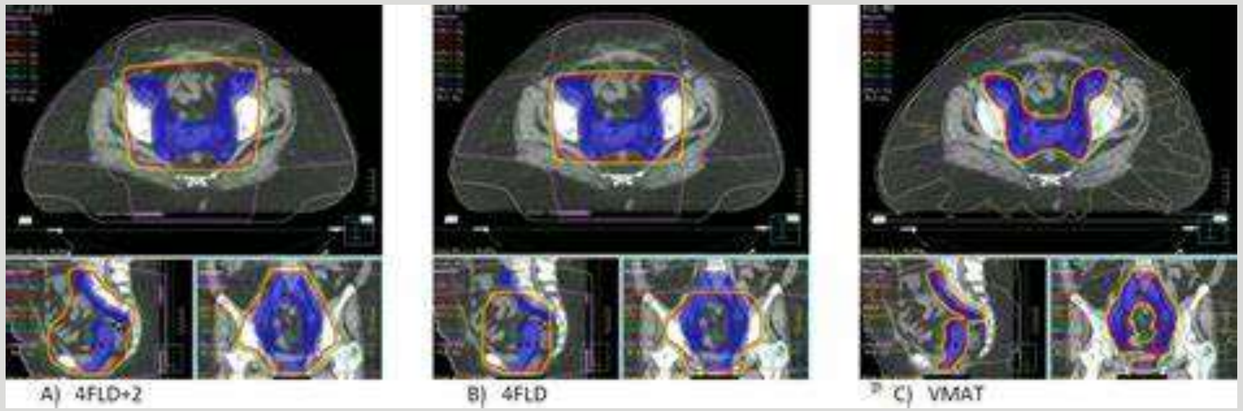
Stage III & IV Disease

- Higher risk of disease progression after complete resection of disease
- Significantly reduced local failure with adjuvant RT at 5 yrs of 2% vs 16% with surgery alone (Sampath et al)
- Post resection CT may be offered , not established that there is improvement in survival
- Surveillance is also a reasonable option
- Docetaxel + Gemcitabine or Doxorubicin used RR 27-36%

NCCN 2B Recommendations for RT

- High rate of initial metastatic failure in LMS
- Adjuvant pelvic RT does not appear to have a survival benefit in LMS
- May reduce local pelvic recurrences , possible for disease that has spread beyond the uterus
- May be considered for higher risk women in order to improve local disease control

Radiotherapy



- 50 Gy/ 25 Fractions / 5 weeks
- 50.4 Gy/ 28 Fractions/ 1.8 Gy
- Followed by BT
- Especially if cervical involvement
- Newer techniques- Decreased dose to OAR
- Bone marrow sparing

Prognostic factors

- Tumour size> 10cm
- Mitotic rate- (20/ 10 HPF)
- Ki 67>10%
- Bcl 2 negative

- Overall Prognosis Poor even in Stage I
- Recurrence rate 53-71%
- Lungs 40%
- Pelvis 13%
- 5 Yrs survival -15-25%
- Median Survival 10 mths

Post treatment surveillance

- Uterine LMS - aggressive tumour with high risk of relapse , even when confined to the uterus
- Physical exam every 3-4 mths x 2yrs
- 6-12 mthly for next 2 yrs

Prognosis	OS
I	76
II	60
III	45
IV	29

2nd Line therapy

- Doxorubicin Based
- Gem alone RR- 20%
- Ifosfamide alone – RR17%
- Ifosfamide +Doxorubicin – RR-30%
- Trabectidin – progression on Anthracyclines- ORR-16%
- Pazopanib
- Erbulin
- Endocrine therapy ORR< 10% Aromatase inhibitors can be considered for ER/ PR expressing u LMS

Metastatic Disease

- Most common sites- Lungs, liver, abdomen & pelvis
- Bone & brain - less common
- If complete surgical resection not possible- treatment intent - palliative
- CT - reasonable option , in pts with good PS, & organ function pemits use of cytotoxic CT
- Gem Doce, superior to gem alone
- Single agent Doxorubicin , Ifosfamide alone- RR17%, Ifosfamide + Doxo-30%
- Endocrine therapy – ORR-10%

Recurrence

- Recurrence < 6 mths- CT
- >6mths - Consider targeted therapy
- Resection of metastatic disease

Smooth muscle tumours of Uncertain Malignant potential (STUMP)

- High malignant features , but not falling into diagnostic criteria of LMS
- Microscopic- Tumour cell necrosis
- necrosis of uncertain type > 10 MF / 10 HPF
- Diffuse atypia
- Borderline mitotic cts
- Favourable prognosis-
- Treatment- only follow up after hysterectomy

Carcinosarcoma

- Composed of an epithelial & a mesenchymal component
- Carcinosarcoma — Adenosarcoma
- Carcinofibroma — Adenofibroma
- Adenomyoma — Atypical polypoid variant

Carcinosarcoma(MMMT)

- Composed of an admixture of malignant epithelial & mesenchymal components
- <5% of all uterine malignancies
- 7th decade
- Most common among sarcomas
- **Risk factors**: Obesity, diabetes, nulliparity, tamoxifen, prior RT

Histogenesis

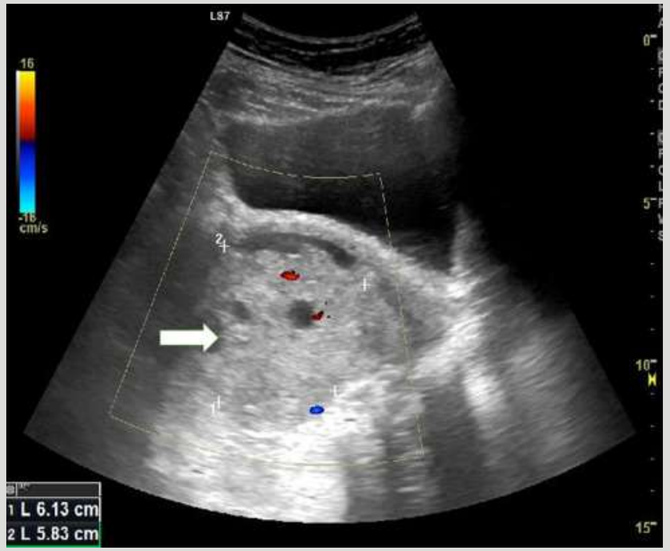
- Collision theory
- Combination theory
- Conversion theory
- Composition theory
- Clear now that arises through conversion & metaplasia
- **Dedifferentiated /metaplastic endometrial carcinoma**

Natural History

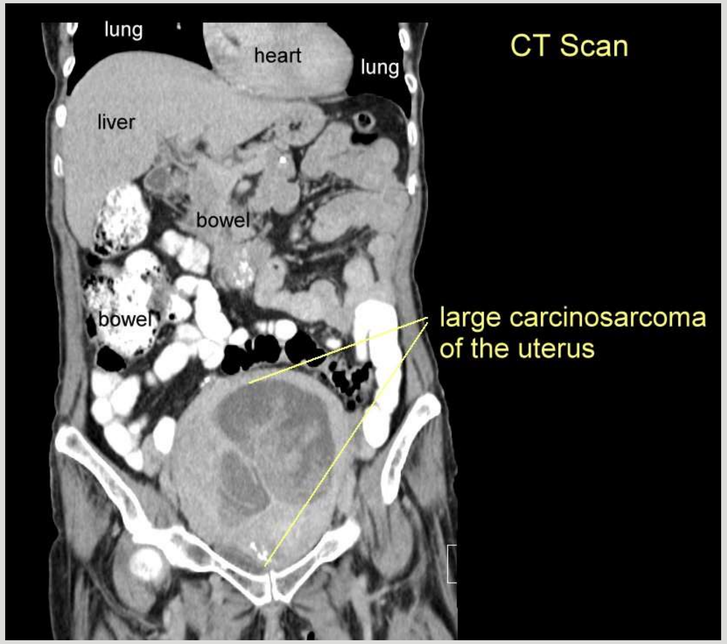
- Late clinical presentation
- Rapid uterine enlargement
- High rate of lymphatic involvement
- Peritoneal & hematogenous spread
- Lymph node involvement 30-40% at diagnosis
- 10% visceral mets
- Commonest – Lungs
- 5 yrs survival - < 10-30%

Imaging

- Ultrasound: Hyperechoic as compared to myometrium
- Expansion of endometrial canal seen
- CT Scan : Heterogenous ,ill defined , hypodense mass with concomitant dilatation of endometrial canal

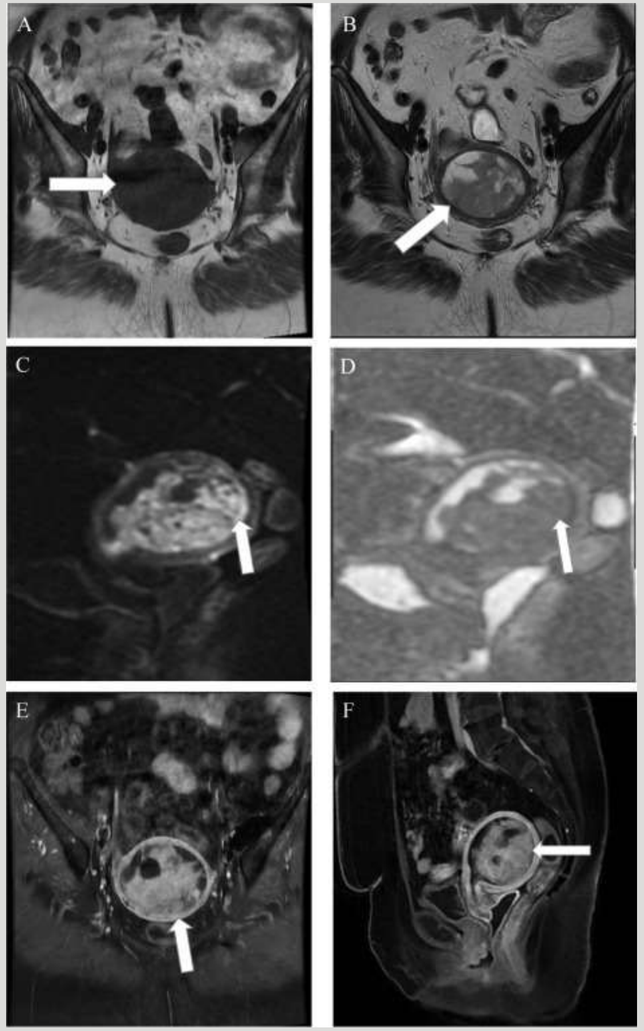


Ill defined heterogenous mass within uterus



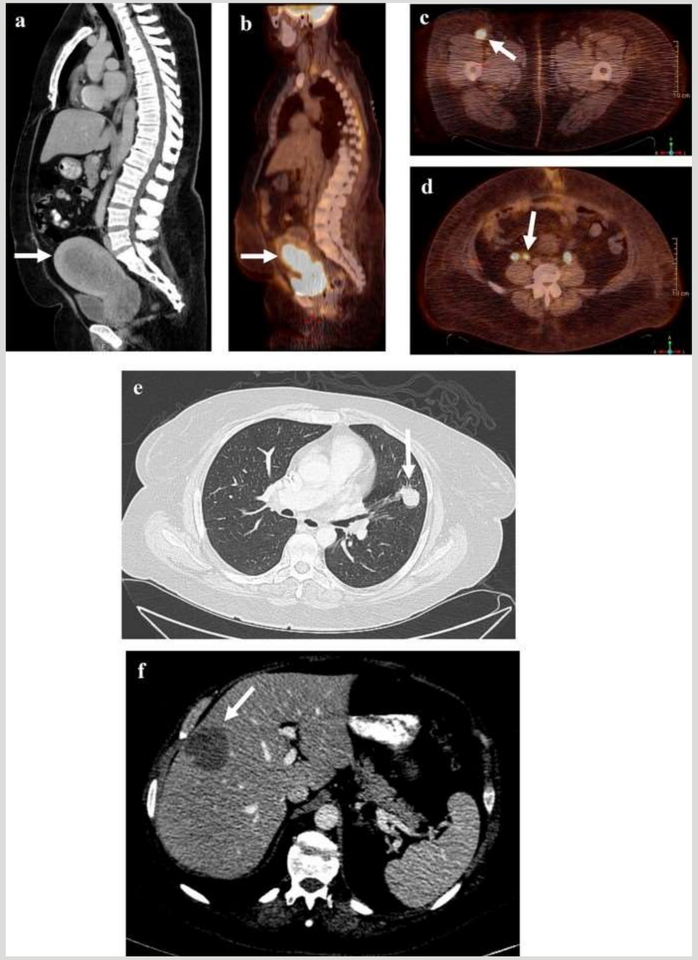
MRI

- Enlarged uterus with a widened endometrial cavity & evidence of deep myometrial invasion
- Heterogenous bulky mass protruding into cervix
- Prolonged intense enhancement



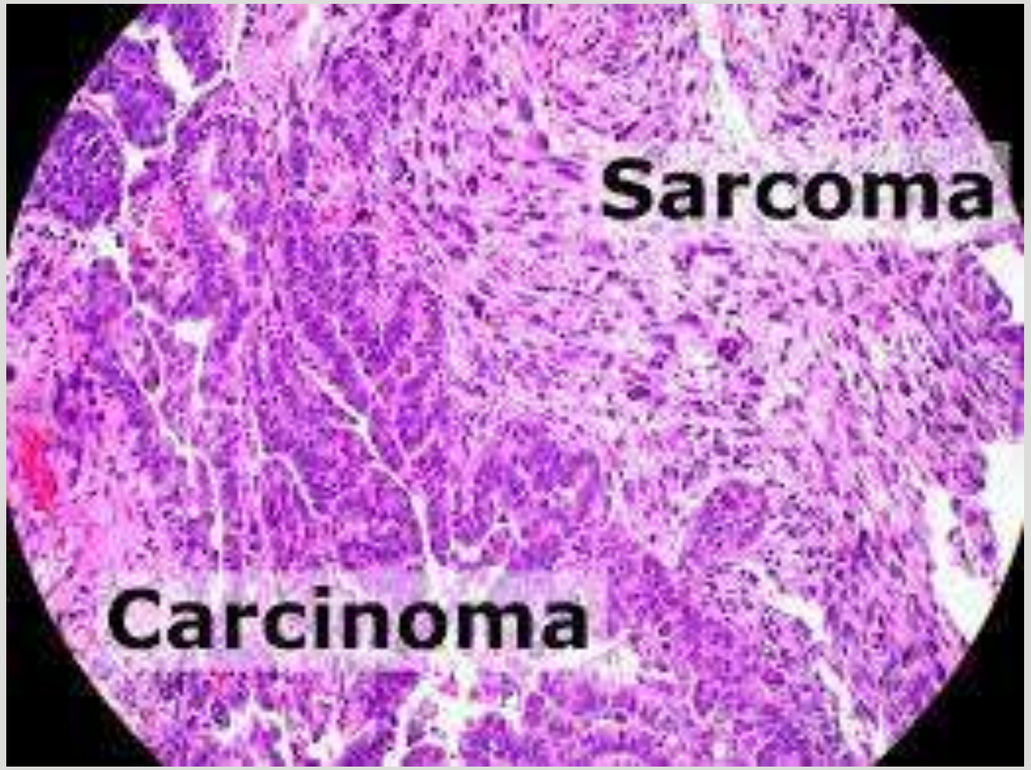
Investigations

- PET CT- Useful for diagnosis & initial staging
- Usually positive, with mean SUV of 10 ±5.5
- CA 125- Elevation preop indicative of extrauterine disease & deep myometrial invasion
- Independent prognostic factor for poor survival



HPE

- Macroscopic : Polypoid, bulky, necrotic, haemorrhagic endometrium , invading myometrium
- Microscopic: Biphasic, most common combination- High grade serous carcinoma & ESS
- CS is a histological diagnosis
- Based on sarcomatous component
- Homologous: native to the uterus-
- Heterologous: Not native - RMS, Chondrosarcoma, liposarcoma



Treatment

Localized disease

Surgery

Adjuvant CT + Adjuvant RT in tumours > Stage IB

Extrauterine disease limited to peritoneum

Surgical cytoreduction
TAH + BSO+ pelvic + PA Lymph node dissection
Cytology of peritoneal washings
Omentectomy
Biopsies of peritoneal surfaces

Extra abdominal Metastases

Palliative

Surgery

CT

Conclusion

- Uterine Sarcomas are very aggressive neoplasms
- No imaging modality can offer reliable preop diagnosis
- Aggressive Cytoreductive Surgery at time of diagnosis offers best survival
- No form of adjuvant treatment has been found to improve overall survival of women with uterine sarcomas
- Radiotherapy has been excluded from the treatment in most guidelines
- Improves local control though has no impact on survival
- Indicated in patients with medical contraindications to surgery, or in the palliative setting
- Hormonal therapy is recommended in Hormone receptor positive primaries

Thank you