University College London Hospitals
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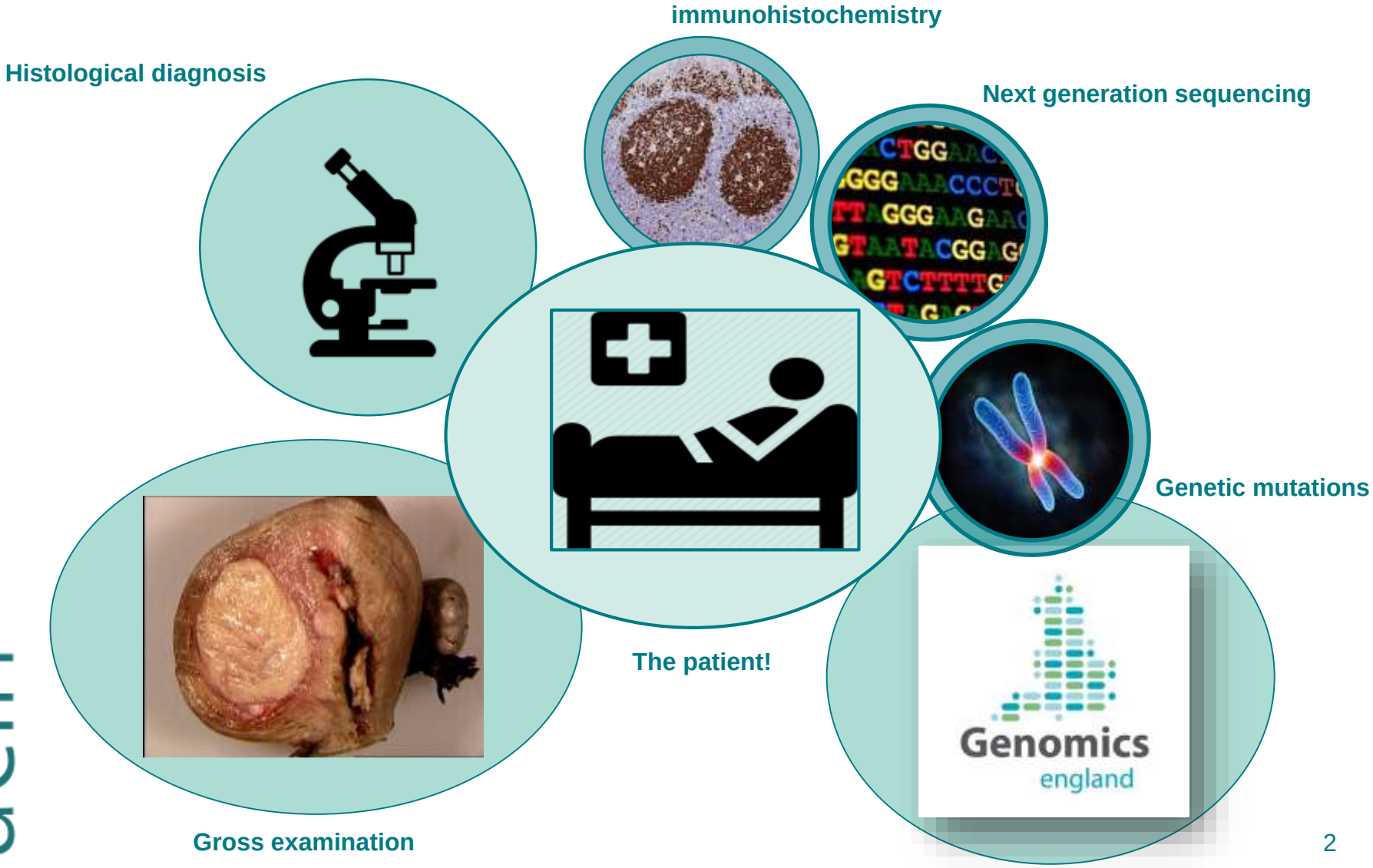
What really matters – When and Why

Pathology of Uterine Mesenchymal Lesions

Nafisa Wilkinson
London

Patient centred approach

University College London Hospitals
NHS Foundation Trust



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Mesenchymal lesions – what matters

- Is it smooth muscle or endometrial stromal?
- Smooth Muscle
  - Benign/ Uncertain Malignant Potential/ Malignant
- Endometrial Stromal
  - Benign/ LGESS/ HGESS/ Undifferentiated U. Sarcoma

Clinical relevance: management options

- If radiologically malignant
  - MDT review
  - CT chest, abdo, pelvis
  - TAH+BSO+omentectomy (ESS)
  - TAH (min) – Leiomyosarcoma

  Referral to sarcoma team (registration)
    - Adjuvant treatment (if indicated)
    - LMS (no good evidence for hormonal mnx)
    - ESS (Anti –oestrogen or progesterone)

    - Recurrences managed by Sarcoma team

Aims

Clinical History – what matters?

Gross examination – sampling- what matters?
Histological examination – when should you worry?

Diagnosing a leiomyosarcoma – when should you worry?

Diagnosing an ESS- What is important?

Immunohistochemistry – How to use it?
Molecular markers – How and when to use them?
Prognostication? Any markers that are reliable?

Clinical History – what matters?

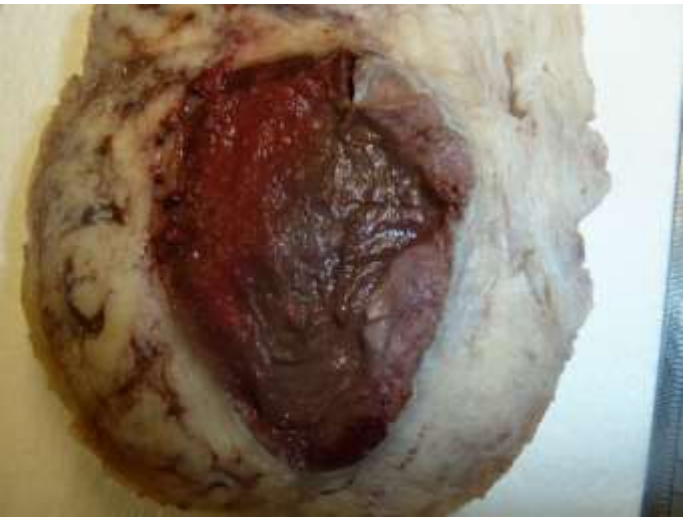
- Age – Young patient with multiple fibroids ? HLRCC syndrome
- Hormonal status- peri or post menopausal (concern for malignancy)
- Drug history –
  - GnRH agonist treatment,
  - Tranexamic acid,
  - Ulipristal Acetate (Esmya)
- Previous procedures – embolisation, laser Rx,
  - rapid growth following embolization (concerning feature)

Gross examination

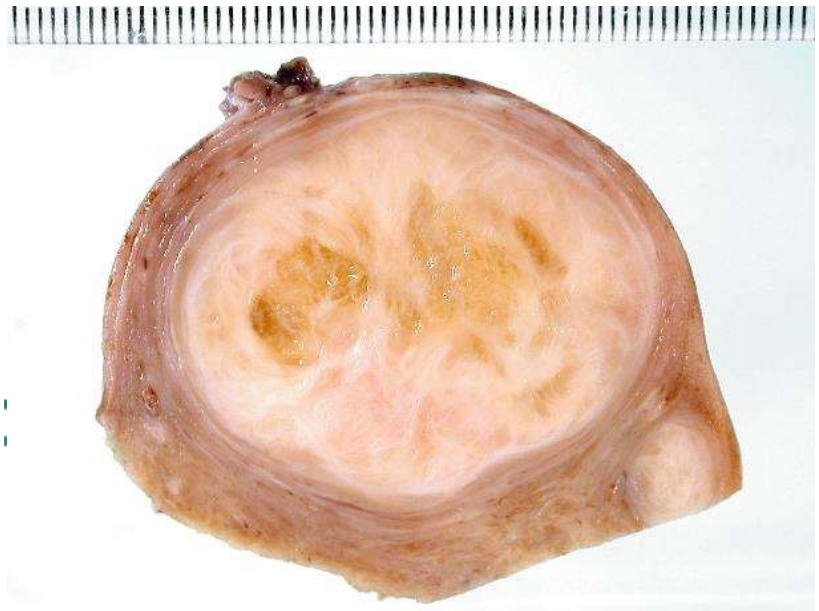
- Size (largest more likely to be malignant)
- Numerous- grossly examine all
  - Hysterectomy: Sample largest 3 or 4
  - Myomectomy: rep sections of each if no worrisome features
- Colour
  - Uniform, white whorled appearance “bulging at you”
  - Yellow - sample
  - Heterogenous- sample, esp Tumour/ myometrial border
  - Polypoid with myometrial component- sample

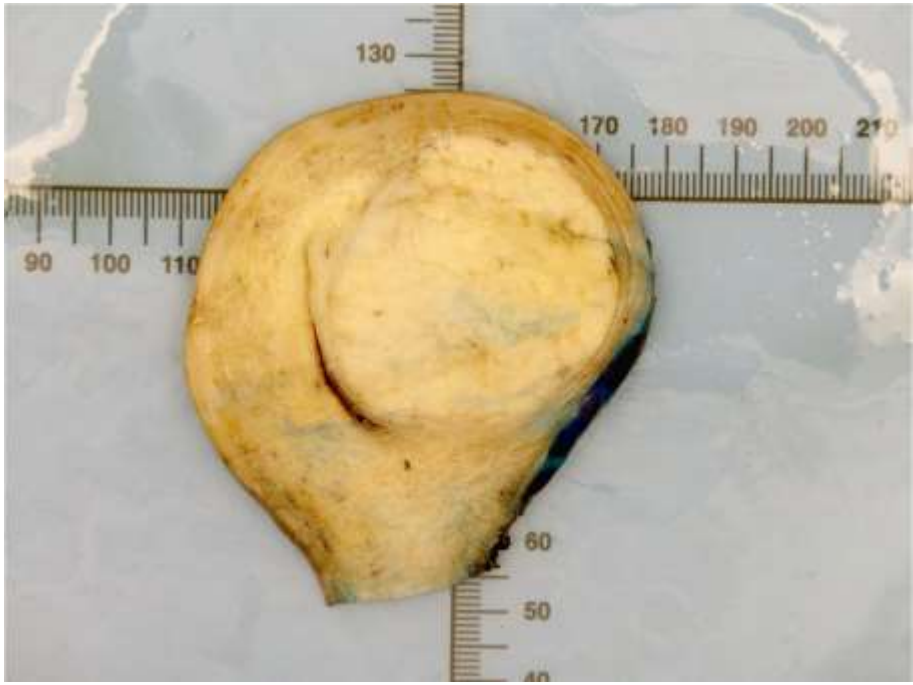
Leiomyoma typical

Appearances that do not matter.

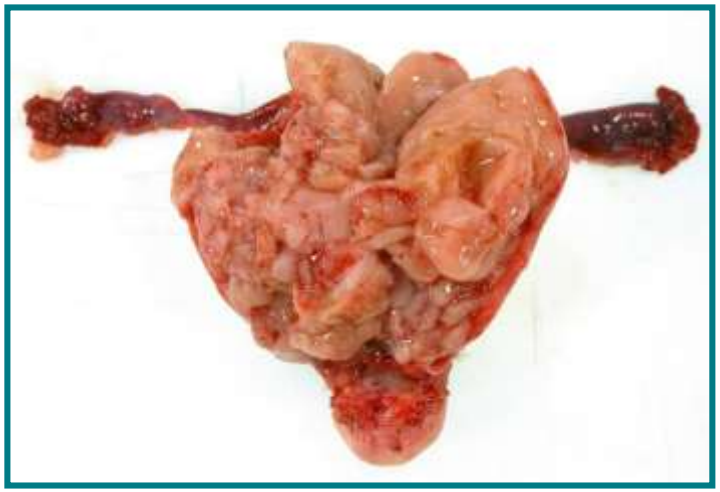


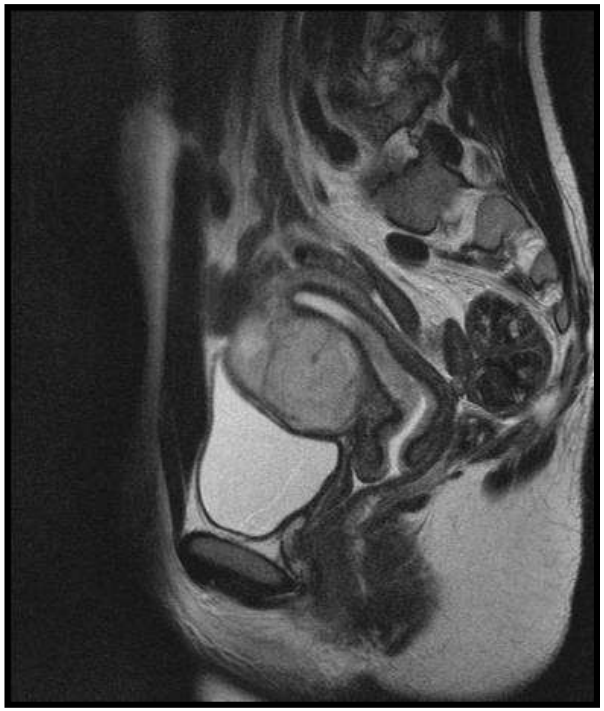
Not typical gross appearance

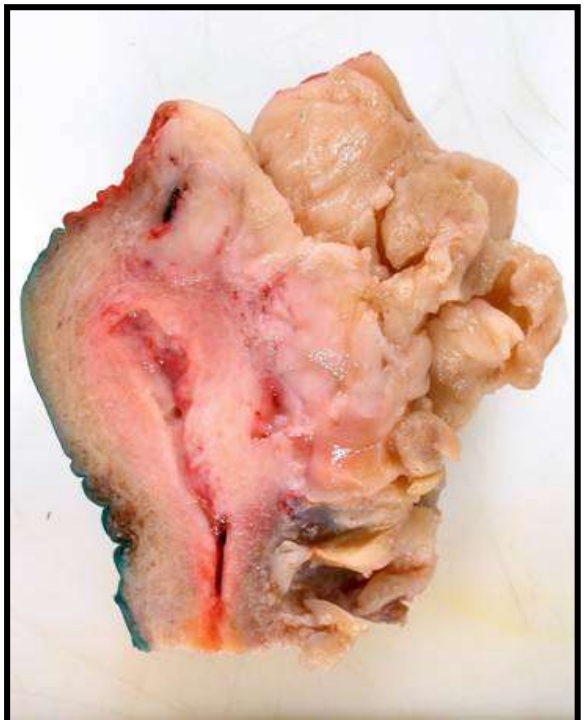




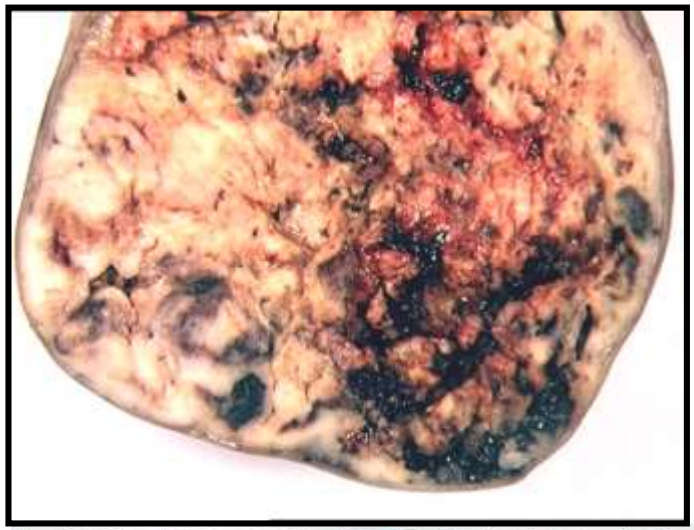
Concerning gross appearance

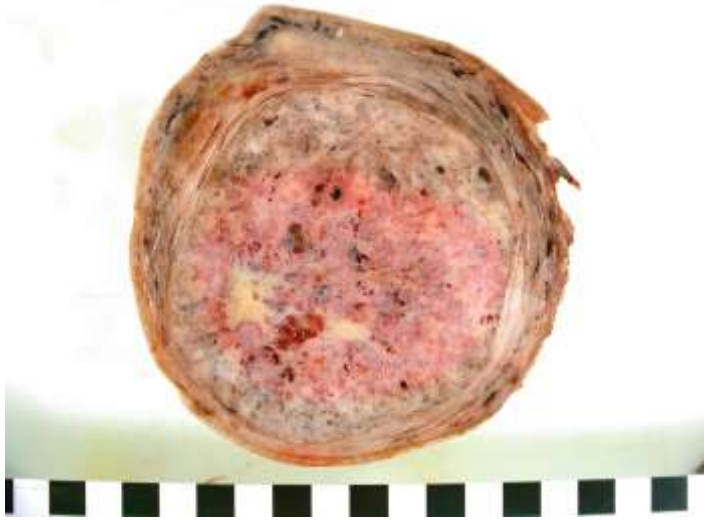


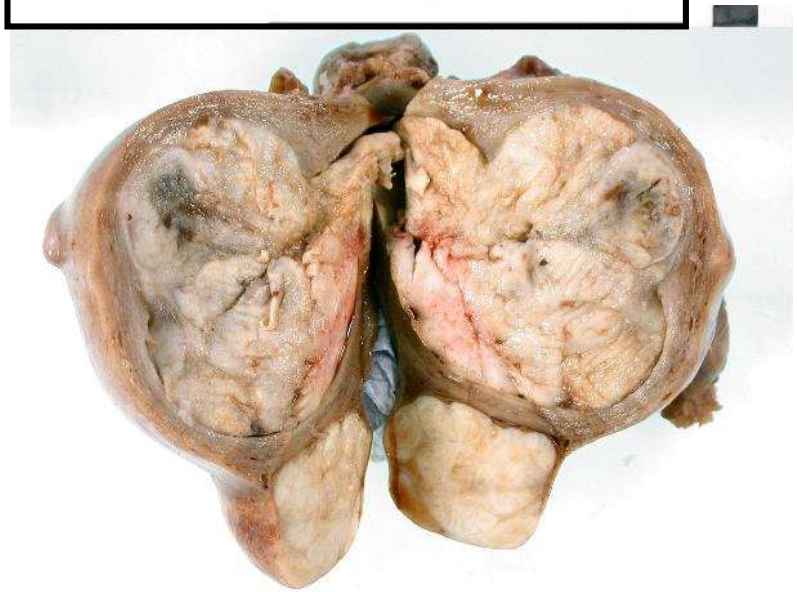


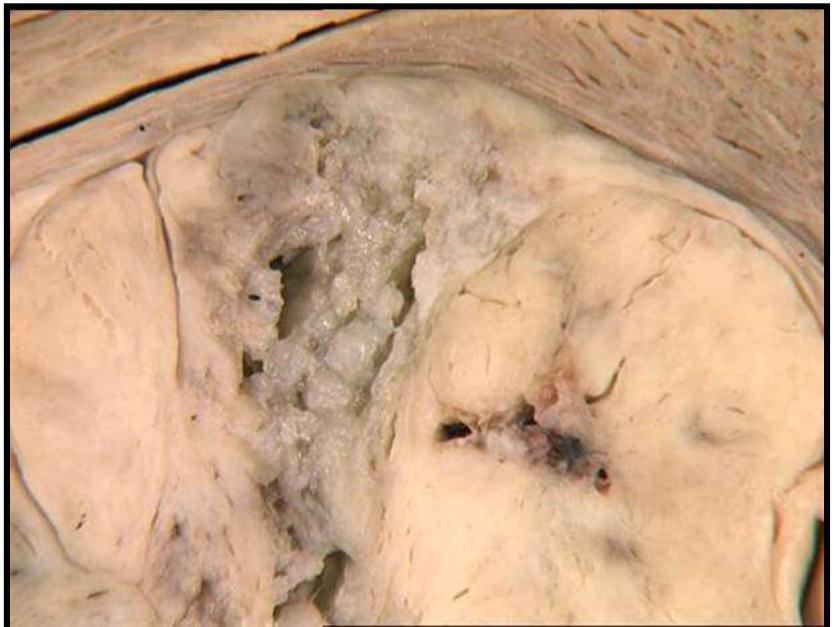


Heterogenous gross appearance









Fixation important to assess mesenchymal lesions

Fresh

Following fixation

Leiomyosarcoma

- Most important diagnosis for the patient
- Account for 1% of all uterine malignancies
- Most patients are post menopausal
- Usually confined to the uterus when diagnosed
- Recurrent disease- lung and pelvis (commonest site of metastasis)
  - Bone, cranial/intracranial, skin and soft tissue
- 5 year survival rate
  - stage I and II is 40-70%
  - 15- 25% for all stages.
- STAGE MOST IMPORTANT PROGNOSTIC INDICATOR

STAGING FOR UTERINE SARCOMAS

Int J Obstet Gynecol 2009, 104, 179

FIGO staging for uterine sarcomas (2009).

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.

Measure maximum tumour dimension

Block adnexa in entirety

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Grading in LMS

- No robust grading system that relates to prognosis
- Soft tissue sarcoma grading not relevant to uterine LMS
- All are high grade at present

Problems with dx of leiomyosarcoma

- Leiomyoma variants that have some but not all features malignancy
- STUMP (Smooth Muscle Tumours of Uncertain Malignant Potential)
- Is it a Leiomyosarcoma?

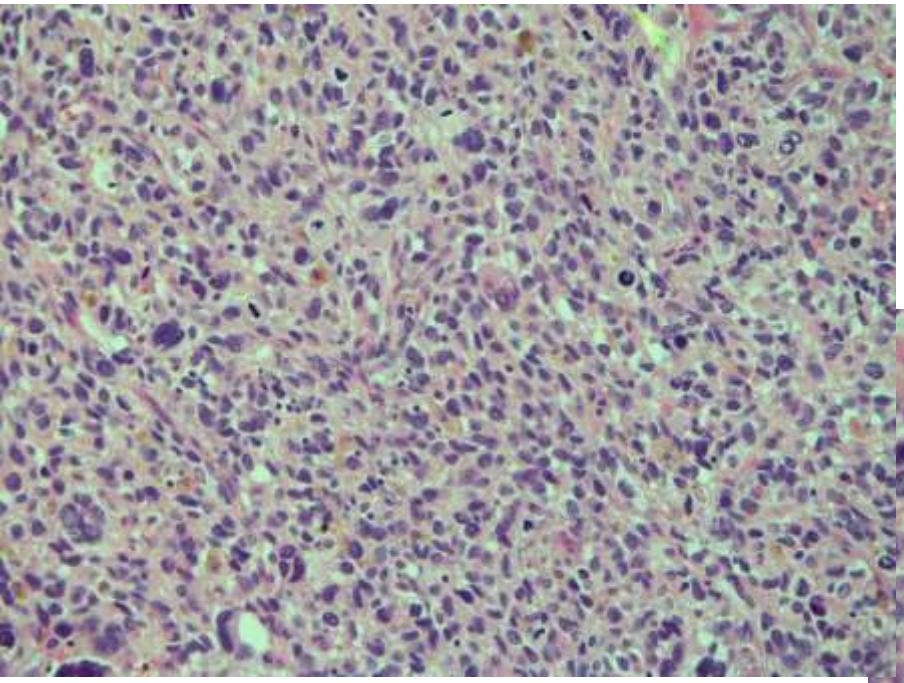
Diagnosis of leiomyosarcoma - 2 of 3 main criteria required for usual type

- Mitotic Activity (increased > 10MF/10HPF)
- Coagulative Tumour cell necrosis
- Cytologic atypia (diffuse)

  - Vascular invasion (10-20%)
  - Infiltrative border often seen (if searched for!)

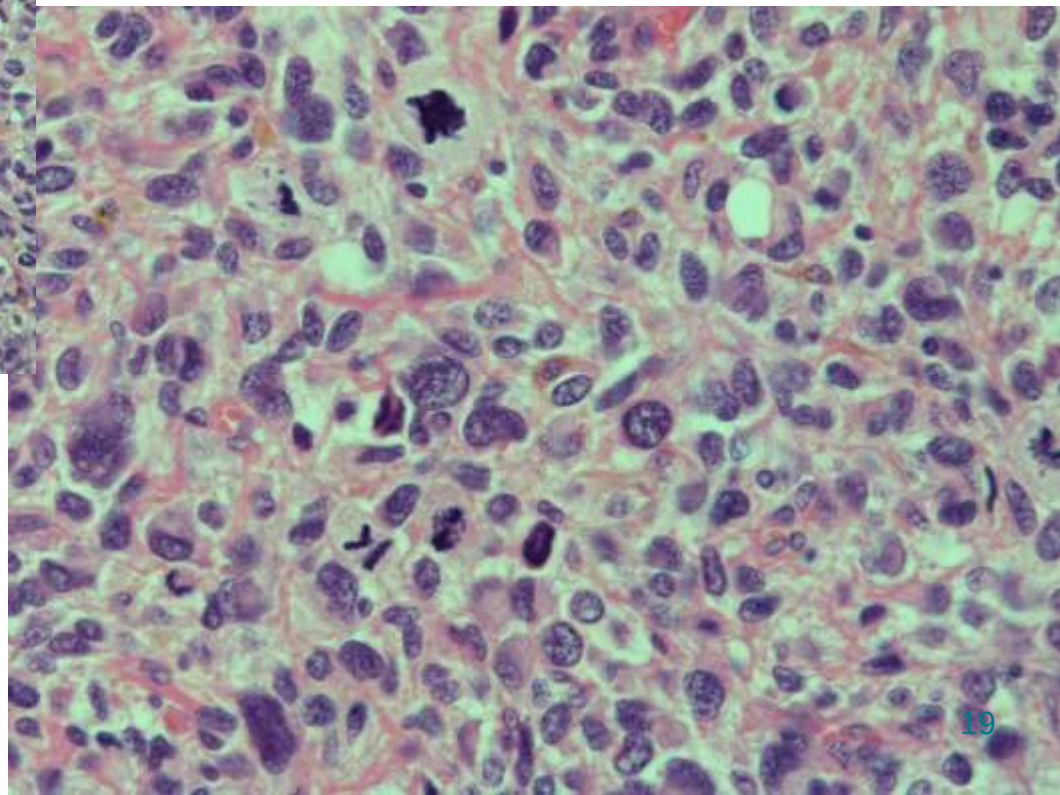
- Bell, Kempson and Hendrickson: Am J Surg Pathol 1994:18;535-558

Diffuse Cytologic Atypia

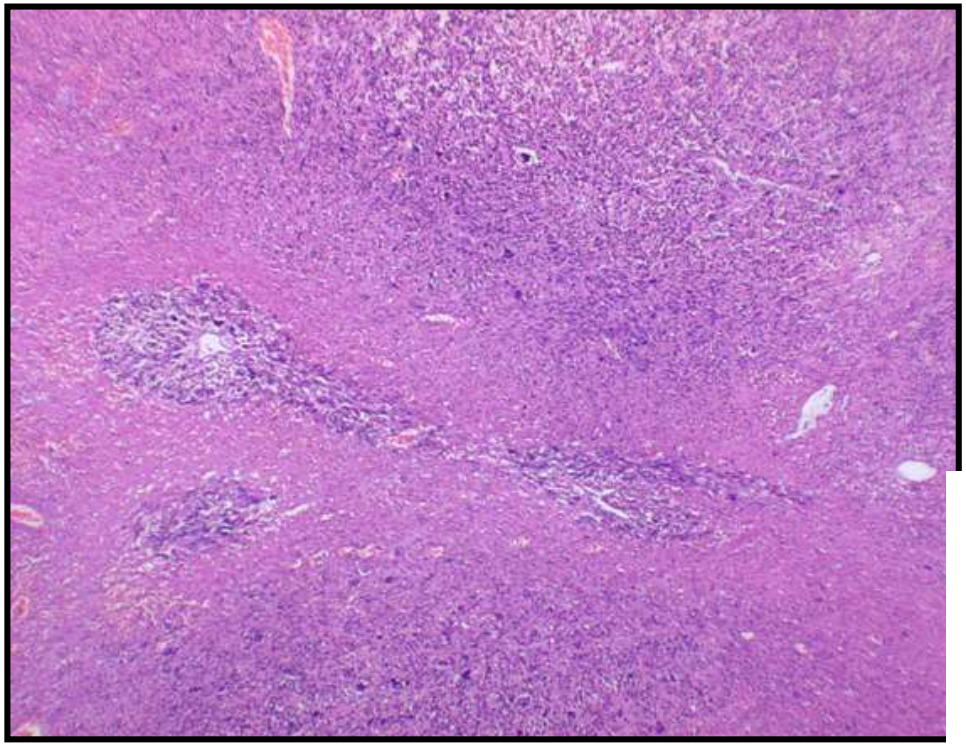


Low power very cellular neoplasm

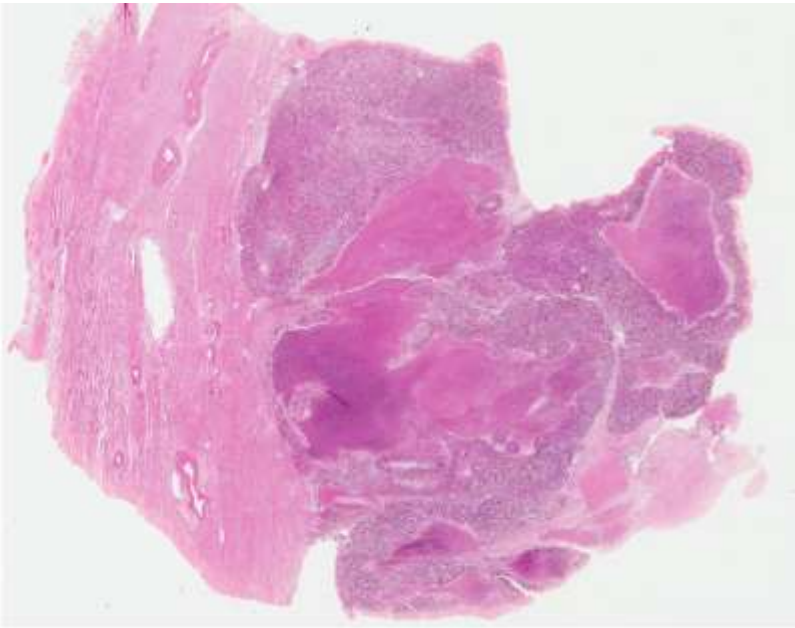
Mitotically active, atypical forms, marked DIFFUSE atypia



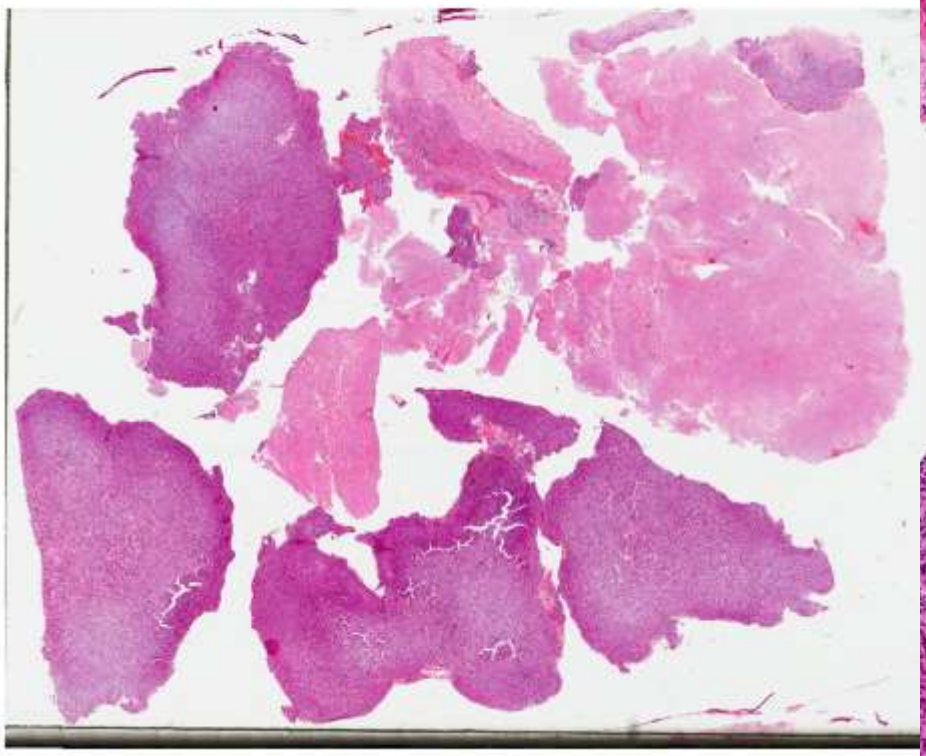
Coagulative necrosis

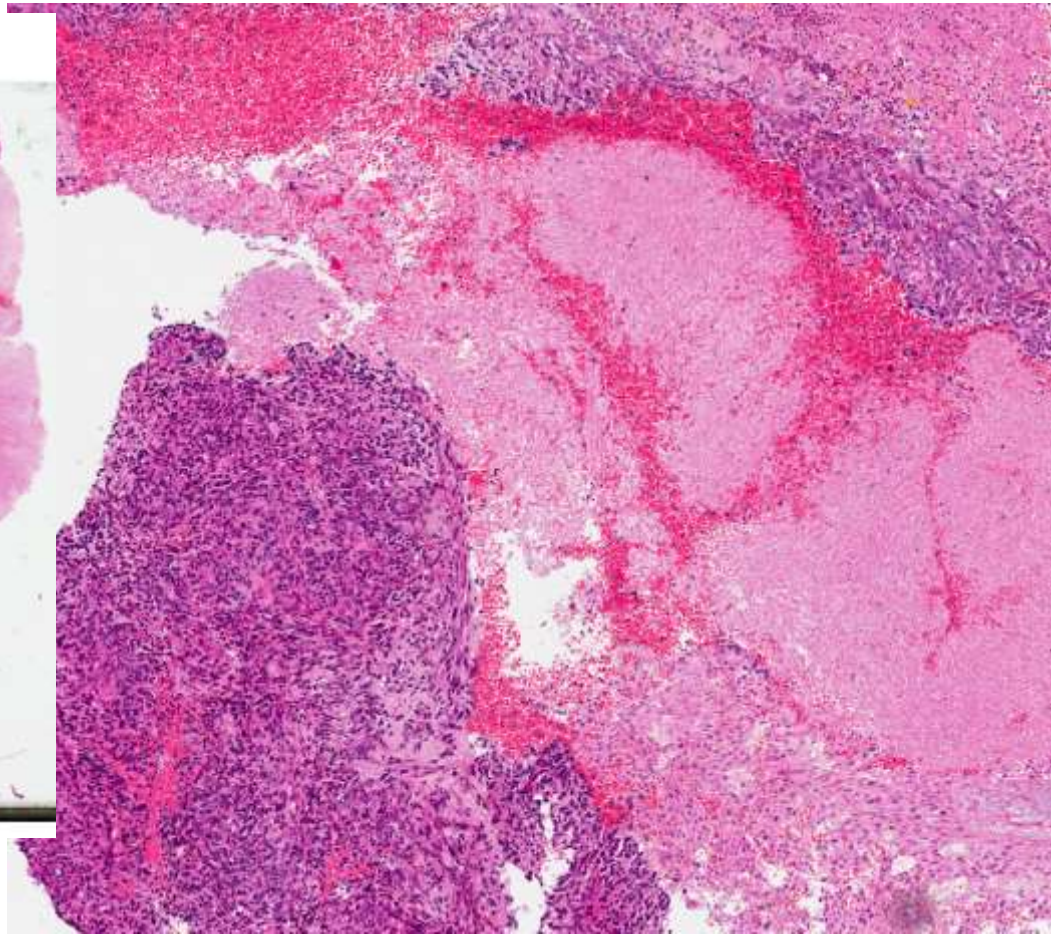


Overtly apparent coagulative necrosis



Leiomyosarcoma: haemorrhage and necrosis

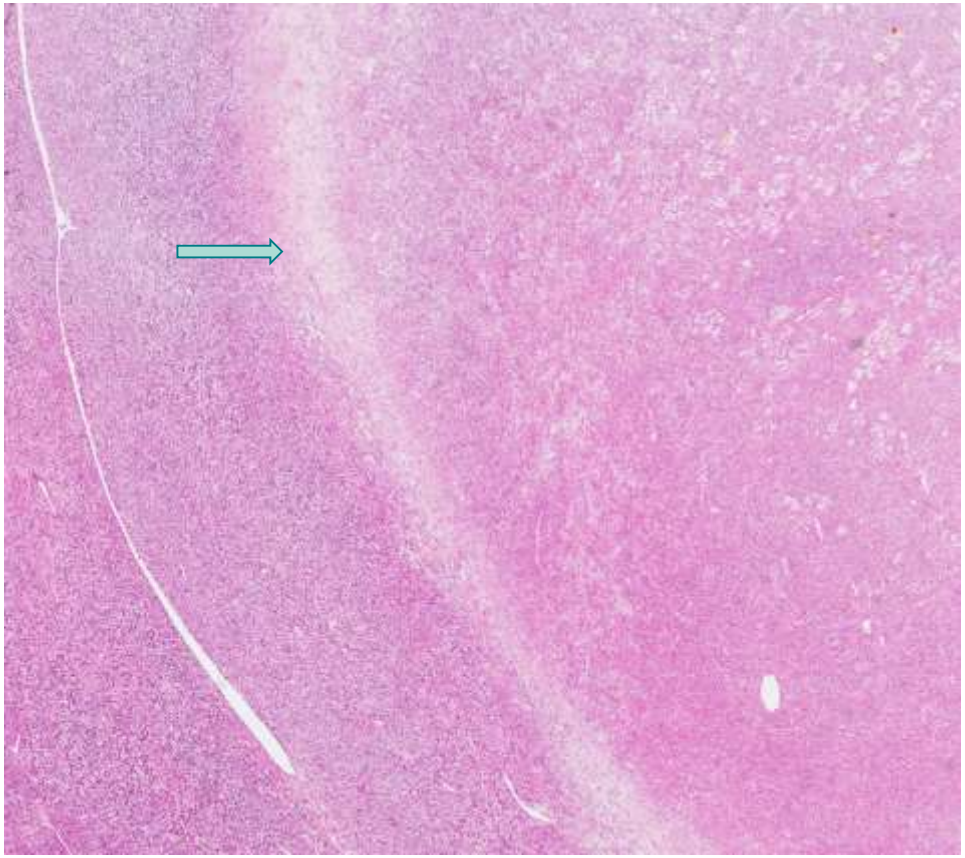


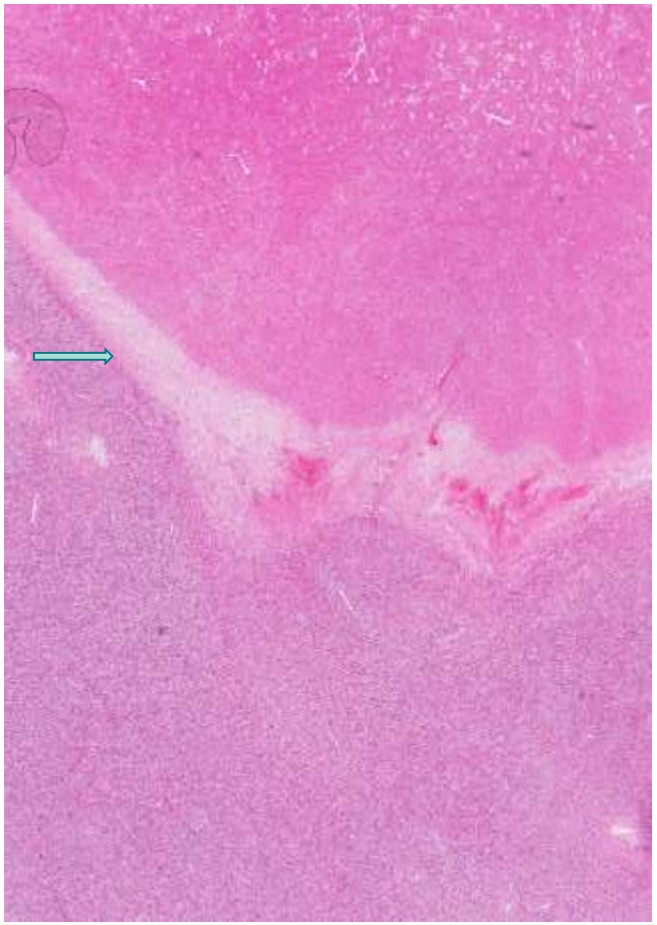


Highly cellular tumour

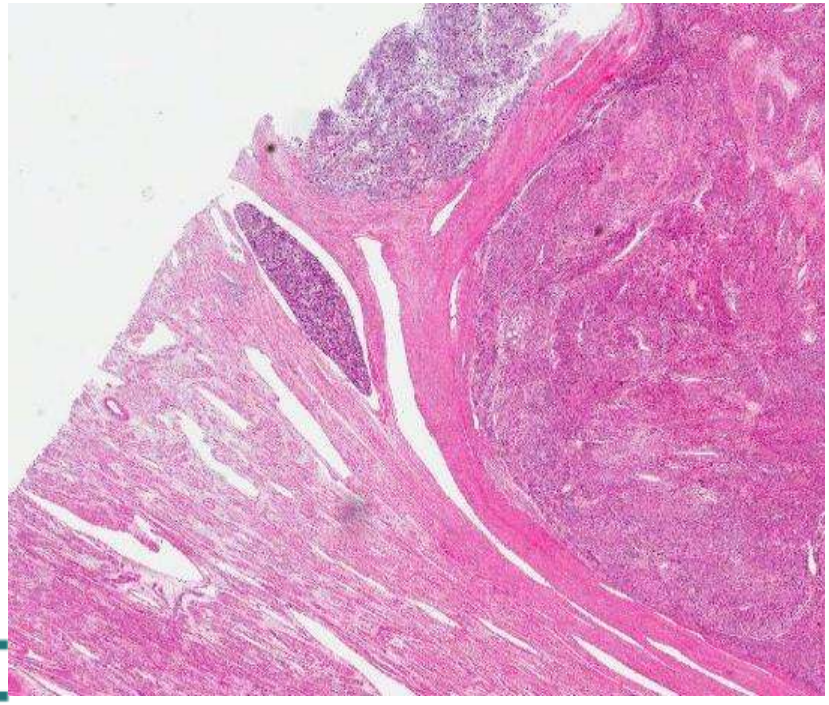
Remember hyaline necrosis is seen in LMS

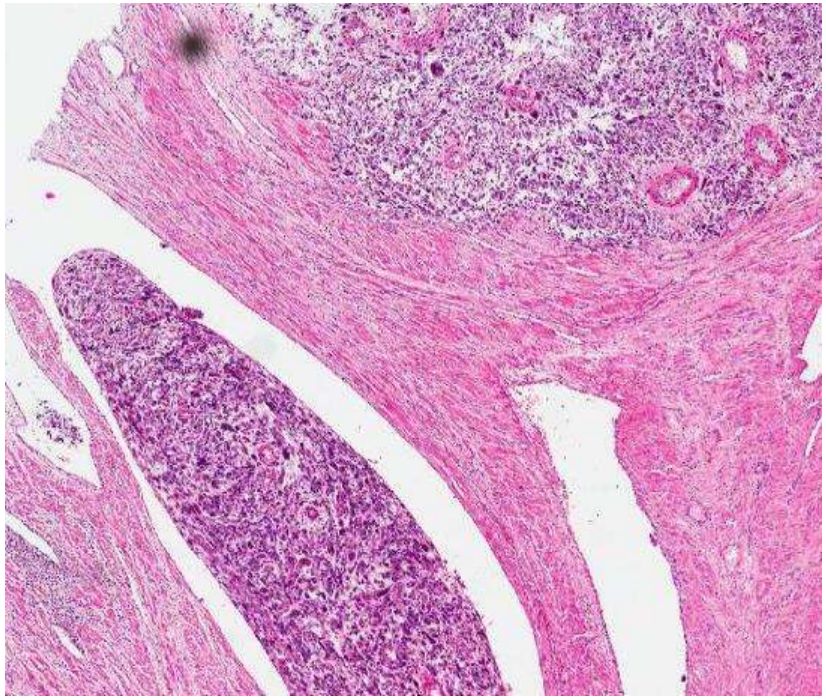
Zone of granulation tissue between viable and non-viable tumour





Sample extensively at tumour/myometrial border





Vascular invasion at advancing edge of tumour

LMS-immunohistochemistry

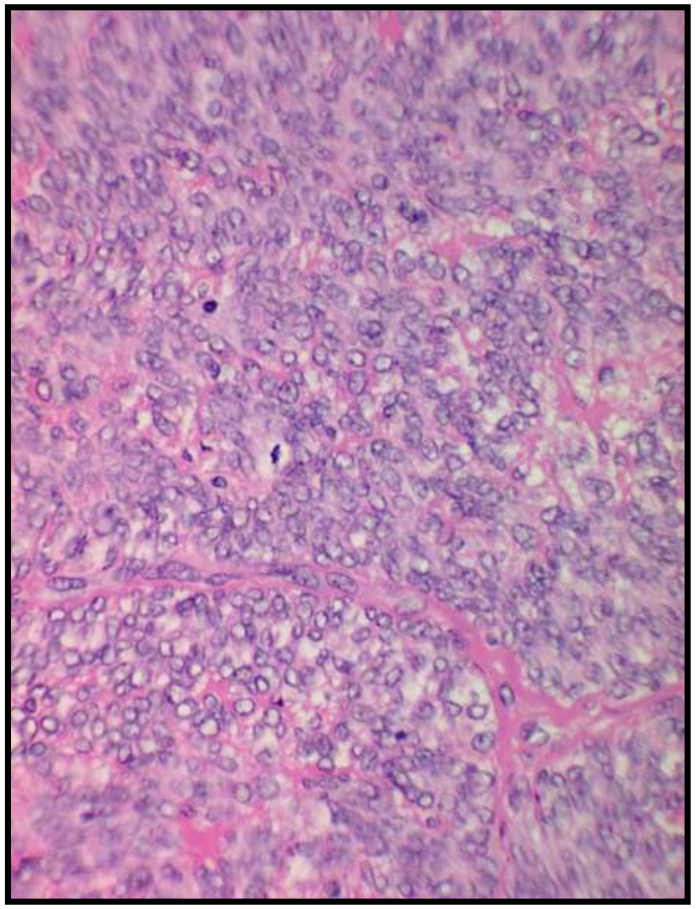
Desmin *
H-caldesmon *
Smooth muscle actin *

p53, P16 and Ki 67

ER, PR and AR positive (30-40%)
C-kit (CD117) and DOG 1 may be positive (no c-kit mutation found)
CD10 can be positive *
Cytokeratins , EMA may be positive

* Diagnostically useful markers

Mitotically active leiomyoma



- check where you count mitoses
- beware submucosal leiomyoma under ulcerated surface!
- Ki-67 very helpful
- Identifies zone of proliferation

No atypia, no coagulative necrosis, smooth border with myometrium.

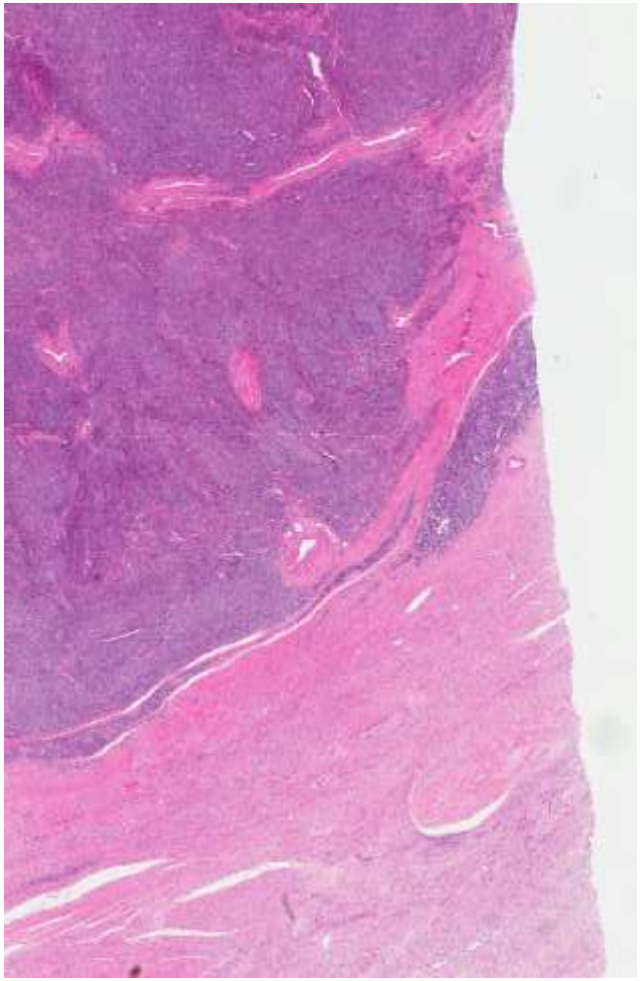
Cellular leiomyomata

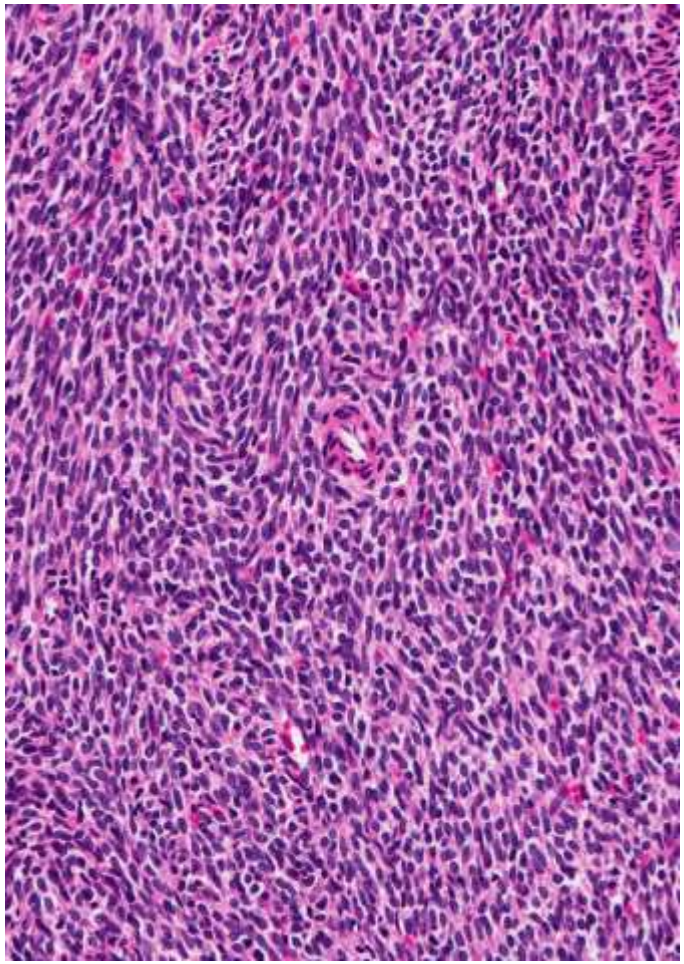
No Atypia

No increase in mitotic activity

Irregular peripheral border

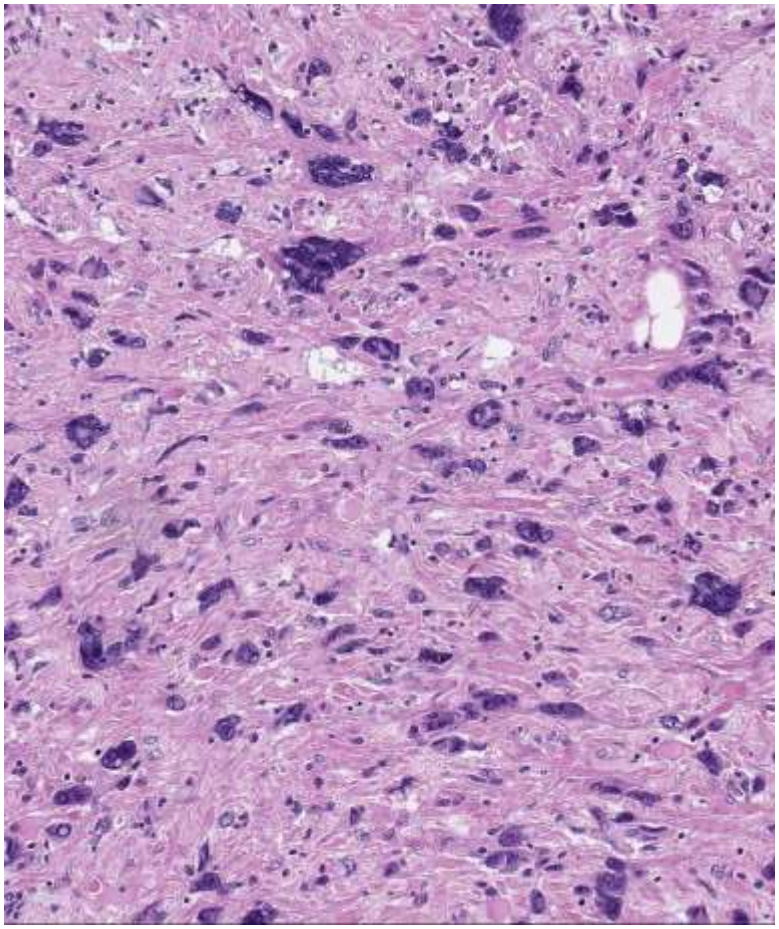
Not infiltrative border

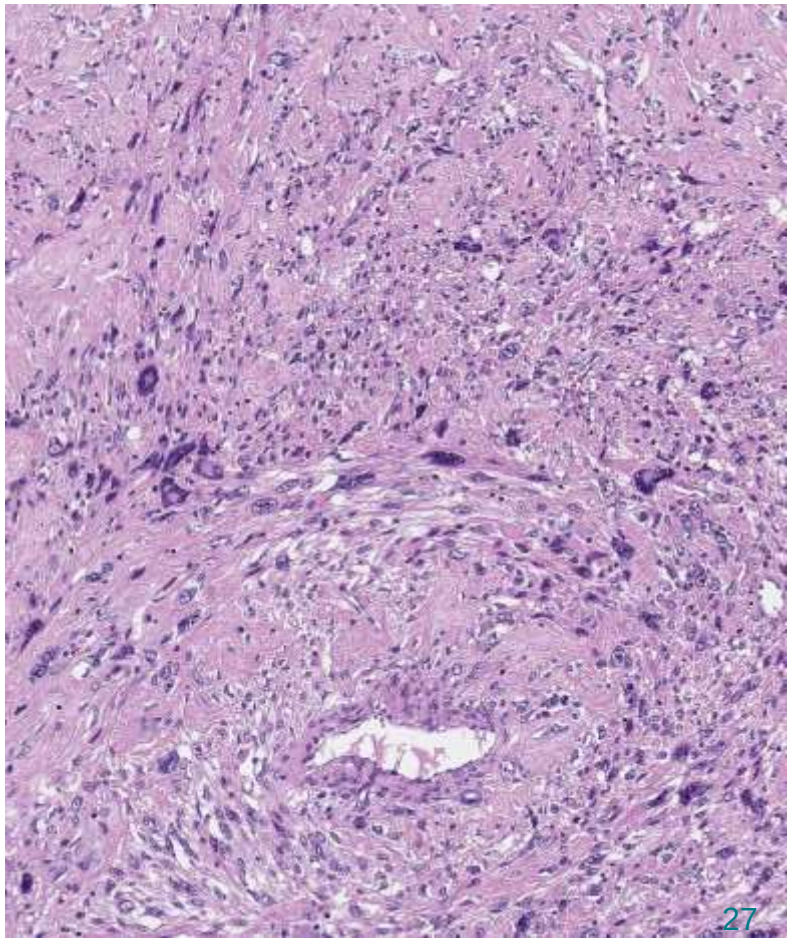




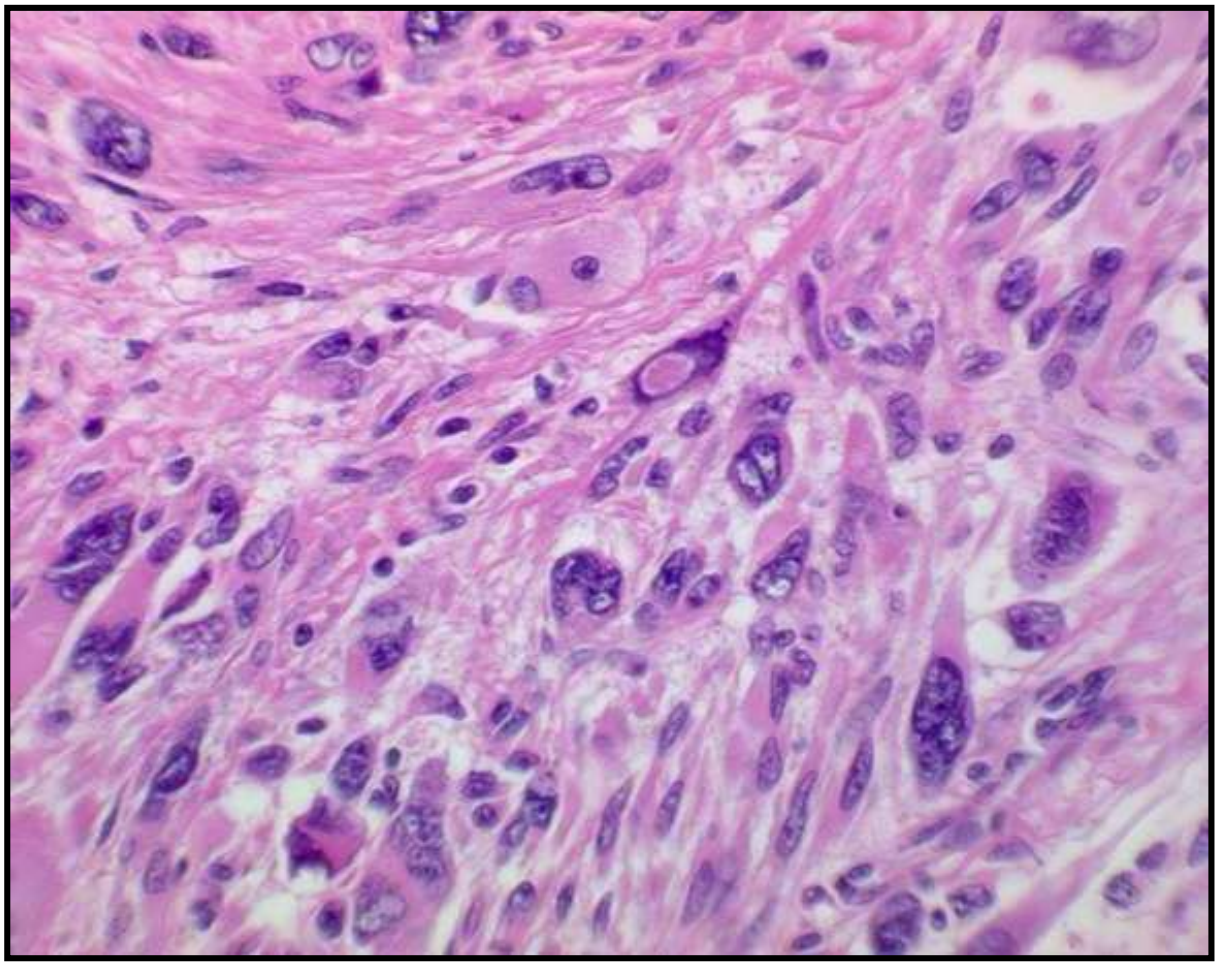
Leiomyoma with bizarre nuclei

Typically, no mitoses or 1-2/ 10 HPF, no coagulative tumour cell necrosis



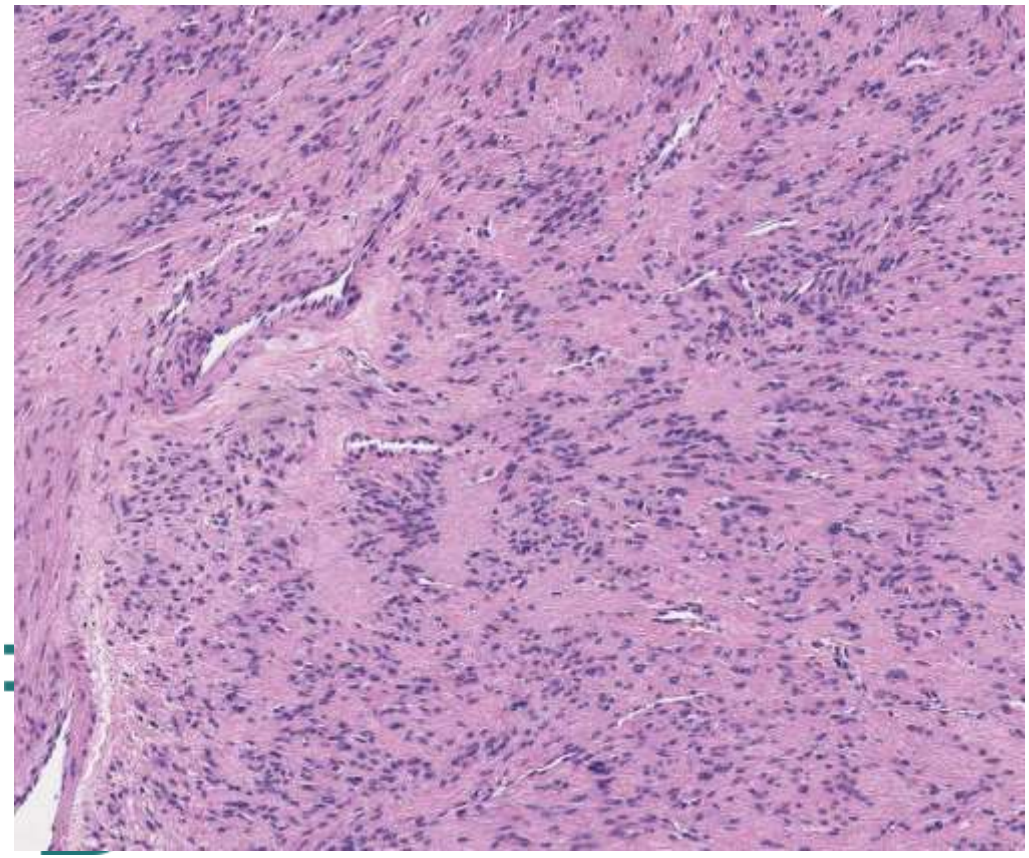


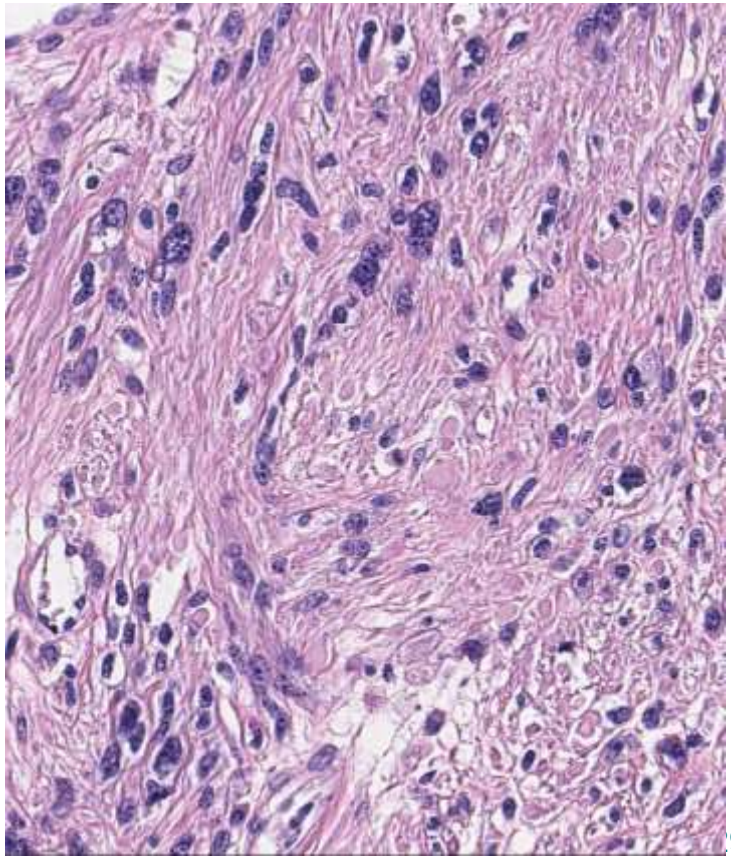
Leiomyoma with bizarre nuclei



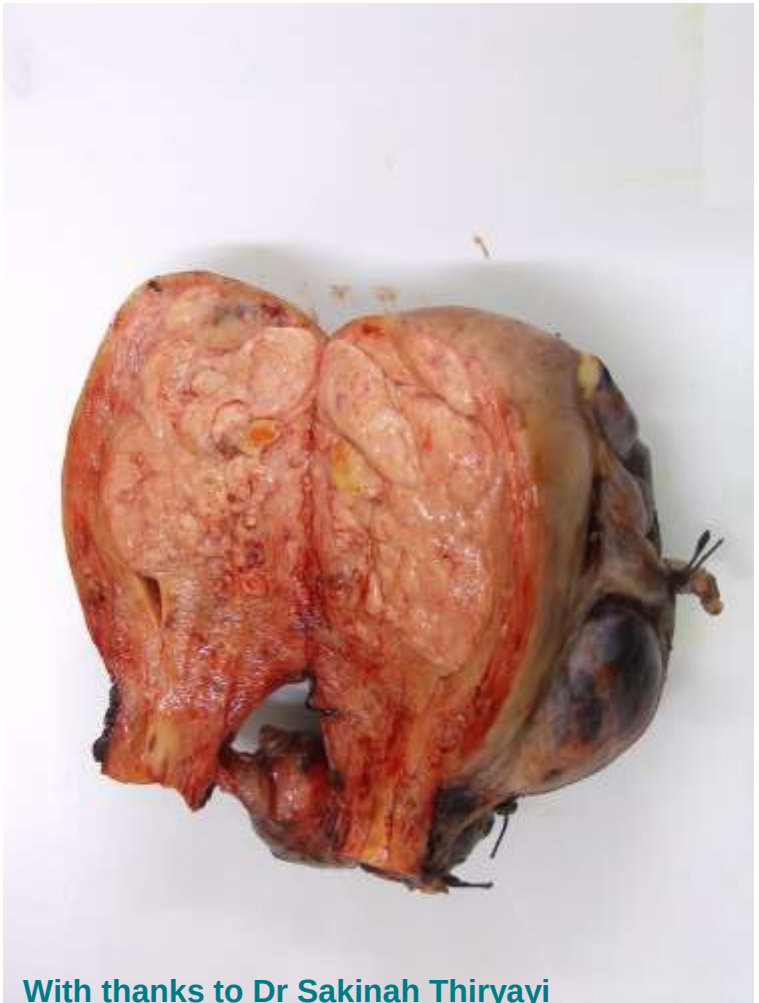
FH deficient leiomyoma (HLRCC)

Younger patients <40 years, multiple leiomyomata, staghorn vessels, eosinophilic globules, per-nuclear halos

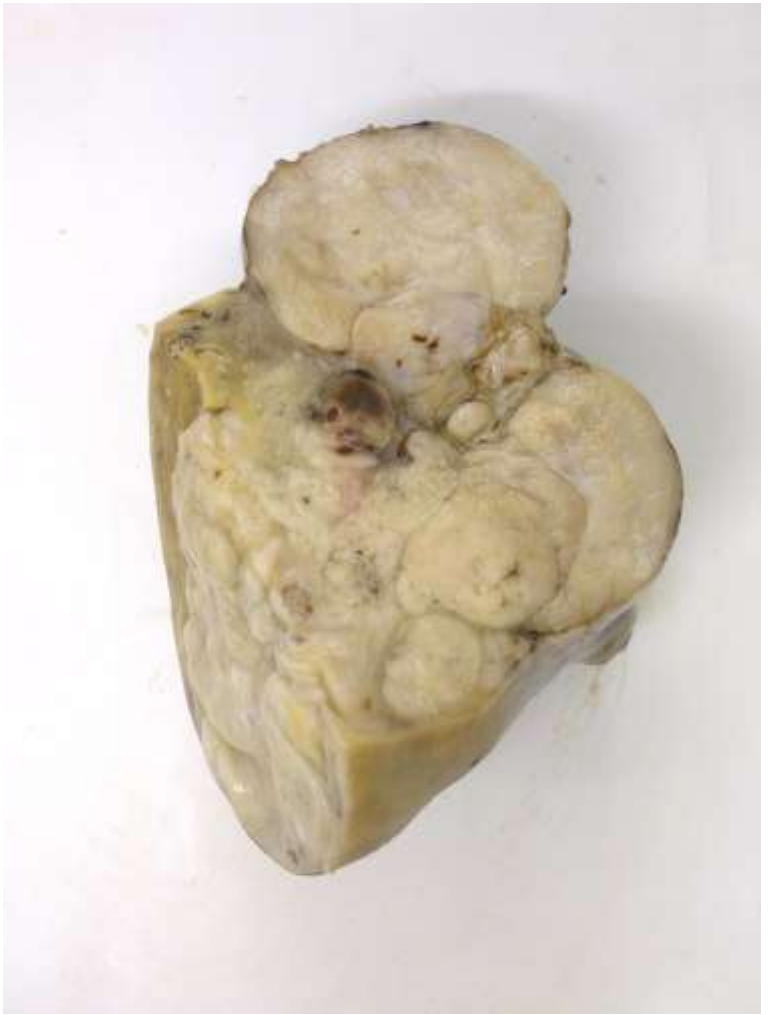




Intravenous leiomyomatosis



With thanks to Dr Sakinah Thiryayi



Intravenous leiomyomatosis

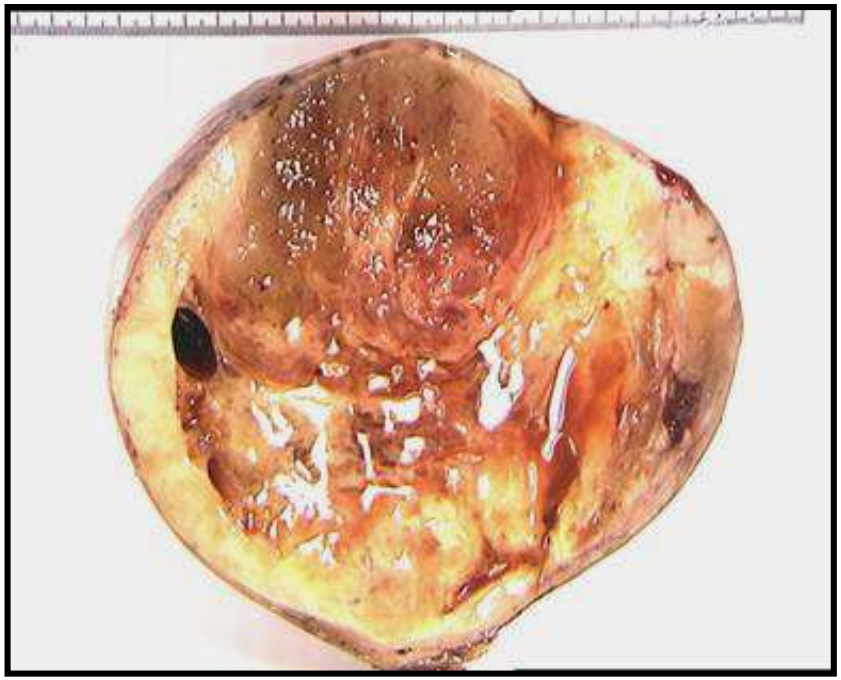
IVL in Uterus

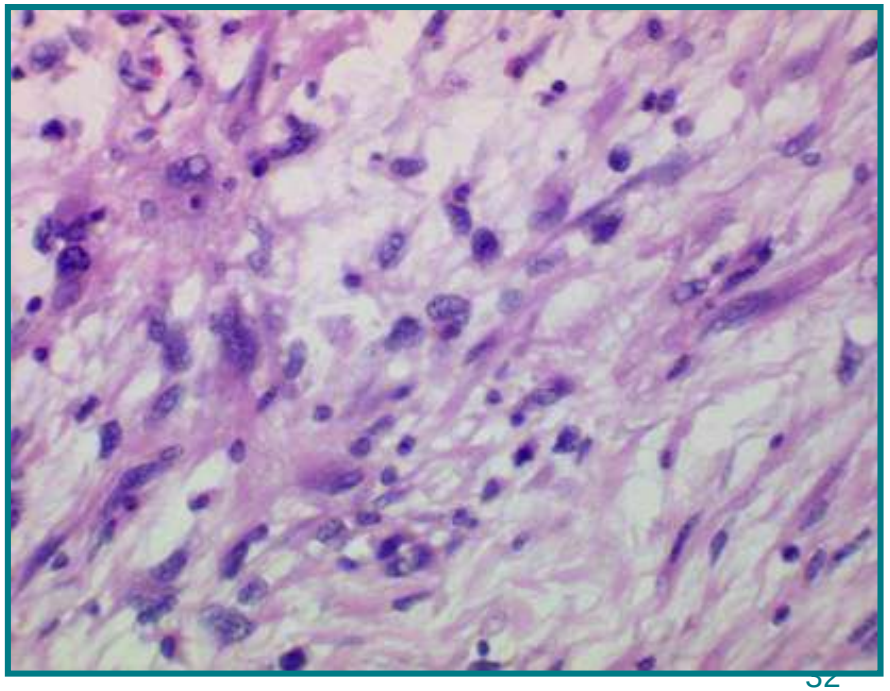
No cytologic atypia or brisk mitotic activity, note IVL can show All the same changes that are seen within intramyometrial leiomyomata

Tumour within right ventricle

With thanks to Dr Sakinah Thiryayi

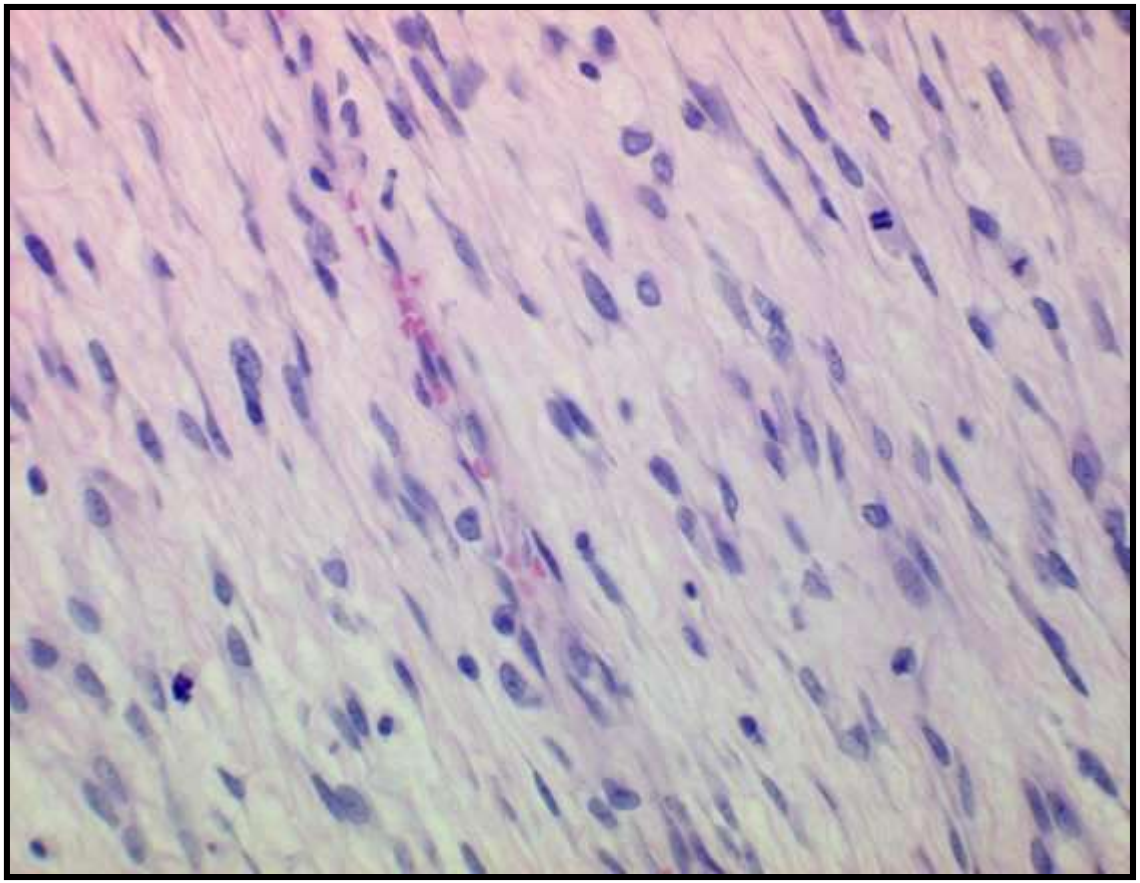
Myxoid leiomyosarcoma



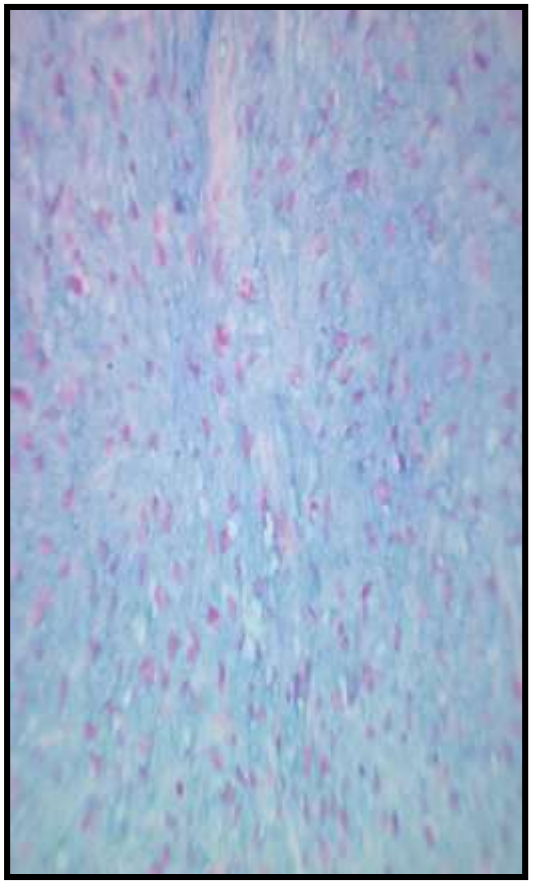


Myxoid Leiomyosarcoma

Mitotic activity



Alcian blue +ve



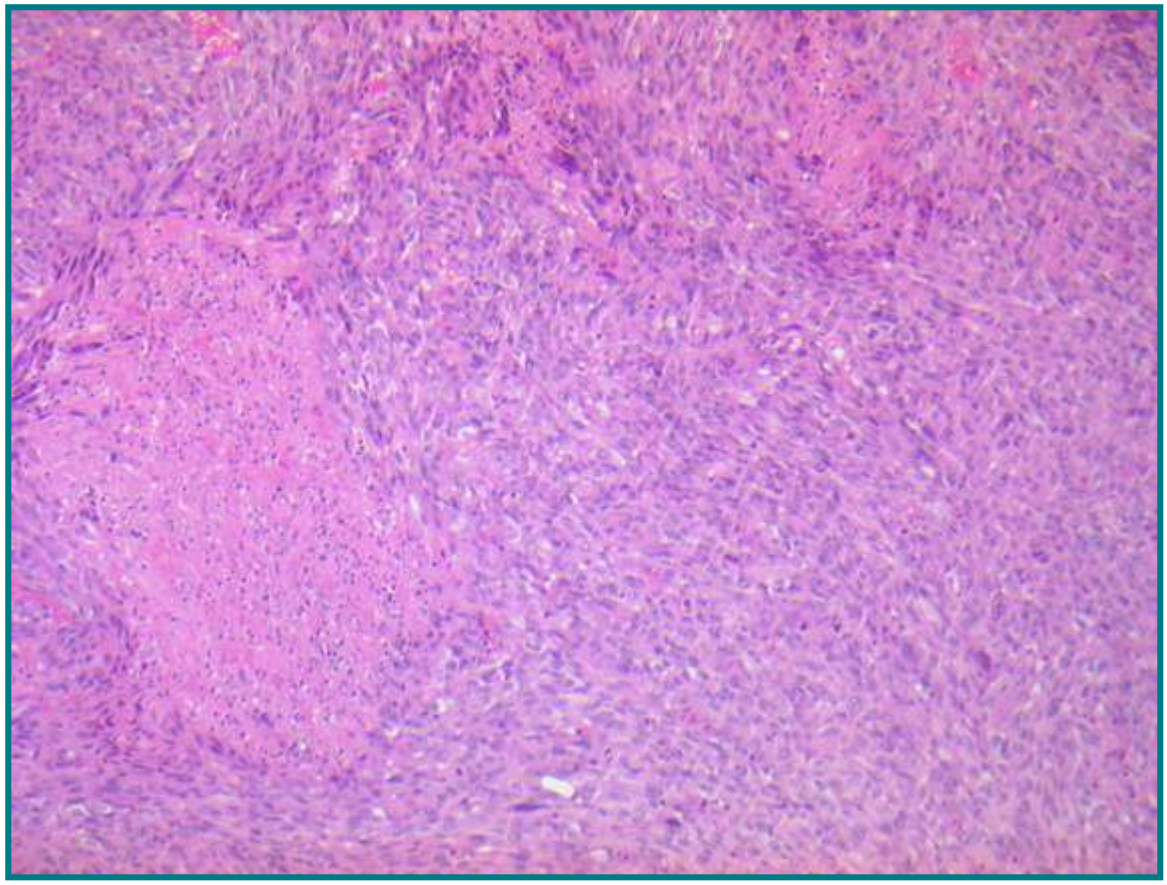
Myxoid Leiomyosarcoma

- Severe cytologic atypia + / - tumour cell necrosis
  - Any Mitotic index
- Mitotic Index > 2MF/10 HPF
  - No cytologic atypia
  - No necrosis

EPITHELIOID LEIOMYOSARCOMA

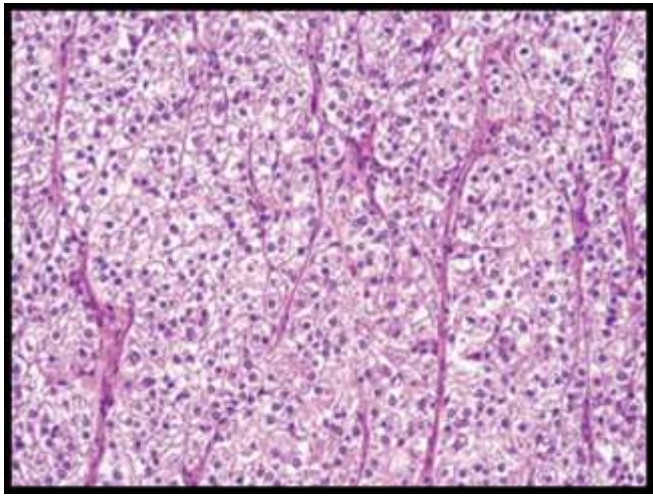
- Very rare especially pure epithelioid tumours
- Few cases in literature
- Diffuse moderate to severe cytologic atypia
- > 3 MF/ 10 HPF
- Necrosis - microscopic

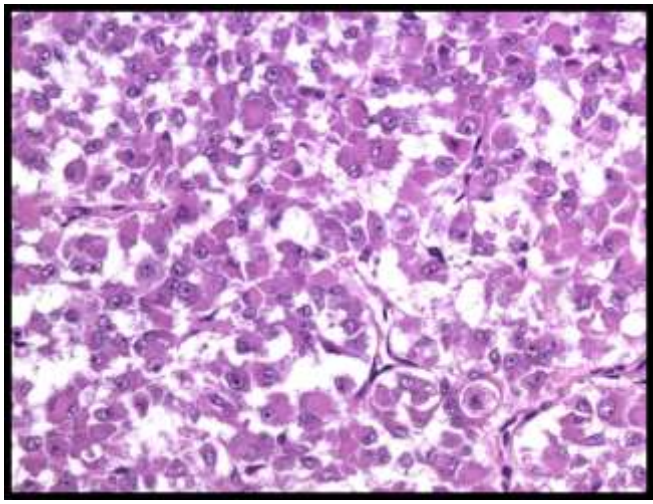
EPITHELIOID LEIOMYOSARCOMA



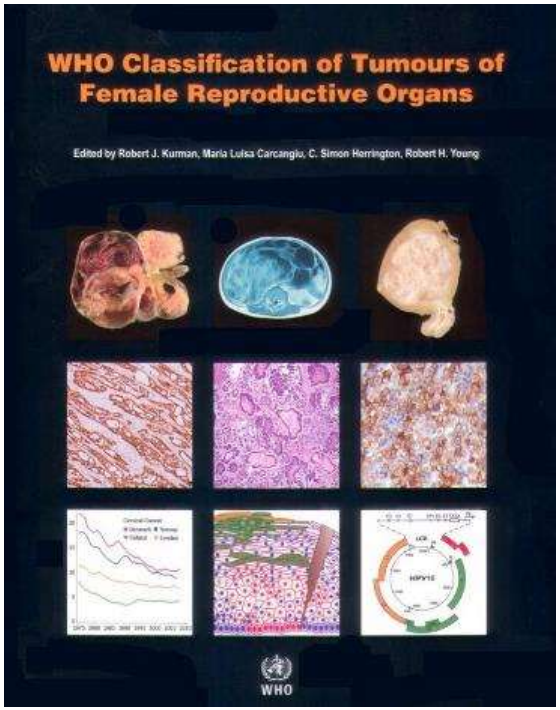
PEComa

- Epithelioid morphology
- Clear /eosinophilic cytoplasm
- Pink granular cytoplasm
- Centrally located/round nuclei
- Nested growth pattern
- Epithelioid and spindled cells
- TSC1 or TSC 2 mutations
- Dysregulation of the mTOR signalling pathway
- mTOR inhibitors may be helpful in Rx





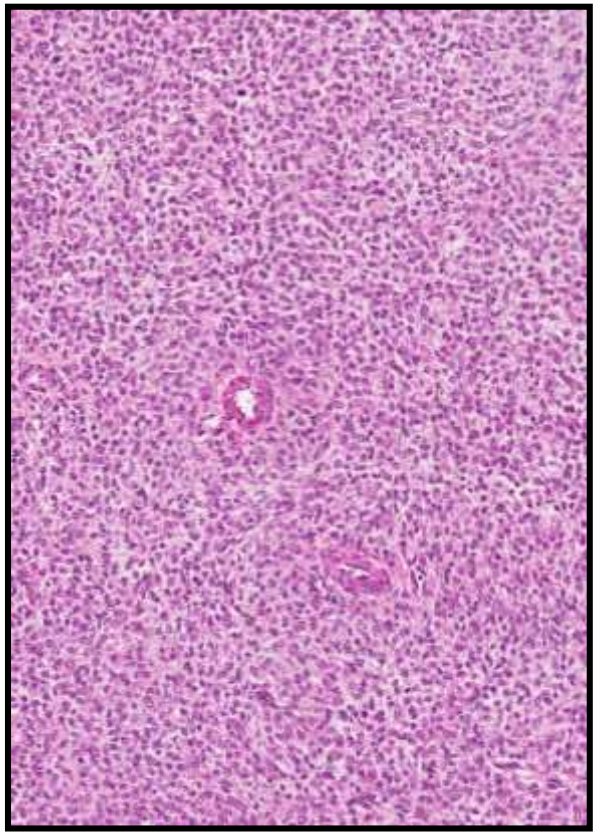
WHO 2014- Updated grading for EST



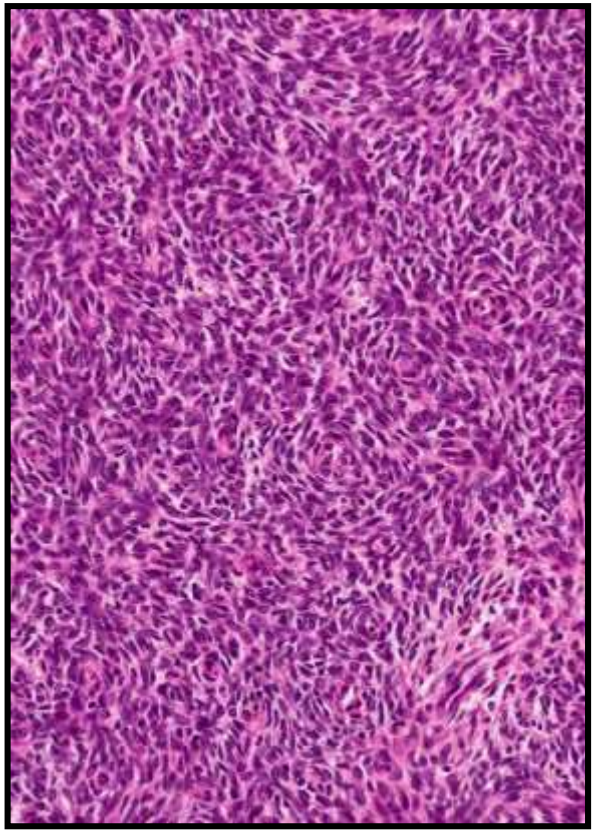
- Endometrial stromal nodule
- Endometrial stromal sarcoma
  - (low grade)
- Endometrial stromal sarcoma
  - (high grade) specific t(10:17)
- Undifferentiated Uterine Sarcoma

Cellular leiomyoma Vs ESN

Cellular leiomyoma



Endometrial stromal nodule

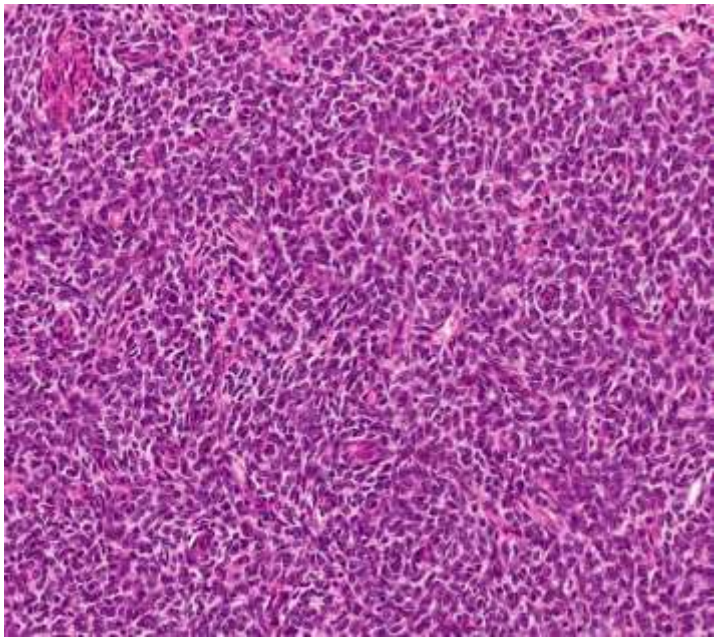


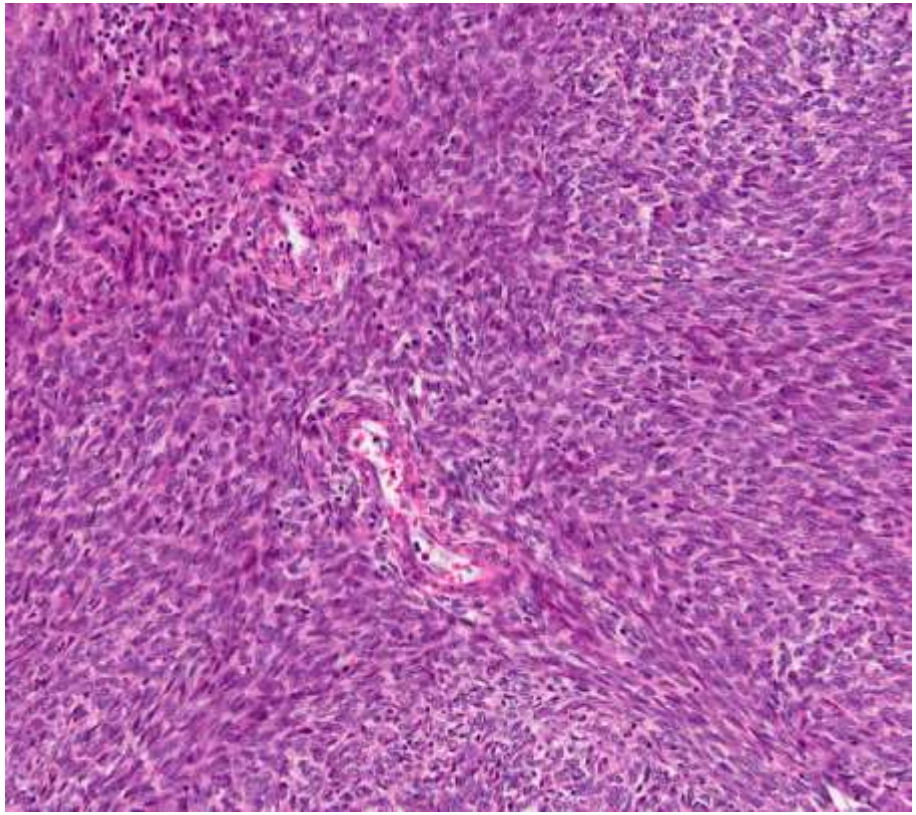
LG ESS

Clinical features

- Age usually < 50 years
- Pelvic or abdominal pain/abnormal vaginal bleeding
- Variable sized neoplasm (polypoid / bulky)
- 1/3rd extrauterine pelvic extension at diagnosis
- May present with metastasis (Ovary common site)
- Indolent and protracted course (characterised by recurrences)
- May be associated with prolonged oestrogenic stimulation, tamoxifen Rx or prior pelvic irradiation

Endometrial Stromal sarcoma - LG



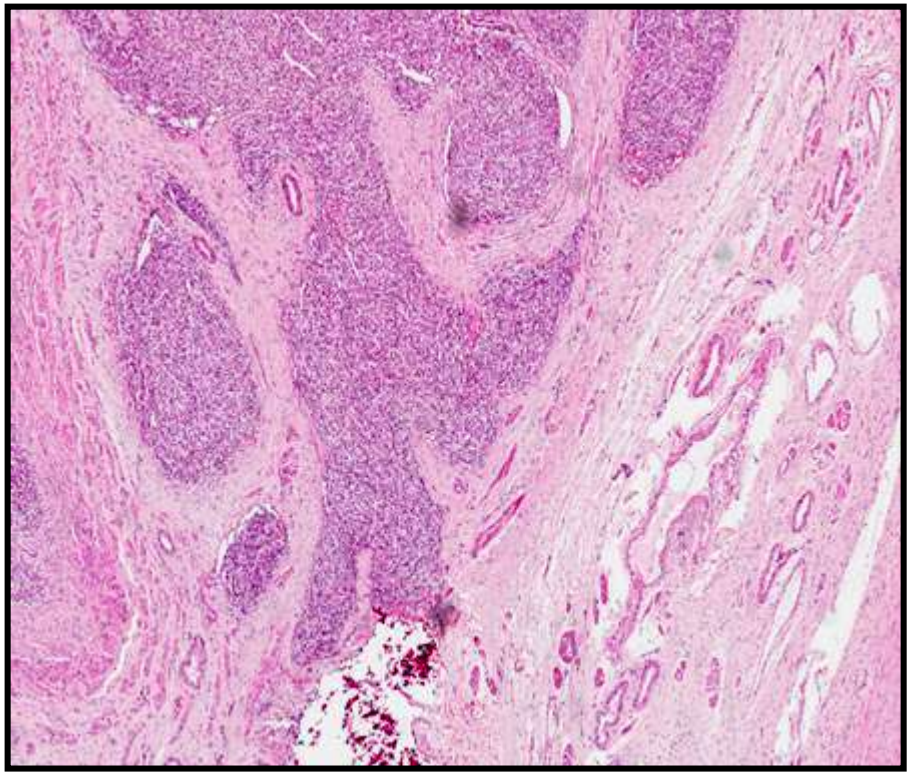


Stromal cells proliferate around small calibre arterioles

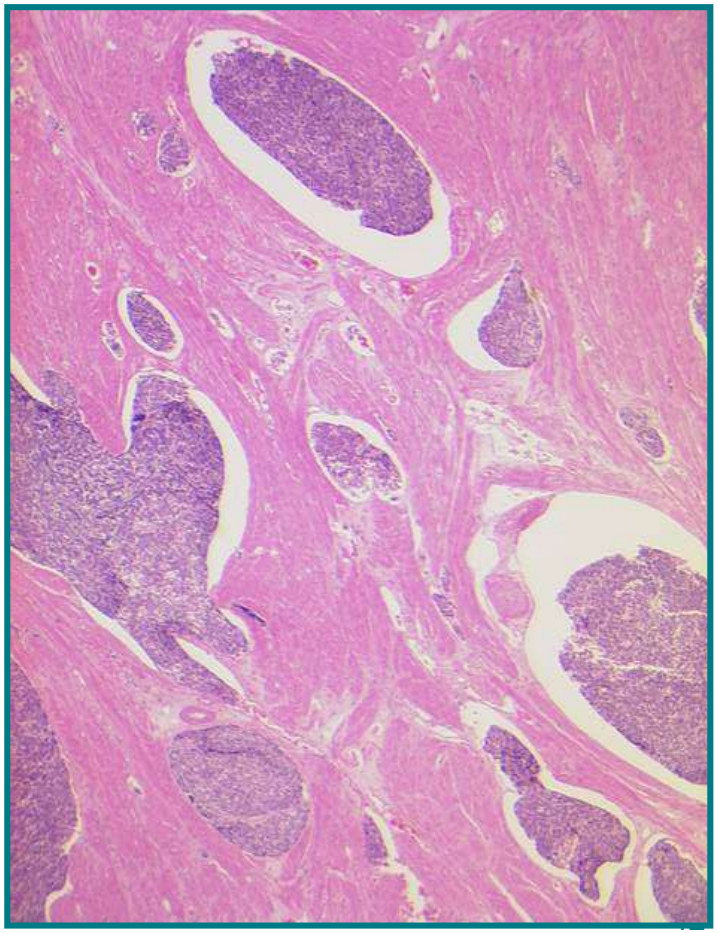
Resembles the stroma seen in the proliferative phase

LGESS –pushing , tongue-like growth

Note no stromal response

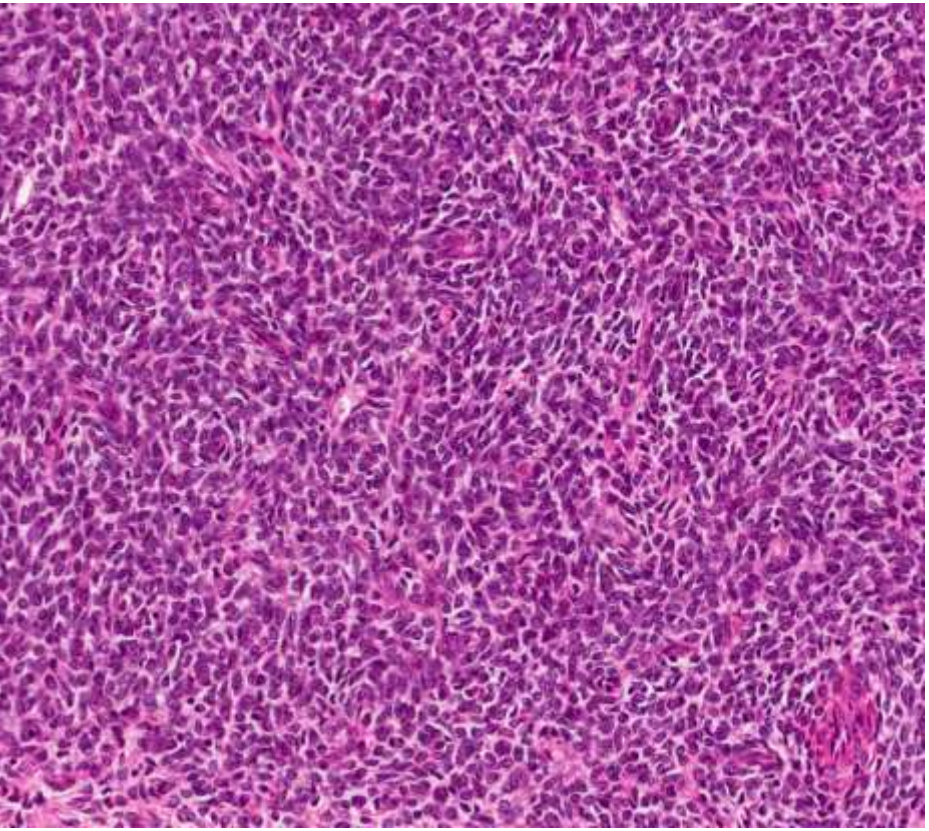


Extensive lymphovascular space permeation

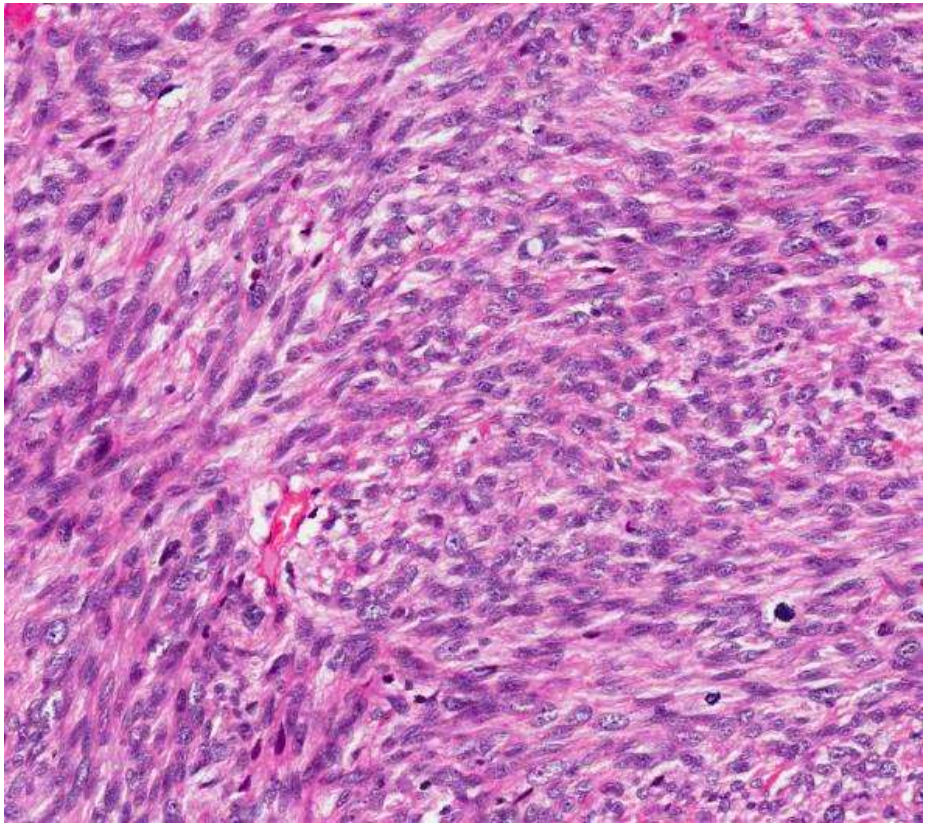


ESS vs Leiomyosarcoma

ESS- Proliferation around arterioles



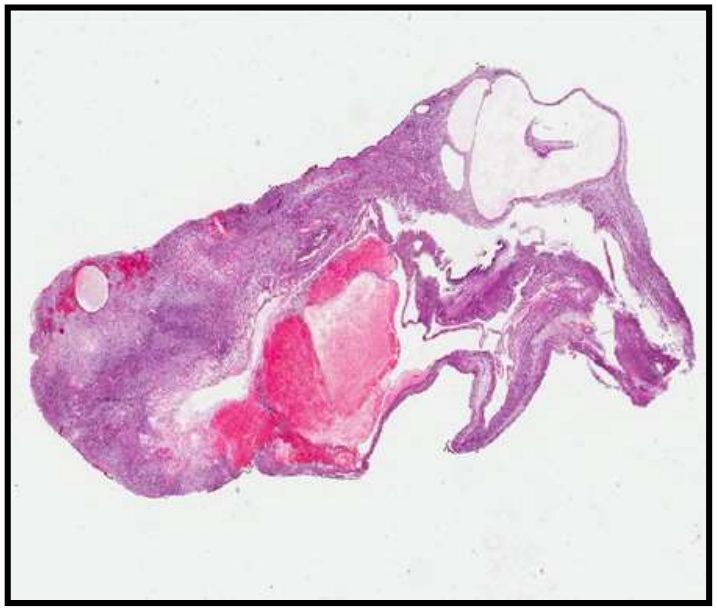
Leiomyosarcoma- proliferation in fascicles

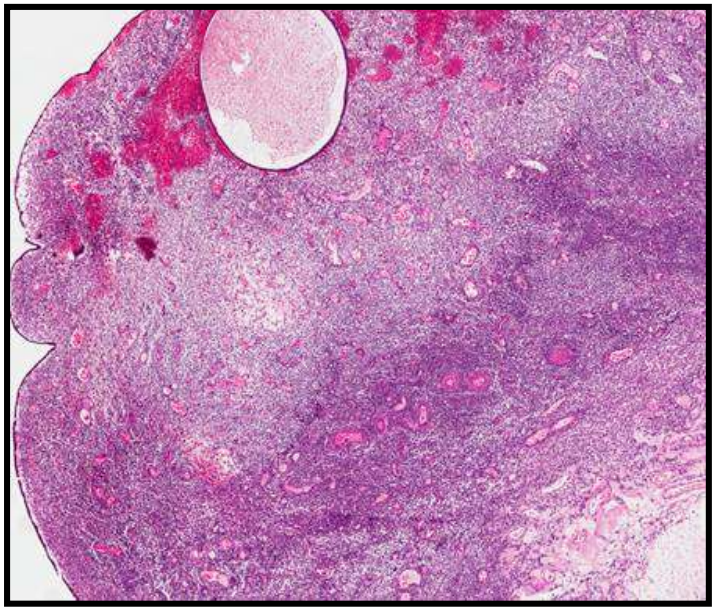


Endometrial stromal tumour

Endometrial stromal proliferation in the absence of glands consider ESS as possible dx

Note if base not identified cannot exclude an ESS on curettage material





LGESS -Immunohistochemistry

- CD10 – strong diffuse positive (usually) *
- ER/ PR/ WT1 : typically positive *
- SMA - often positive
- Desmin- occasionally positive *
- H-caldesmon –negative (+ ve smooth muscle * differentiation)
- C-Kit (CD117) – may be positive but no c KIT mutations
- Aromatase
- Androgen receptor –may be positive (sex cord like areas)
- AE1/AE3 – epithelial differentiation
- Inhibin/ calretinin/melan-A and CD99- may be positive
- * = Diagnostically useful markers

ESS LG – Molecular genetics

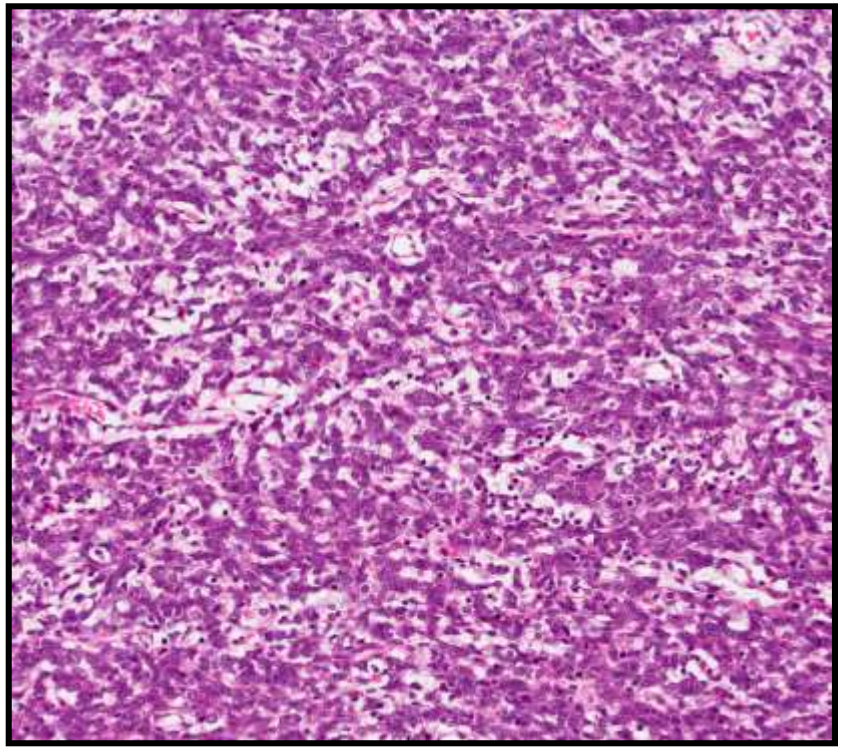
- t(7;17) -80%
  - JAZF1-SUZ12
- t(6;7)- 6%
  - PHF1-JAZF1
- t(6;10) -4%
  - EPC1-PHF1

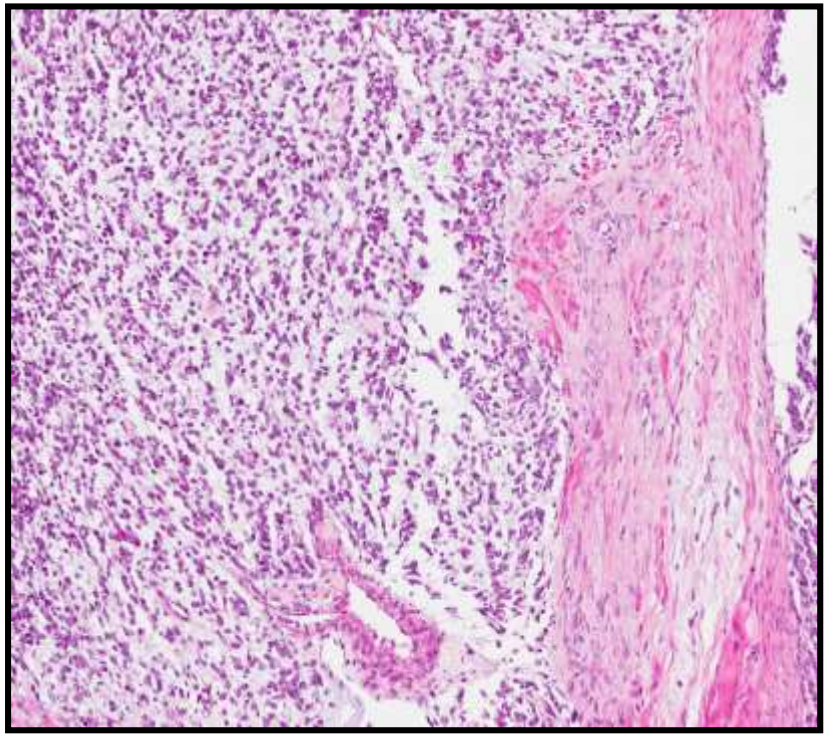
- Am J Surg Pathol 2011; 35: 1364-72 Chiang S et al
- Frequency gene rearrangements endometrial stromal tumours

ESS Low Grade

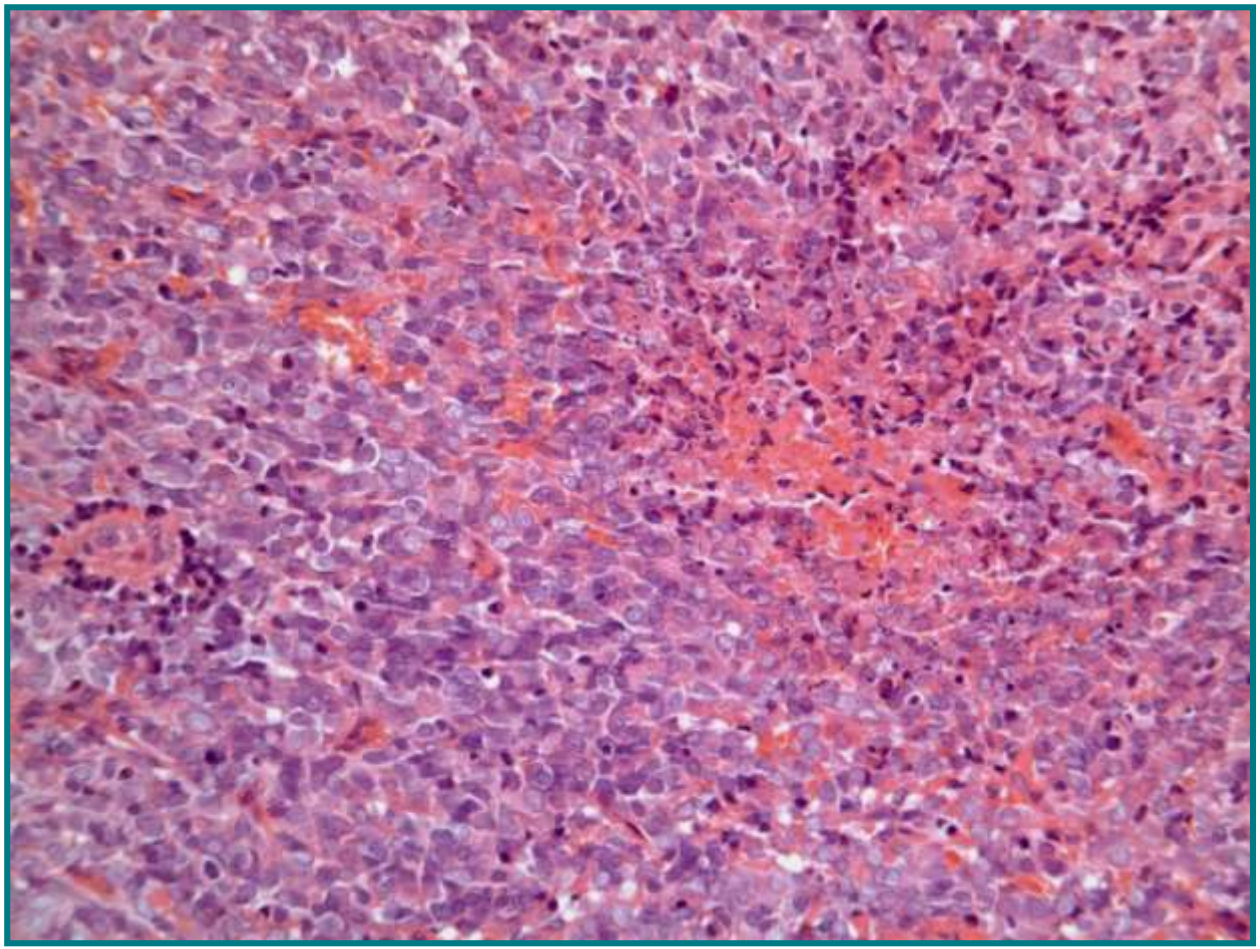
- Molecular genetics useful
- Pelvic tumour – ER , PR positive
- Not given history of previous ESS (low grade).
- Establishes dx in most cases

HGESS- Dual Cell population



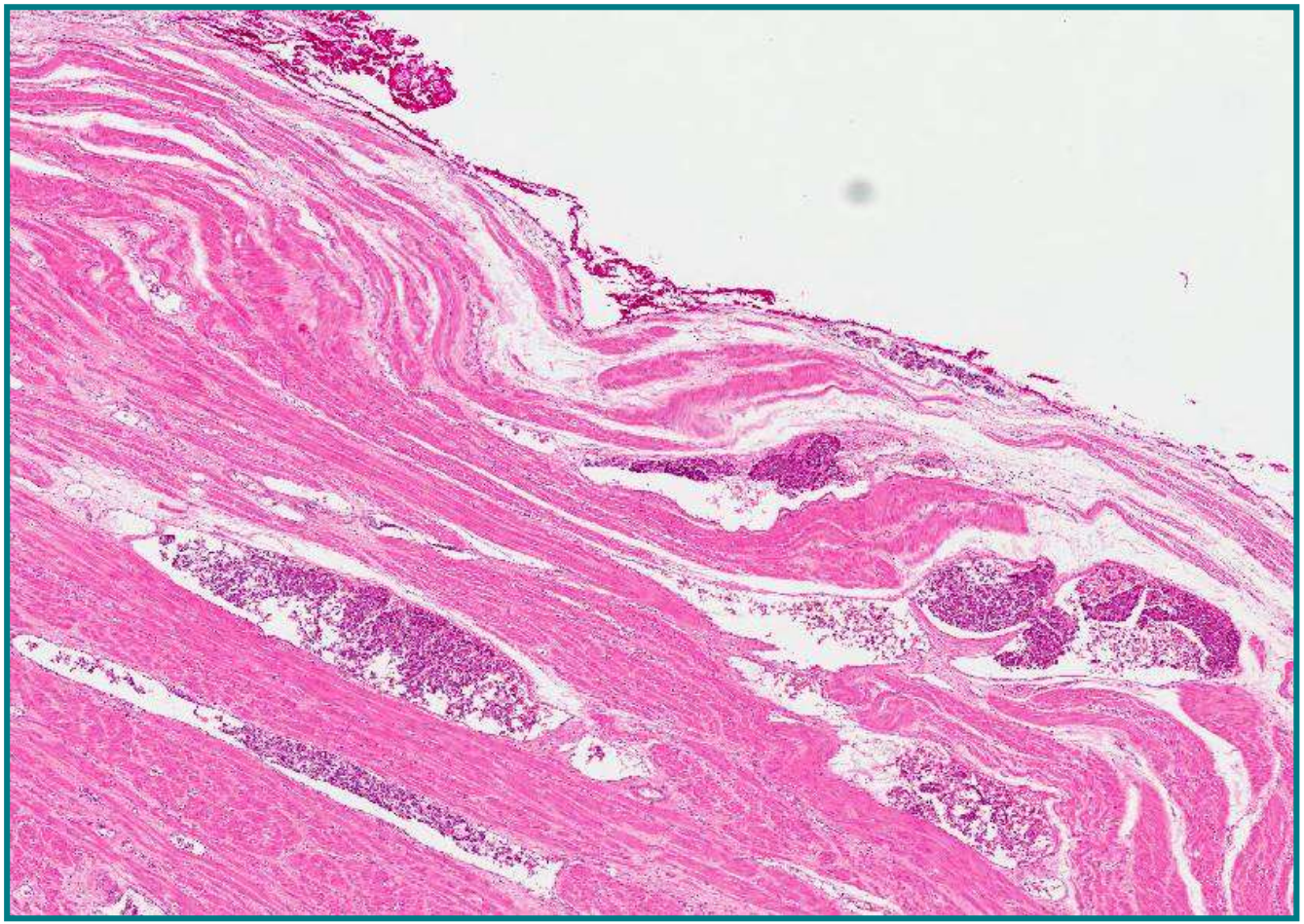


Round cell component



Necrosis seen

Extensive LVSI

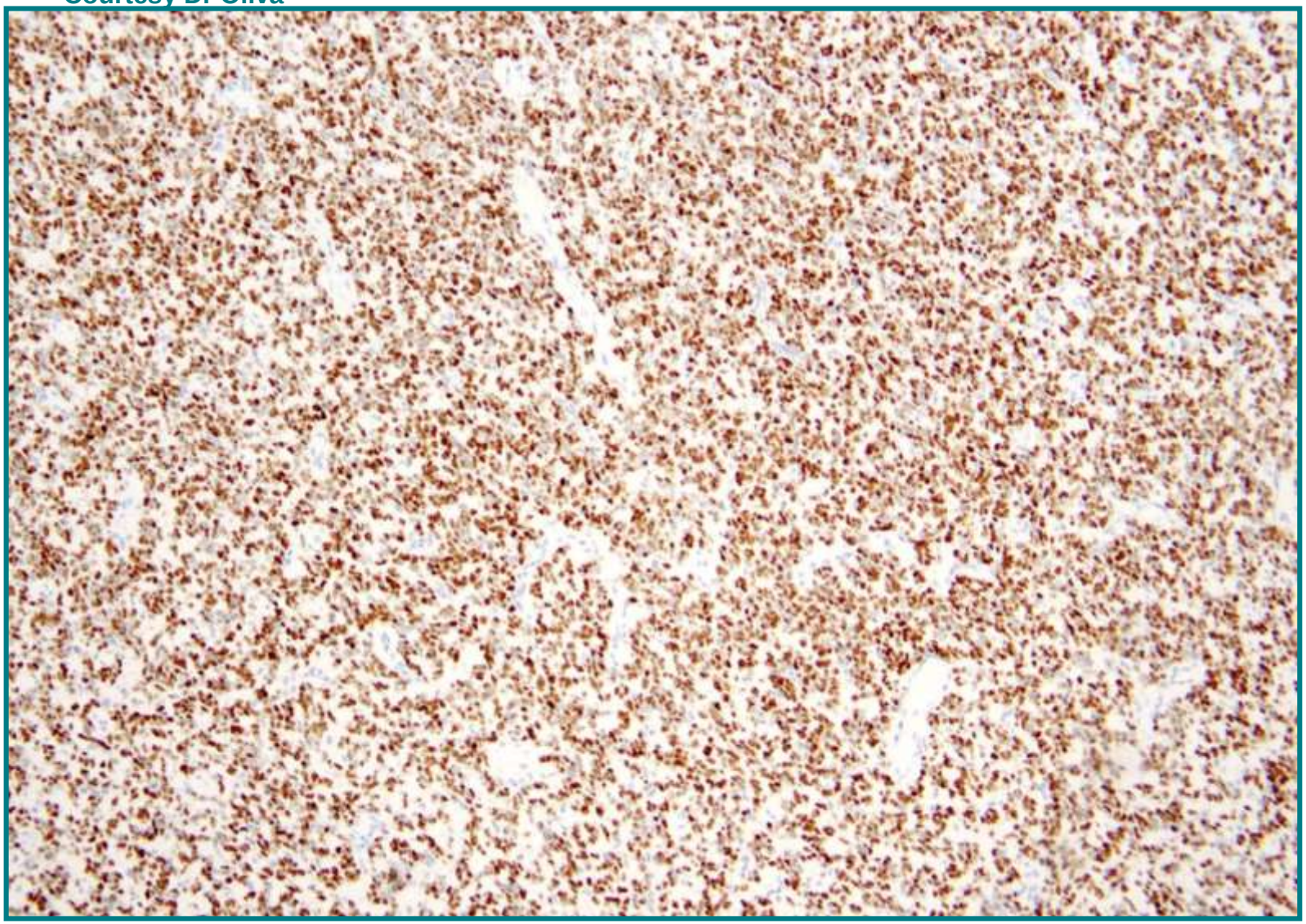


HG ESS

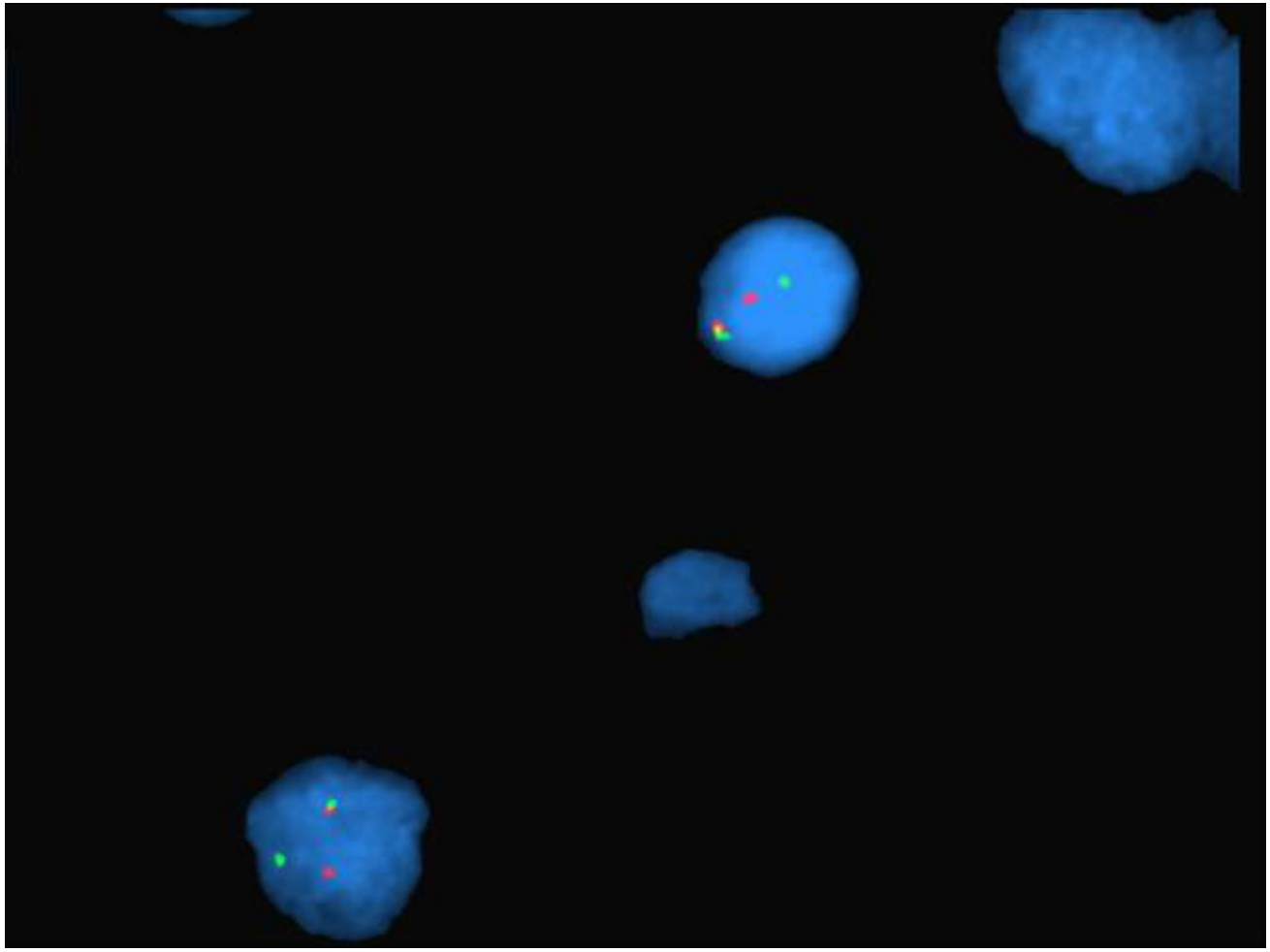
- Immunohistochemistry
- High grade component
  - CD10 –ve
  - ER –ve
  - PR –ve
  - Cyclin D1 (>70%) strong, diffuse, nuclear +ve
  - C KIT (cytoplasmic strong)
  - DOG 1(-ve) in high grade and low grade areas
  - Beta-catenin (cytoplasmic) no nuclear positivity
  - Negative for:
  - EMA, SMA, desmin, caldesmon, HMB-45, Melan A and cytokeratin

Cyclin D 1 diffuse positive

Courtesy Dr Oliva



FISH t(10;17)(q22;p13)



Courtesy of Drs Lee and Oliva , YWHAE-NUTM2 ESS

Undifferentiated uterine sarcoma

- Definition
- A tumour arising in the endometrium or myometrium,
  - lacking resemblance to proliferative phase endometrial stroma
  - with high-grade cytological features
  - and no specific type of differentiation
- Rare tumour, patients post menopausal, mean age 60 years
- Prognosis: Poor.
  - Patients present with high stage disease (>60%).
  - Even patients with stage I disease DOD within 2 years
- Adjuvant therapy no therapeutic benefit

Undifferentiated Uterine sarcoma

- Heterogeneous group of sarcomas with high mitotic activity and necrosis lacking diagnostic criteria for:
  - ESS (high grade)
  - Leiomyosarcoma
  - Rhabdomyosarcoma
  - Adenosarcoma with sarcomatous overgrowth
  - Carcinosarcoma (esp when sarcoma has overgrown carcinoma)
  - Undifferentiated or dedifferentiated endometrial carcinoma
  - Complex Karyotype (many structural and numerical aberrations)

Endometrial Stromal Sarcoma: prognosis

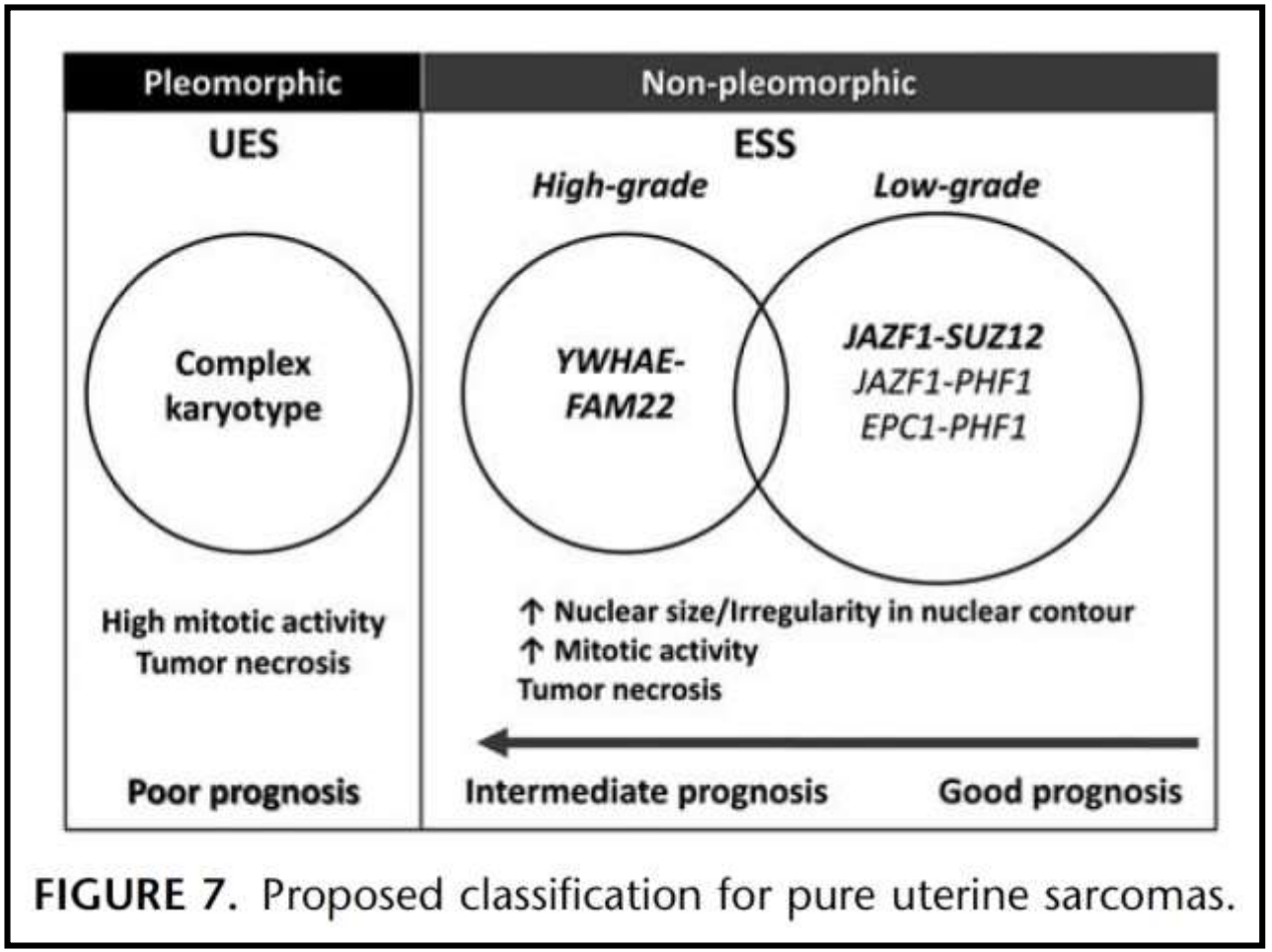


FIGURE 7. Proposed classification for pure uterine sarcomas.

Am J Surg Pathol, 2012: 36, 641-653

Smooth muscle tumour of uncertain malignant potential

WHO 2014

Uterine smooth-muscle tumours with spindle-cell differentiation of uncertain malignant potential.

Tumour cell necrosis	Moderate-to-severe atypia	Mitotic count (per 10 HPF)	Mean mitotic count in tumours with recurrence (per 10 HPF)	Cases with recurrence
Absent	Focal/multifocal	< 10	4 (range 3–5)	13.6% (3 of 22 cases) {68 ,811}
	Diffuse	< 10	4.3 (range 2–9)	10.4% (7 of 67 cases) {129,145,1865,1981}*
Present	None	< 10	2.8 (range 1–4)	26.7% (4 of 15 cases) {41,68,129}
Absent	None	≥ 15	Not applicable	0% (0 of 39† cases) {129,811}

*One of the four tumours also had epithelioid cells
†Three had ≥ 20 mitotic figures per 10 HPF; an unknown proportion also had counts between 10 and 14 {129}.

Leiomyoma with bizarre nuclei

Downes and Hart

- MIB-1 BZL <10%
- Suggests Leiomyosarcoma >15%

Some consider any SMT with diffuse moderate to severe atypia

No tumour cell necrosis

>5 to < 9 MFs /10HPF leiomyosarcoma others STUMP

- Small number have recurred.

Leiomyoma with bizarre nuclei

- Croce, Young and Oliva 2014 Am J Surg Pathol 38
  - 59 cases
  - Mitotic counts 0 to 7/10 HPF (average 1-2/10HPF)
  - 37 (63%) had <2 MF/10 HPF
  - 19 (32%) had 2-5 MF/10 HPF
  - 3 (5%) had 6,7,7 MF/10 HPF
    - 2 with focal and 1 diffuse BN
    - 2.9,5.7 and 5.5. years FU respectively
  - None recurred (follow-up 1 to 13 years)

STUMP – sample carefully and generously

- SMT with coagulative necrosis but < 10 MF/ 10 HPF
- SMT with diffuse cytologic atypia,
  - <10MF/10HPF and no necrosis or unsure about necrosis
- SMT with focal or multifocal moderate to severe atypia but
  - <10 MF/ 10 HPF
- SMT with no necrosis or atypia
  - but > 15 MF/ 10 HPF

Leiomyosarcoma

- No reliable prognostic markers
- Adjuvant treatment is used to variable effect
- Need to await specific markers before significant impact on Rx
- NGS of tumours and precision medicine may be the answer

NCI and the precision medicine initiative @ www.cancer. gov

Mesenchymal tumours

- Thorough sampling of tumours that look unusual
  - especially at the tumour/ myometrial border.
- Use immunohistochemistry as a panel
- Investigate carefully before labelling a stromal neoplasm an undifferentiated uterine sarcoma (much worse prognosis).
- Use molecular markers for low grade and HG ESS to support diagnosis
  - especially of pelvic tumours which are recurrent stromal sarcomas.
- Have a low threshold for referral of these tumours as they are rare.