



# An Update on Uterine Mesenchymal tumours

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# Uterine Mesenchymal Tumours

- Smooth Muscle
  - Benign
  - Unusual SMT mimics of LMS
  - STUMP
  - Leiomyosarcoma
- Endometrial Stromal Tumours (WHO 2014)
  - Stromal nodule
  - Low grade (ESS)
  - High grade (ESS)
  - Undifferentiated Uterine Sarcoma (UUS)

# Uterine Mesenchymal Tumours

- Uterine Tumour resembling ovarian sex cord tumours
- Rhabdomyosarcoma
- Perivascular epithelioid cell tumour (PEComa)
- Rare
  - Benign: lipoma, haemangioma and lymphangioma
  - Malignant: angiosarcoma, liposarcoma, osteosarcoma, chondrosarcoma
- Myxoid smooth muscle tumours
  - Benign/ malignant
- Epithelioid smooth muscle tumours
  - Benign/malignant

# ESS : journey through terminology





# ESS

- Norris and Taylor 1966
- Endometrial Stromal Sarcoma (morphological classification)
  - Cells resemble endometrial stroma in proliferative phase
- 35 cases in study:
  - range of Mitotic activity and nuclear atypia

# Norris and Taylor 1966

- Mitotic activity
  - $>10\text{MF}/10\text{ HPF}$  (50% 5 year survival)
  - $<10\text{MF}/10\text{ HPF}$  (100% 5 year survival but 30% recurred)
- Nuclear atypia
  - greater in high grade vs low grade group but overlap noted.
- This lead to stratification of ESS on MI
  - low grade ESS
  - high grade ESS

# Evans HL 1982

- Cancer 1982
- ESS should be separated from poorly differentiated endometrial sarcoma (resemblance to endometrial stroma and arborising vasculature)
- Poorly differentiated ES:
  - Larger cells
  - Nuclear Hyperchromasia
  - Pleomorphism
  - Stromal vasculature not prominent
  - Frequent necrosis
  - Increased mitotic activity but **MA was not itself an important prognosticator**

# Change KL et al 109 ESS (largest study) 1990

- **Primary uterine endometrial stromal neoplasms. A clinicopathologic study of 117 cases**

Chang KL, Crabtree GS, Lim-Tan SK, Kempson RL, Hendrickson MR

[Am J Surg Pathol.](#) 1990 May;14(5):415-38

- Primary uterine tumour > 0.5 cm in size resemble Prolif Endo
- Serpentine infiltration through myometrium
- Intravascular growth
- Mitotic rate does not predict recurrence in Stage I patients

# Silverberg and Kurman (1992)

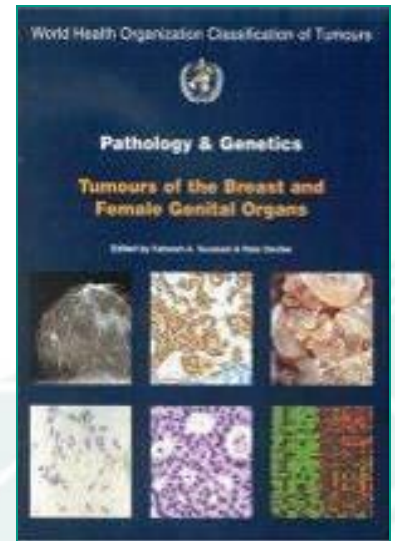
- Recognised 3 categories:
  - Low grade ESS
  - High Grade ESS
  - Undifferentiated Sarcoma
- Made case: importance that tumour must morphologically resemble stromal cells of proliferative endometrium

# ESS

- WHO classification (2003)
- ESN (endometrial stromal nodules)
- ESS ( “low grade” endometrial stromal sarcoma)
- UES (Undifferentiated endometrial sarcoma)

## Prognosis

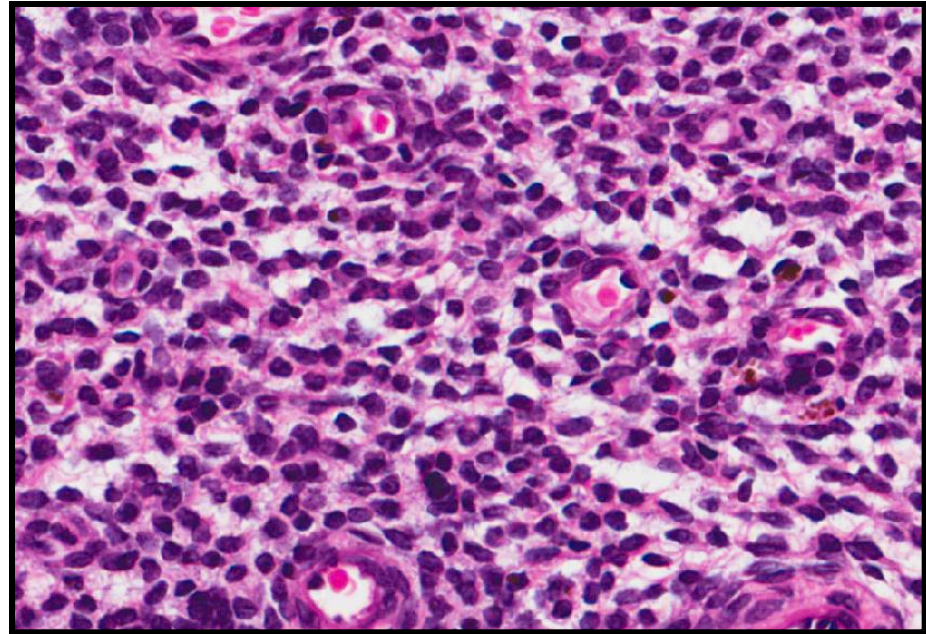
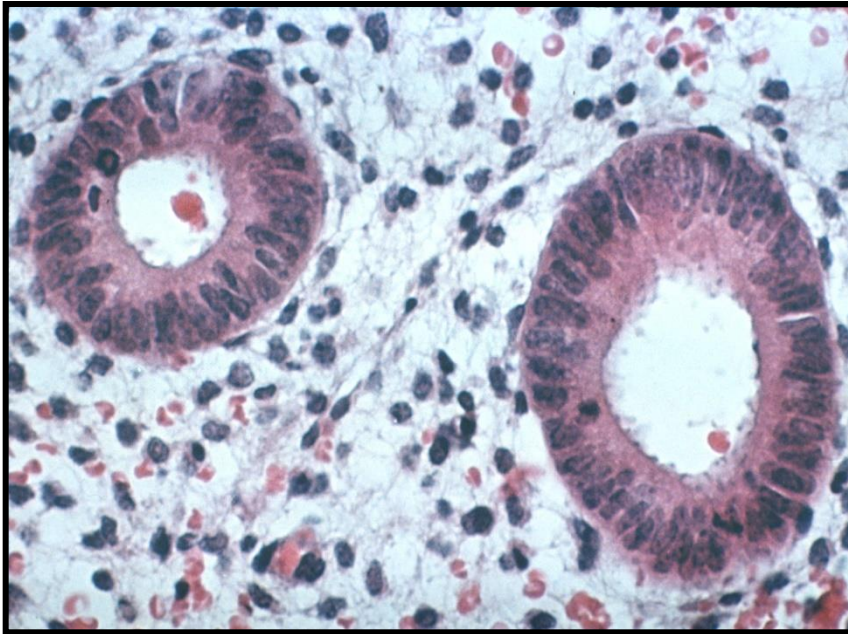
	5 year survival
ESS	85%
UES	<50%





# Classification

- Greater emphasis placed on morphology of tumour cells



Must resemble stroma of proliferative phase of endometrium

# ESS ( WHO 2003)

- Dichotomous system : based on cytology
  - ESS (low grade) : tumour cells resemble stroma of proliferative phase of endometrium
  - UES (high grade endometrial sarcoma) no resemblance to proliferative phase endometrial stroma
  - Lacks specific differentiation
  - No longer differentiated on mitotic activity but :
    - On degree of nuclear atypia
    - Tumour necrosis

# WHO 2003- Demise of HG-ESS!

- Rationale for demise of HG- ESS:



1. High mitotic activity: Discourage mislabelling of classic low grade ESS as high grade based on mitotic activity
2. Misclassification: Recognition that tumours that had been labelled as HG ESS bore no morphological resemblance to endometrial stroma and were undifferentiated pleomorphic uterine sarcoma

# The Grey zone

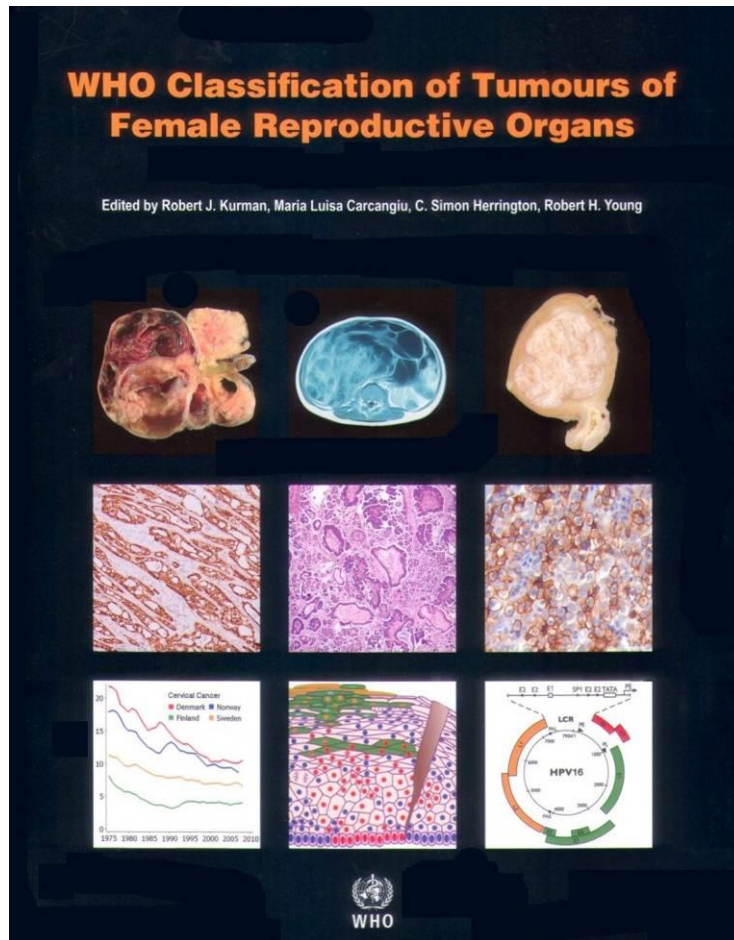
- Chang et al did recognise a subgroup of ESS that showed nuclear atypia and increased mitotic activity that could **not** be labelled as low grade ESS
- Low grade ESS with some high grade features
- Low grade transformation into high grade ESS
- 2003 Terry Rollason: made a case to retain HGSS recognising that rare cases encountered where low grade ESS juxtaposed to HGESS (Haines and Taylor editors Fox and Wells)

# High grade sarcoma

- Kurihara et al 2008
  - UES-U (with nuclear uniformity)
  - UES-P (with nuclear pleomorphism)- reflects high grade sarcoma
- Sample size was small 31 cases
  - 18 LGESS
  - 7 UES-U (uniform)
  - 6 UES-P (pleomorphism)
- No apparent clinical differences with regards to clinical outcome between these two groups (57% vs 60 %)



# 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



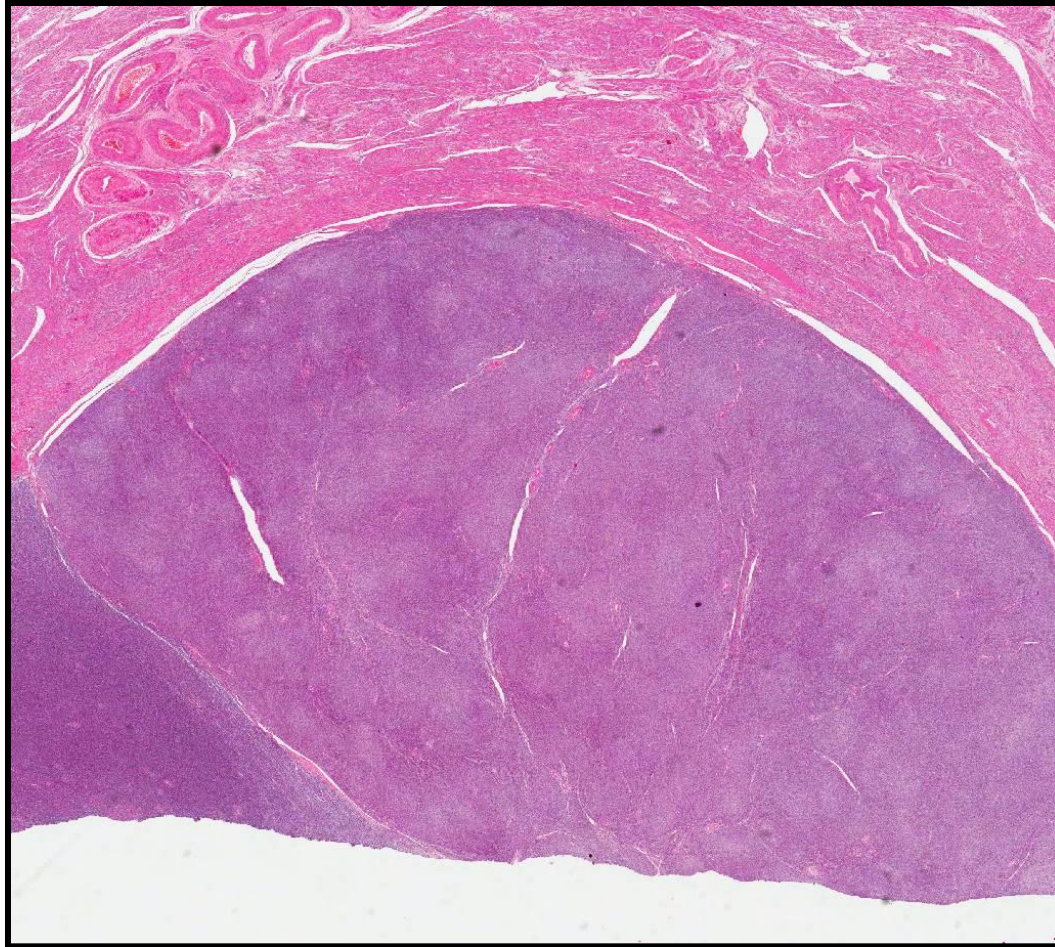
# ESN (Stromal nodule)

- Rare neoplasm
- 23-86 years (mean 53 years)
- Definition: WHO
- Benign endometrial stromal tumour that has a **well-circumscribed** margin and is composed of cells that resemble proliferative phase endometrial stroma. Finger-like projections or immediately adjacent nests of tumour cells (measuring , **3mm in greatest extent** from the main mass) and , **< 3 in number** are acceptable. Lymphovascular invasion excludes the diagnosis.

# Endometrial stromal nodule

- Grossly fleshy yellow/tan
- Histology
  - Cellular
  - Hyalinised
  - Cysts (34%)
  - Infarct type necrosis (68%)
- Up to 3mm focal irregularity allowed (Tavasoli and Norris 2002)
  - < 3 in number
  - Lobulated or finger-like projections into adjacent myometrium
  - Endometrial Stromal tumour with limited infiltration
  - Am J Surg Pathol 2002;26:567 -581

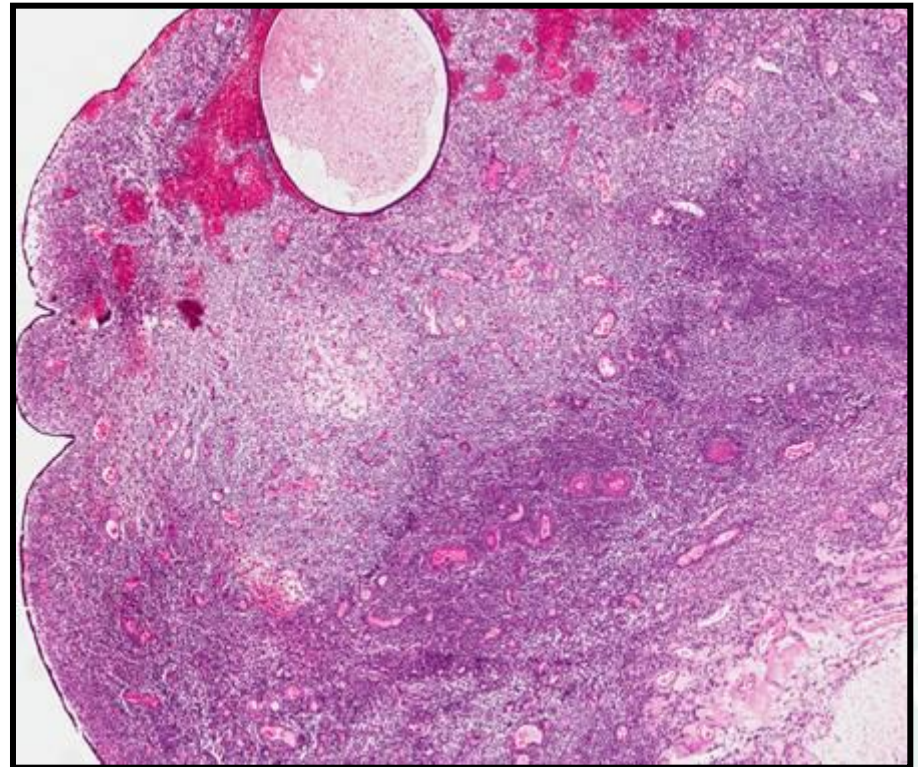
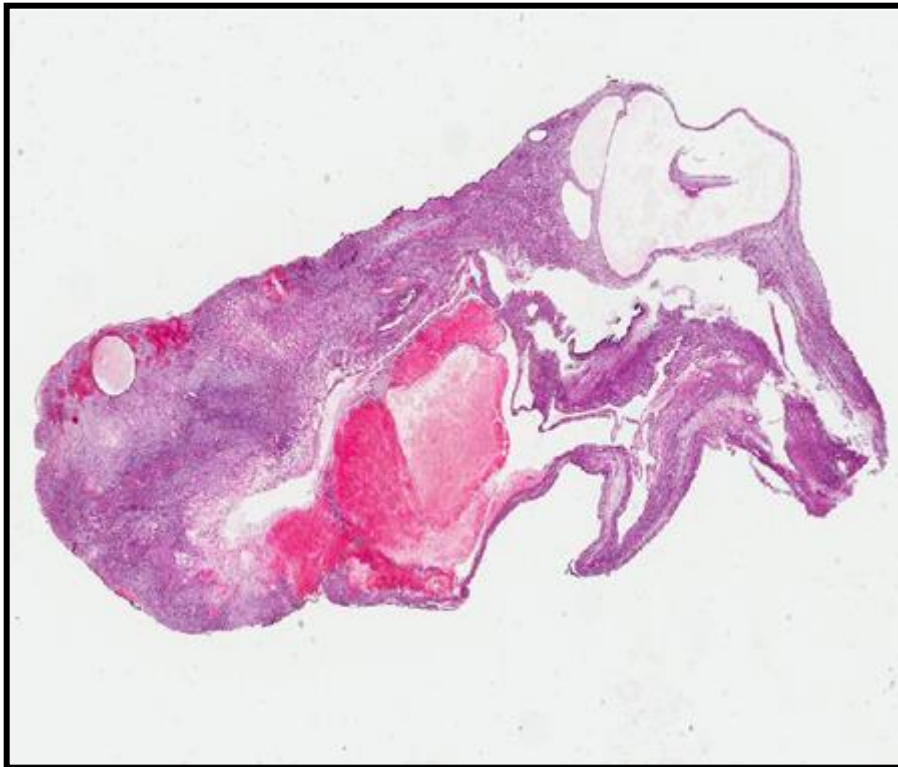
# Endometrial stromal nodule





# ES neoplasm "endo polyp"

Note base not identified. Diagnosis cannot be made



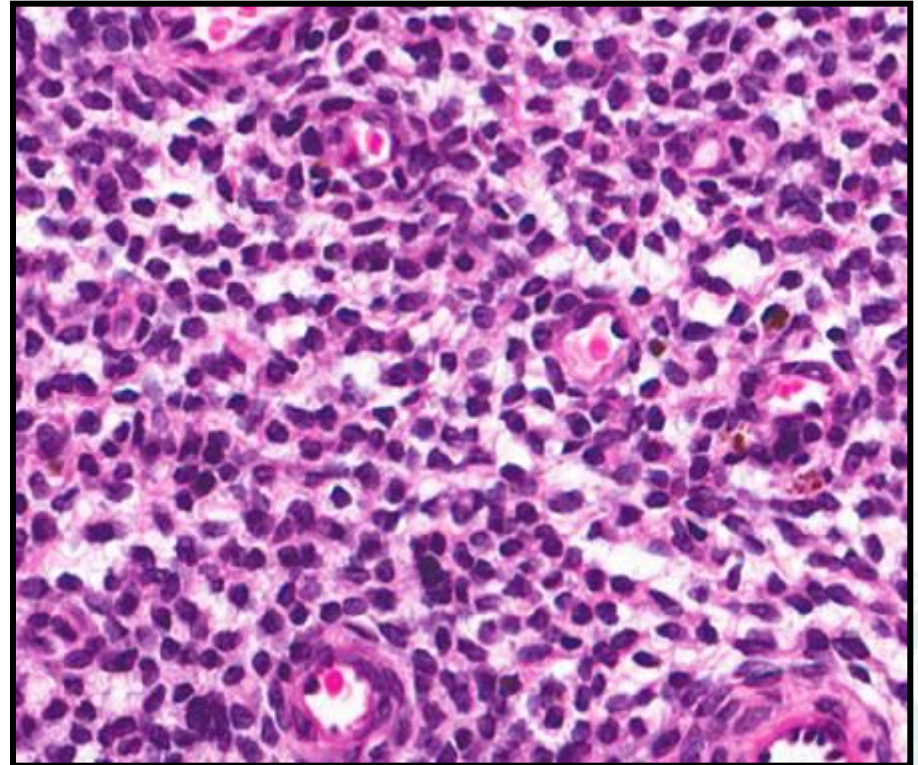
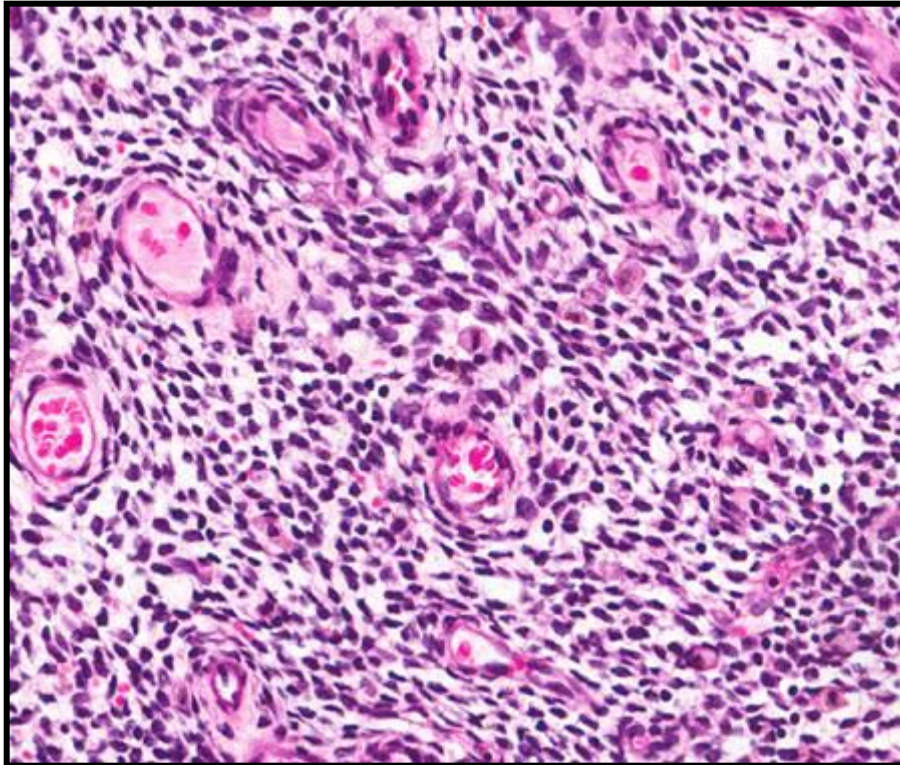
Cellular polypoid lesion no glands as part of lesion

# ESN vs ESS

- Cannot be differentiated on curettage material unless entire lesion represented in curettage material
- Infiltrative margins/vascular invasion (required)
- Hysterectomy
- EXAMINE PERIPHERY CAREFULLY.



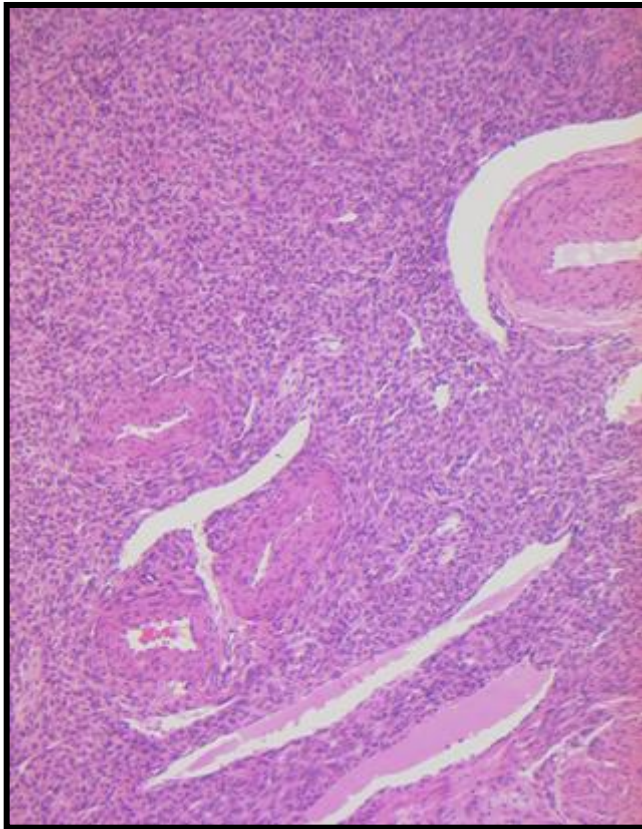
# HP endo "polyp"



Need hysterectomy to make a definitive diagnosis

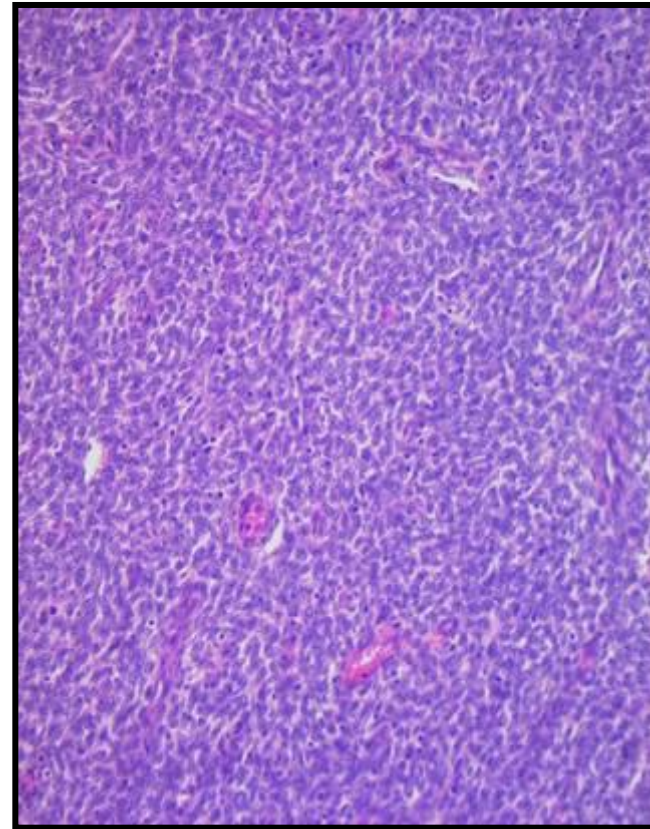


# Stromal nodule vs. HC leiomyoma



Cellular leiomyoma

Fascicular growth

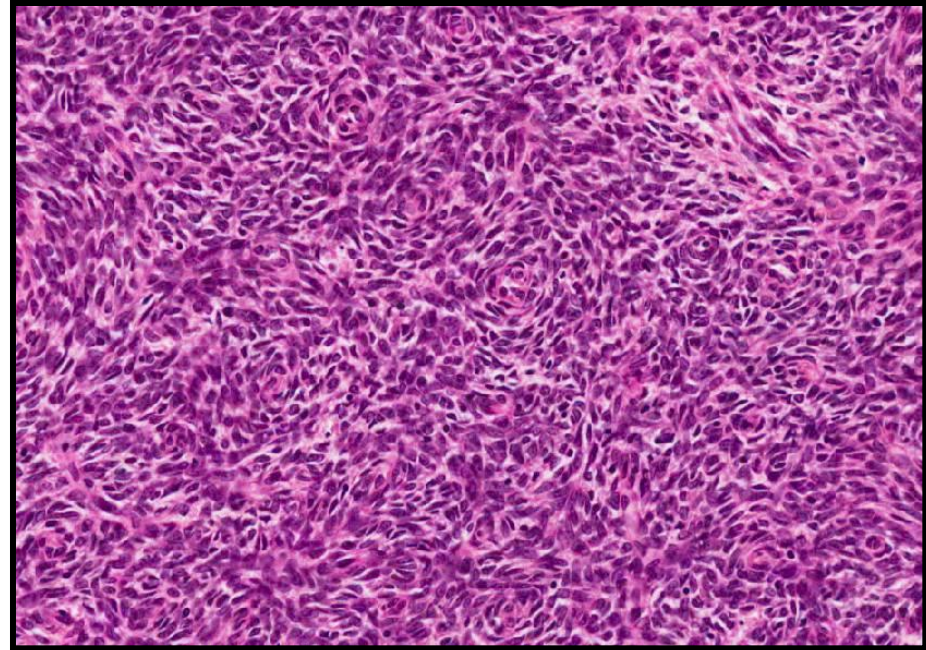
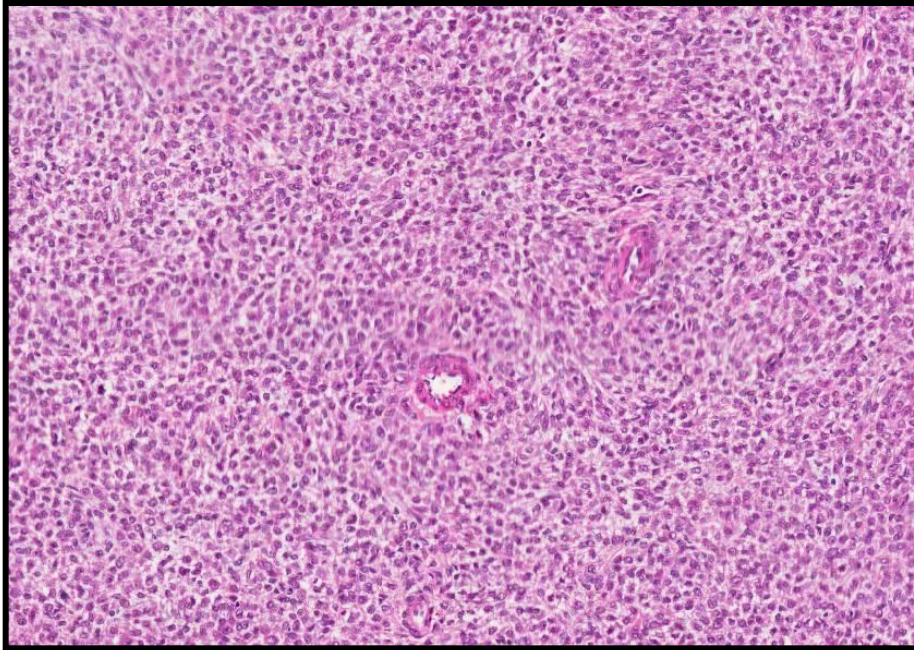


Stromal nodule



# Cellular leiomyoma vs. ESN

ESN



Small vessels and cellularity compare with endometrial stromal neoplasm

# Endometrial Stromal Sarcoma

- Main site of origin
  - Uterine corpus
- Extra- Uterine Sites
  - Ovary
  - Peritoneum

# Endometrial stromal sarcoma- low grade

## Clinical features

- Age usually < 50 years
- Dysfunctional uterine bleeding
- Pelvic or abdominal pain
- Variable sized neoplasm (polypoid / bulky)
- Indolent and protracted course (characterised by recurrences)



# Endometrial stromal sarcoma



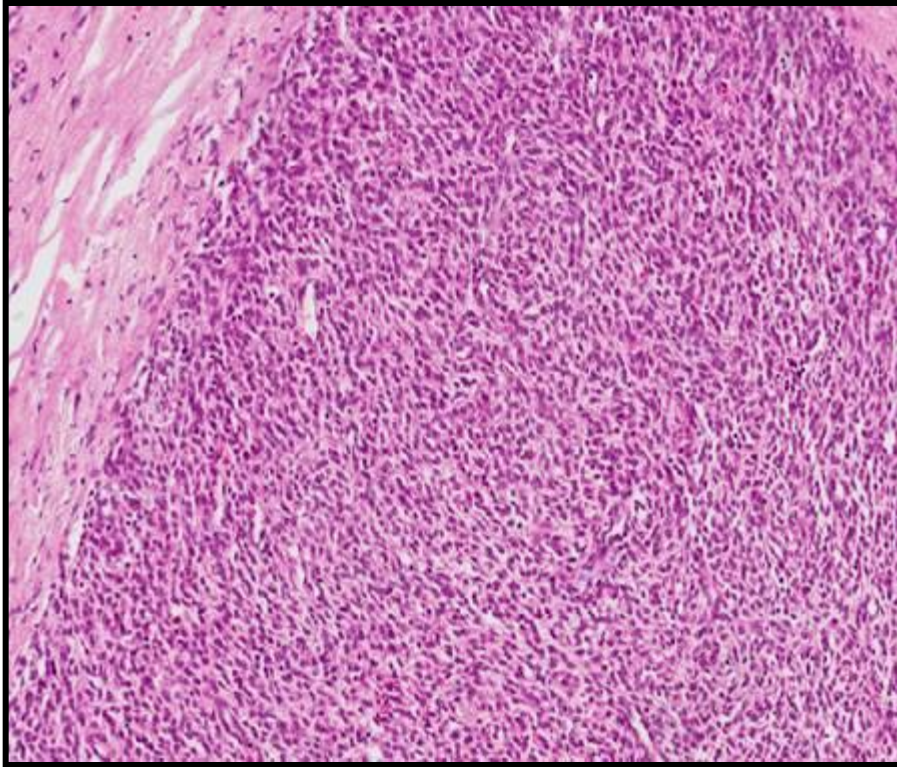
# Endometrial stromal sarcoma



Cystic change

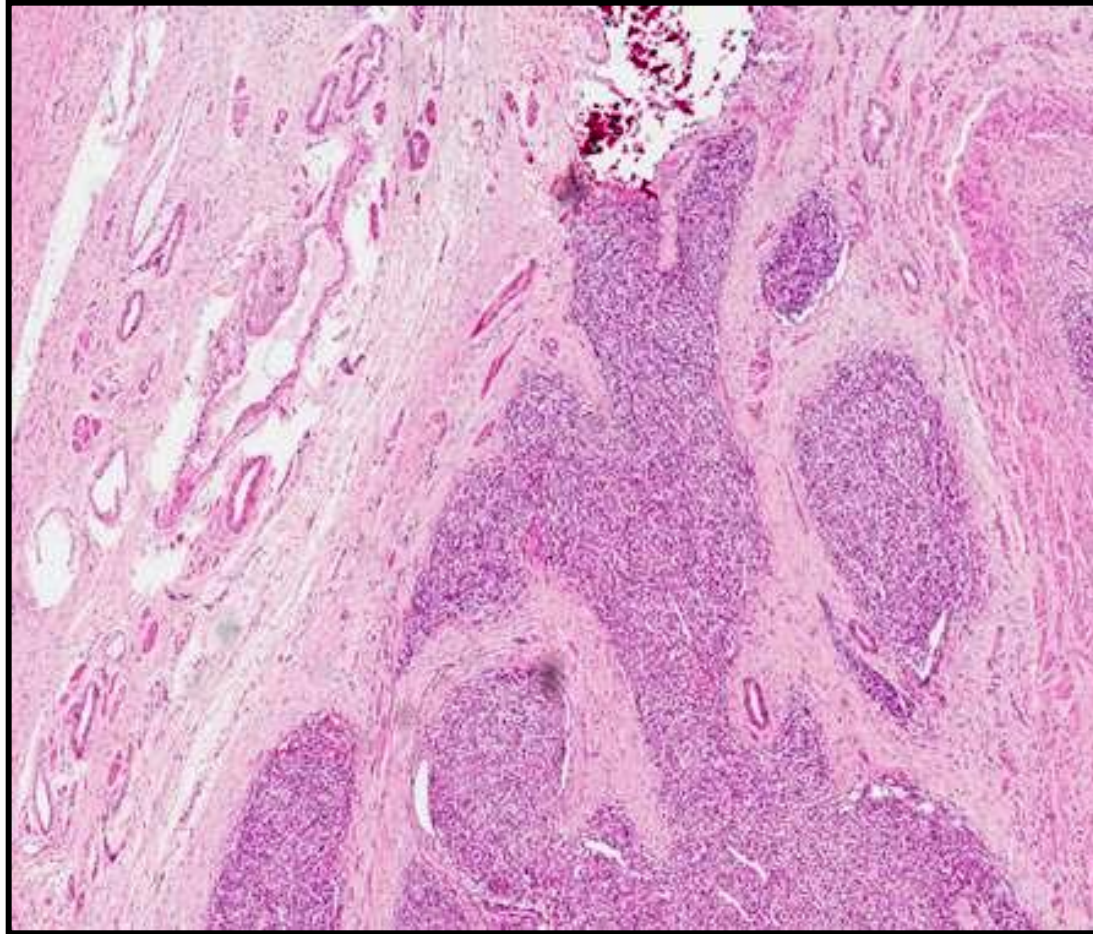


# LG Endometrial Stromal Sarcoma-cells



- Proliferation of small, round to oval monomorphic cells
- Scant cytoplasm
- Nuclei have smooth contours (round to oval in shape)

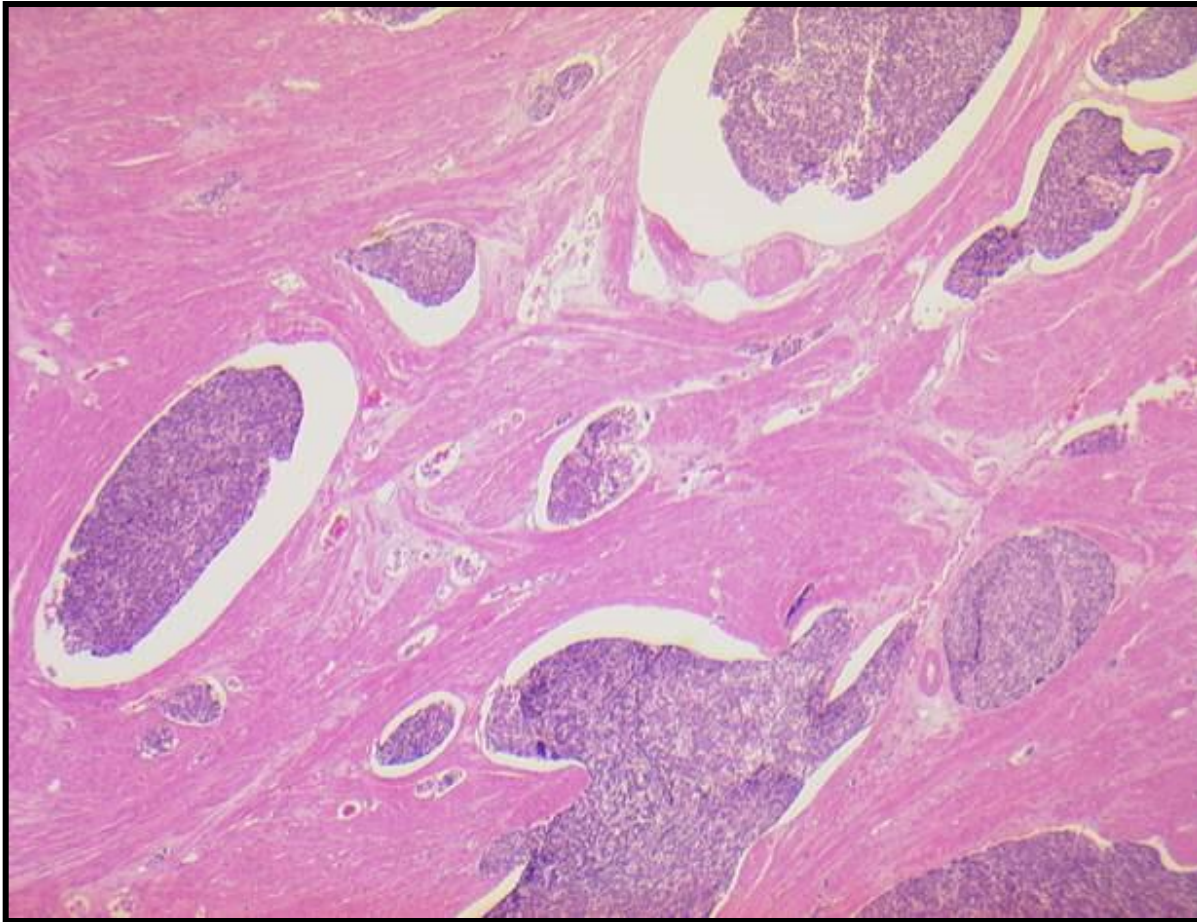
ESS



Finger like myometrial permeation



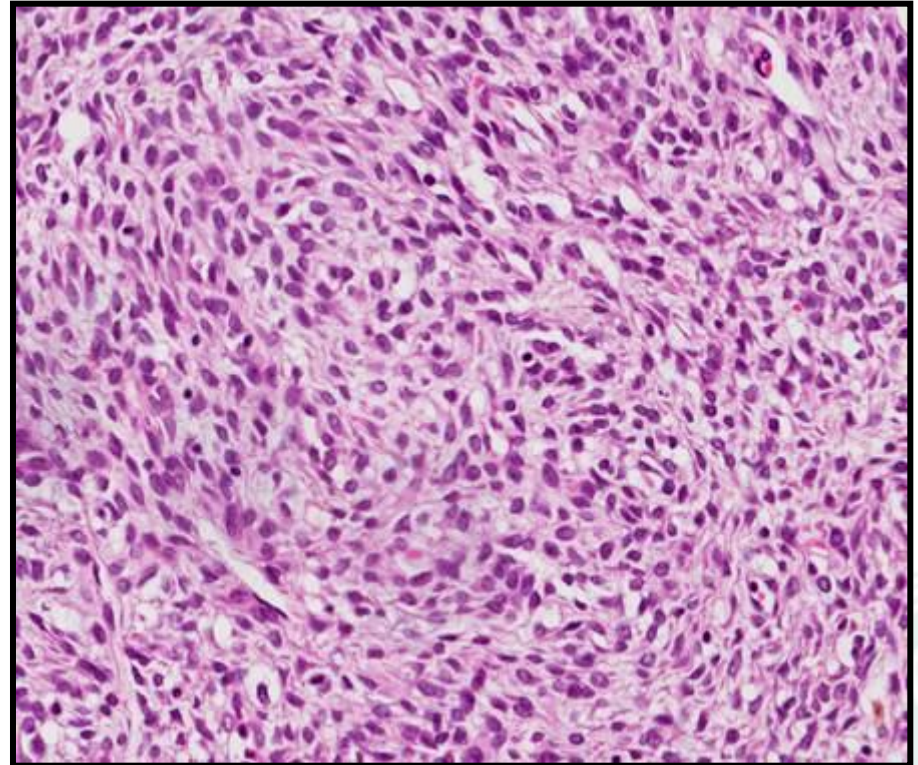
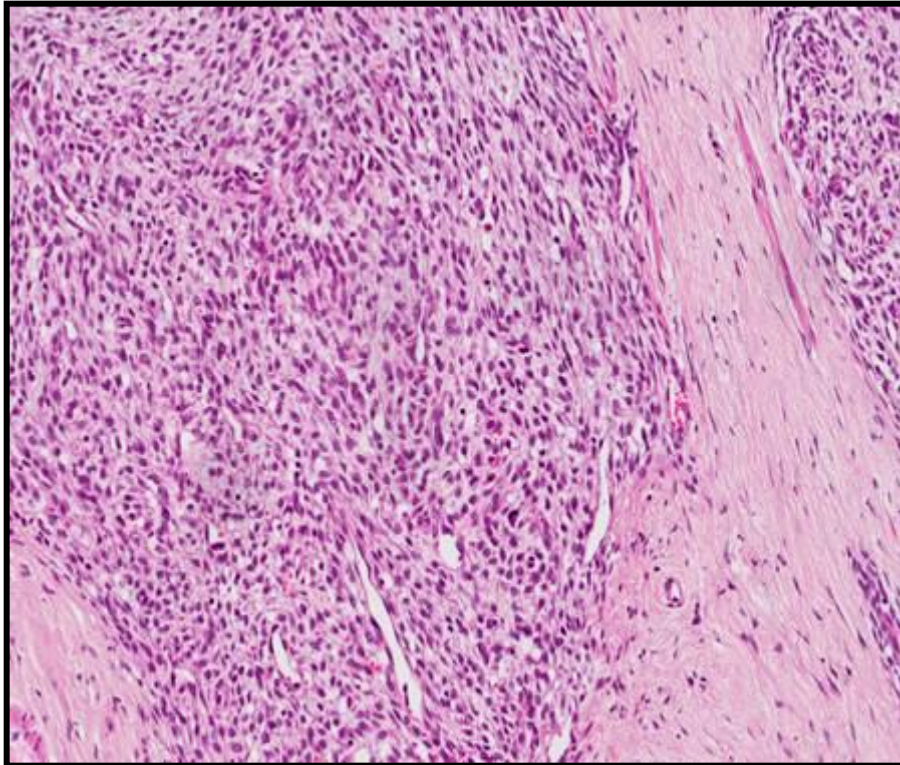
# ESS- lymphovascular permeation



Lymphovascular permeation - conspicuous feature

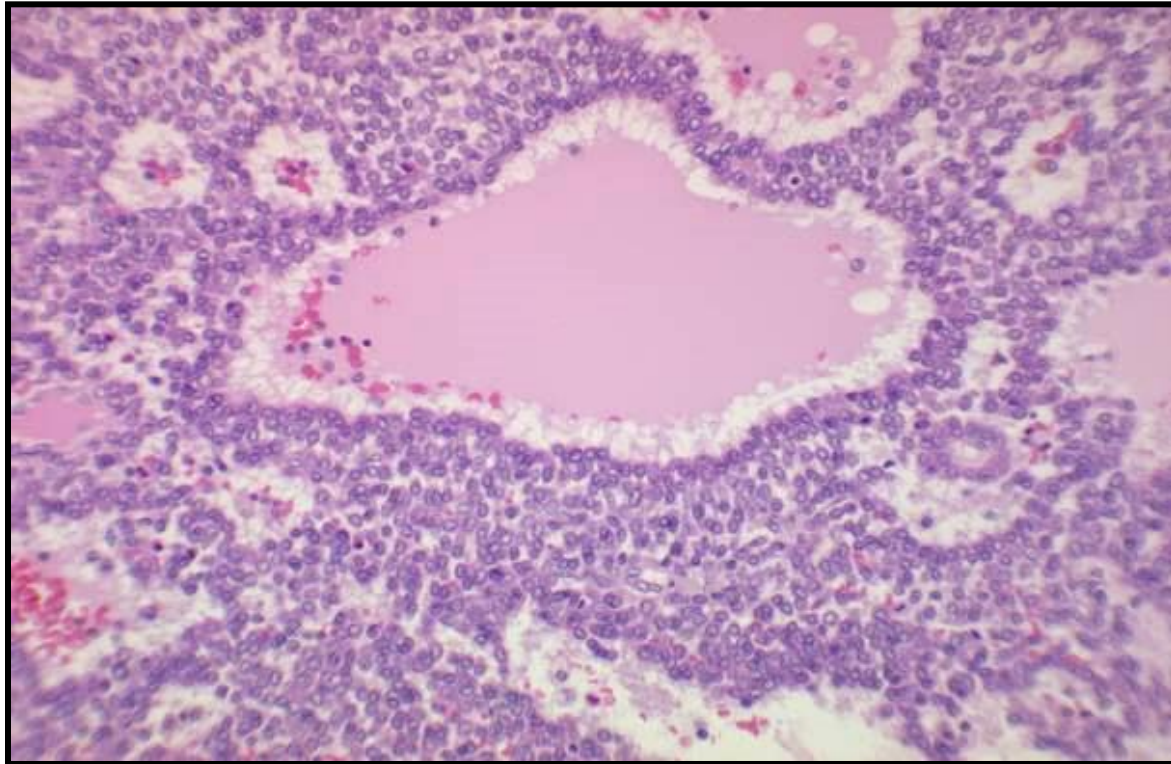


# ESS "low grade"



Stroma resembles proliferative phase stroma

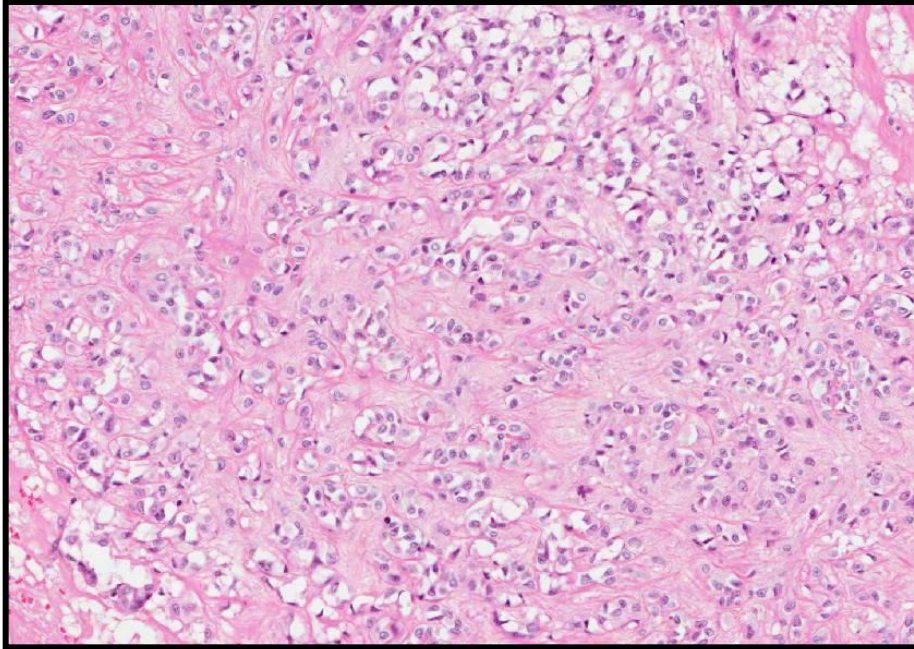
# Endometrial stromal sarcoma



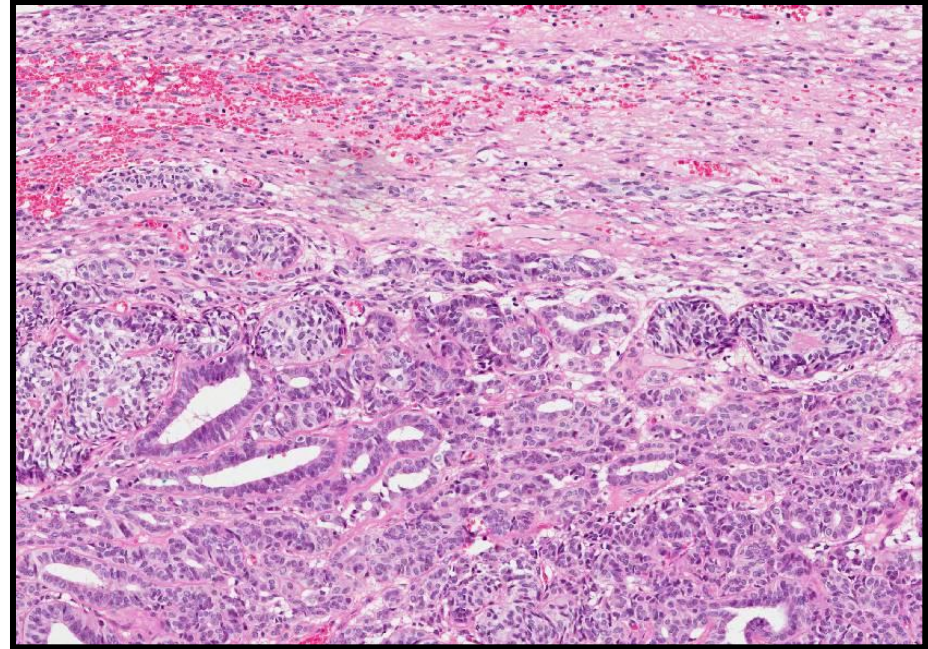
Cystic change



# ESS



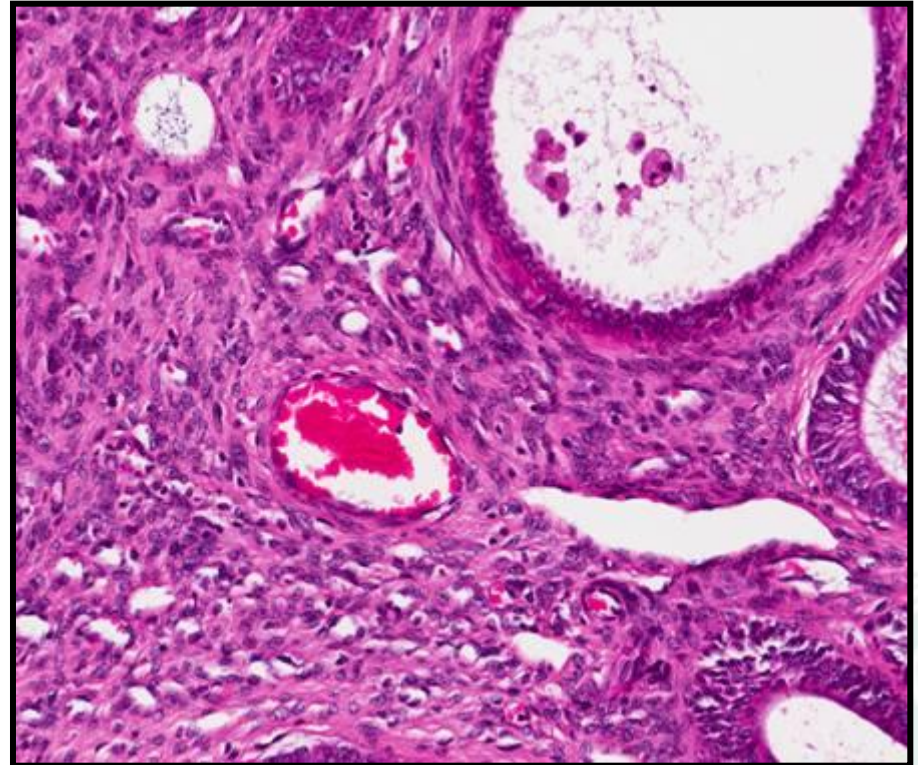
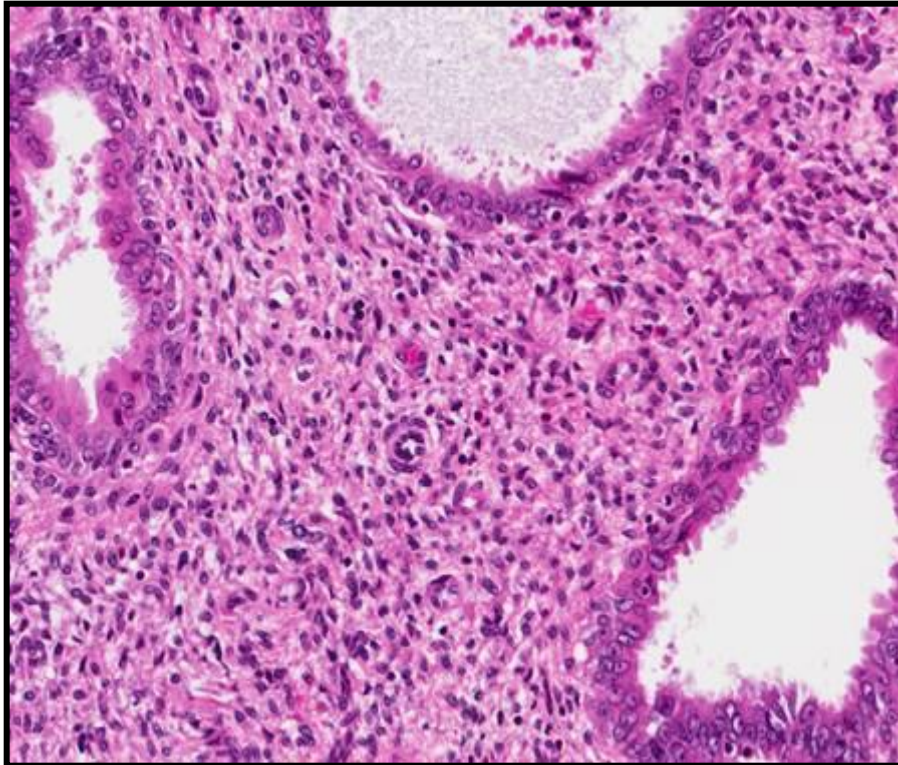
Extensive hyalinisation



Glandular differentiation



# ESS with glandular differentiation



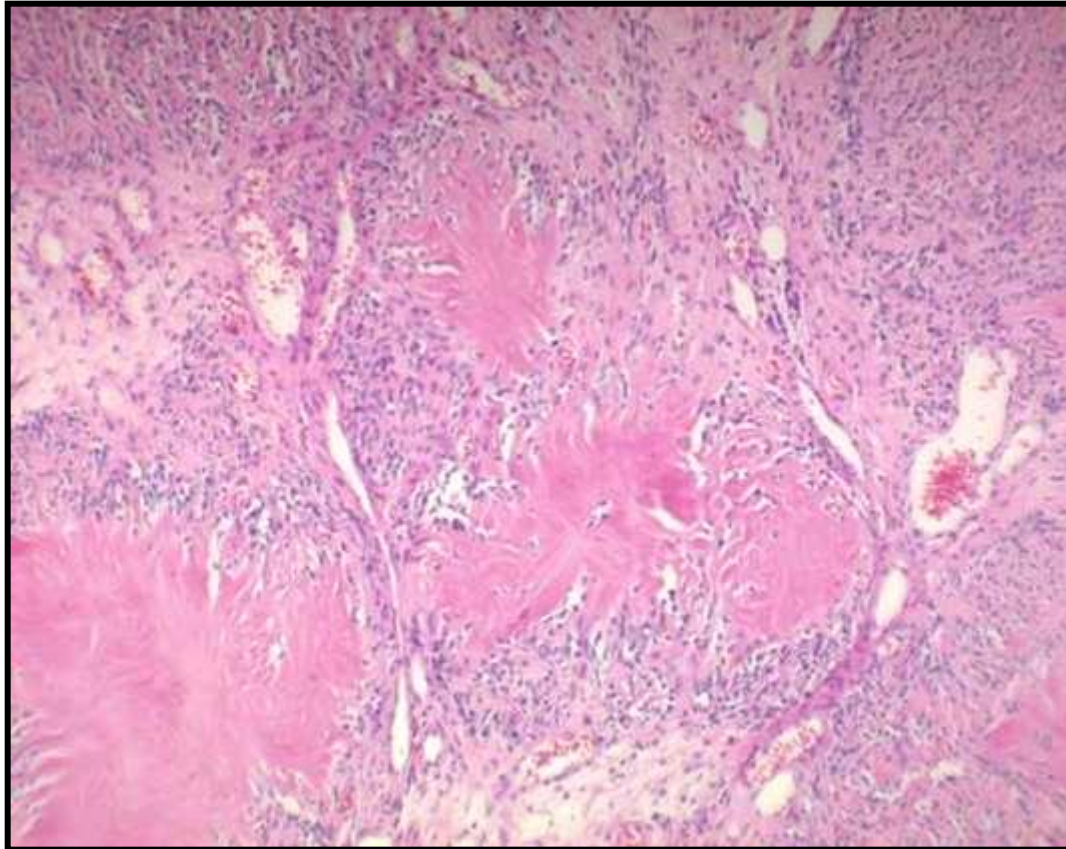
Marked stromal cellularity with familiar small calibre arterioles

# ESS with glandular differentiation

- Clement PB, Scully RE. Endometrial stromal sarcomas of the uterus with extensive endometrioid glandular differentiation: a report of three cases that caused problems in differential diagnosis. *Int J Gynecol Pathol.* 1992 Jul.;11(3):163–173.
- McCluggage WG, Ganesan R, Herrington CS. Endometrial stromal sarcomas with extensive endometrioid glandular differentiation: report of a series with emphasis on the potential for misdiagnosis and discussion of the differential diagnosis. *Histopathology.* 2009 Feb. 1;54(3):365–373.

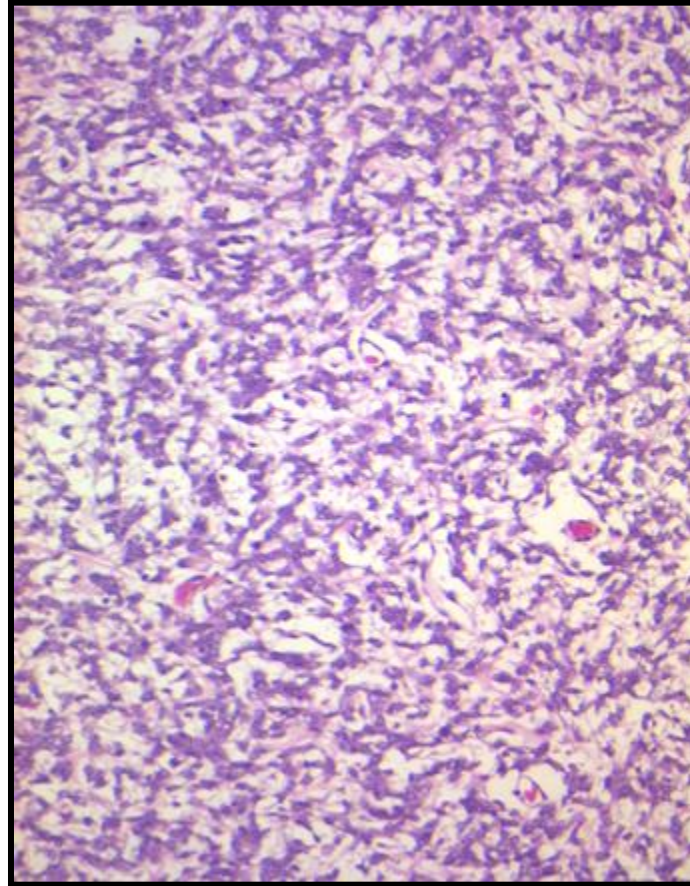


# Endometrial stromal sarcoma



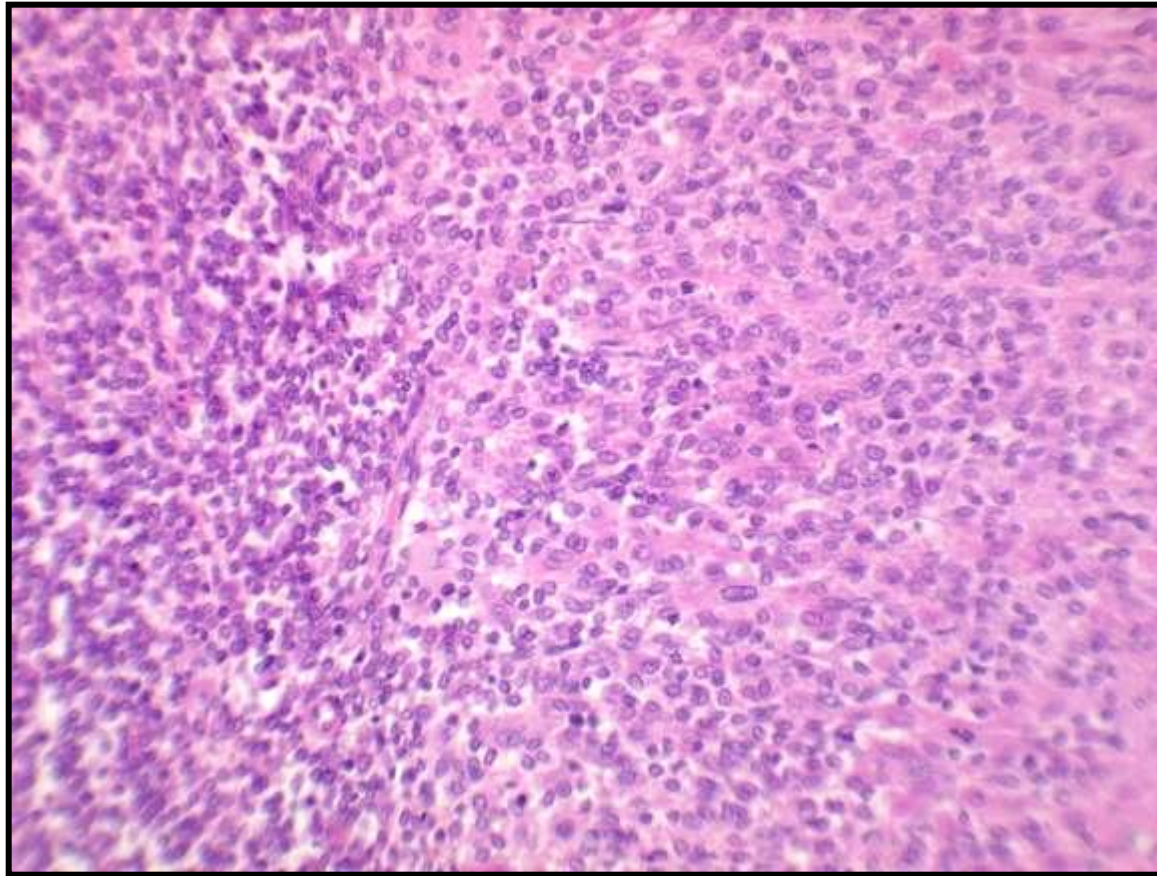
“star-burst” pattern of hyalinisation  
suggests SM differentiation

# Myxoid differentiation



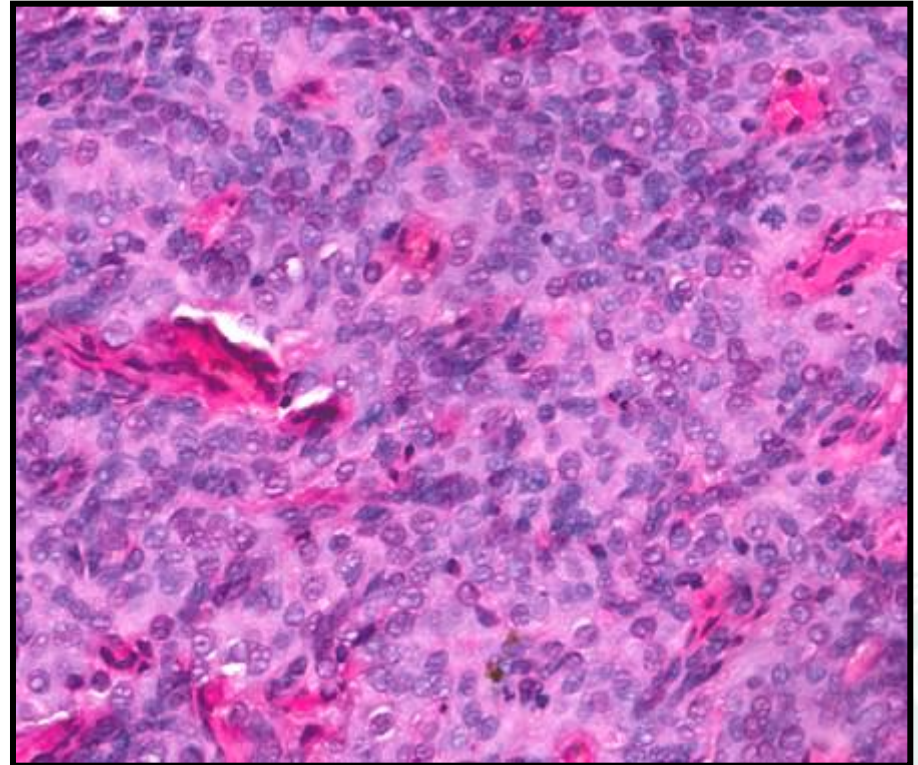
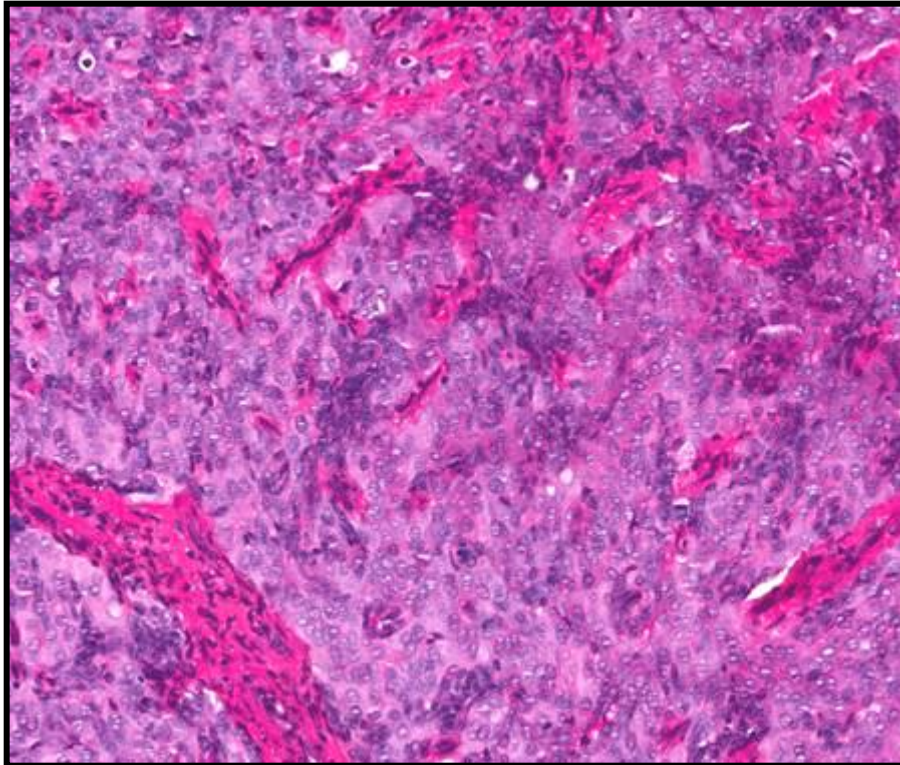


# ESS with SM differentiation



Dual cell population

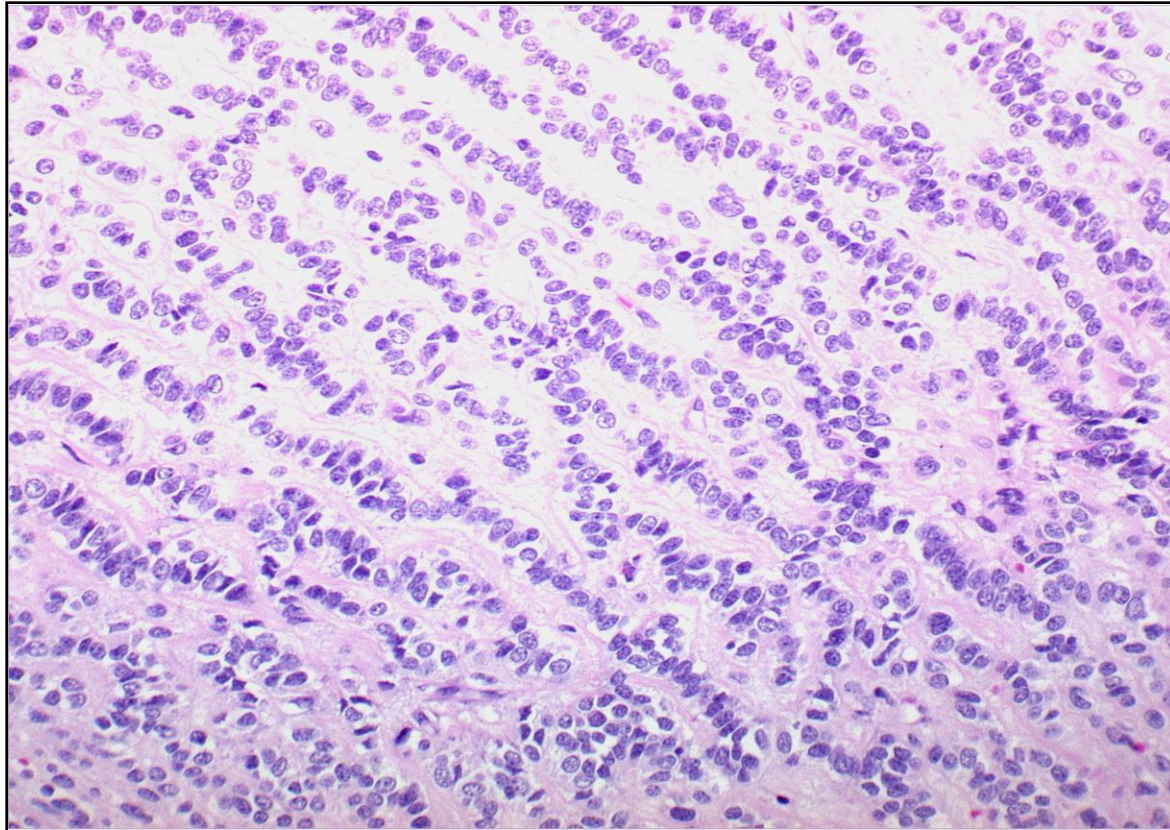
# ESS epithelioid differentiation



Distinct epithelioid areas



# ESS sex cord like pattern



# Endometrial stromal sarcoma

- Variants
  - Fibrous/myxoid foci
  - Smooth muscle differentiation
  - Sex-cord like differentiation
  - With endometrial glands
  - Epithelioid morphology
  - Pseudopapillae formation
  - Granular eosinophilic cytoplasm
  - Clear cytoplasm
  - Rhabdoid features/ skeletal muscle differentiation



# Immunohistochemistry of LGESS

- 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

# ESS (low grade)

## 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 Sep;35(9):1364-72
- **Frequency of known gene rearrangements in endometrial stromal tumours**
- Chiang S et al.

# JAZF1-SUZ12 and JAZF1-PHF1

- Genetic fusions- fusion oncoprotein (transcriptional dysregulation)
- Oncogenic influences mediated through altered transcriptional control in endometrial stromal progenitor cells
- Different genotypes
  - Exhibit similar clinical behaviour
  - Low grade histological features
  - Some genetic re-arrangements may be associated with specific variants (PHF1 rearrangement associated with sex cord differentiation)

# Re-birth of HG ESS (WHO 2014)

- YWHAE-FAM22 (NUTM2)
  - Arise from uterus
  - Grossly visible mass which is myoinvasive (1-12 cm size)
  - May have extra-uterine component
  - Tongue-like myoinvasion
  - Vascular invasion
  - Arborizing stromal capillary network
  - Dual cell component (high grade round cell component and low grade spindle cell component)
  - Reminiscent of round blue cell component



## The Clinicopathologic Features of *YWHAE-FAM22* Endometrial Stromal Sarcomas: A Histologically High-grade and Clinically Aggressive Tumor

*Cheng-Han Lee, MD, PhD,\*† Adrian Mariño-Enriquez, MD,\* Wenbin Ou, PhD,\*  
Meijun Zhu, PhD,\* Rola H. Ali, MD,† Sarah Chiang, MD,‡ Frédéric Amant, MD,§  
C. Blake Gilks, MD,† Matt van de Rijn, MD, PhD,|| Esther Oliva, MD,‡  
Maria Debiec-Rychter, MD,¶ Paola Dal Cin, PhD,\* Jonathan A. Fletcher, MD,\*  
and Marisa R. Nucci, MD\**

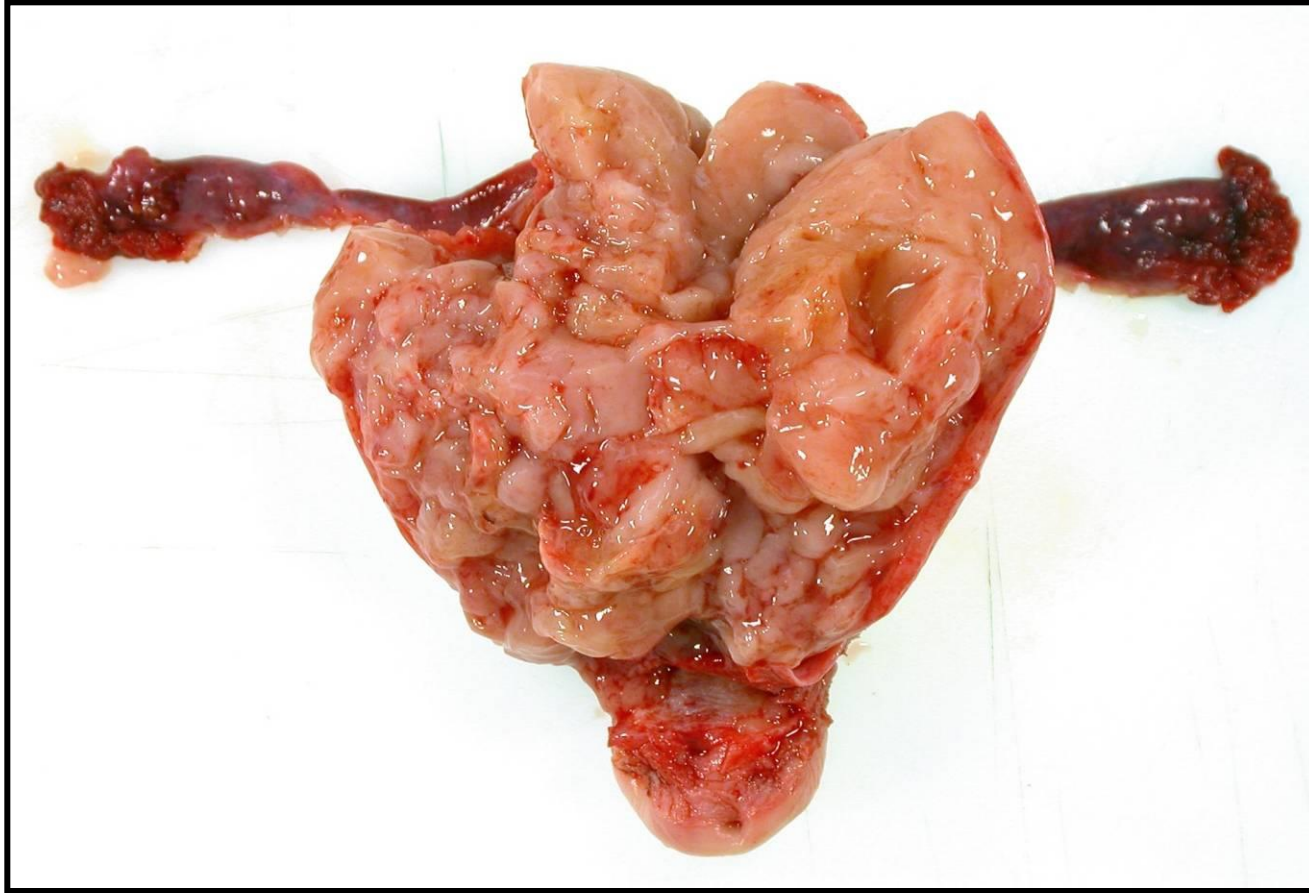
*Am J Surg Pathol* 2012; 36, 641-653



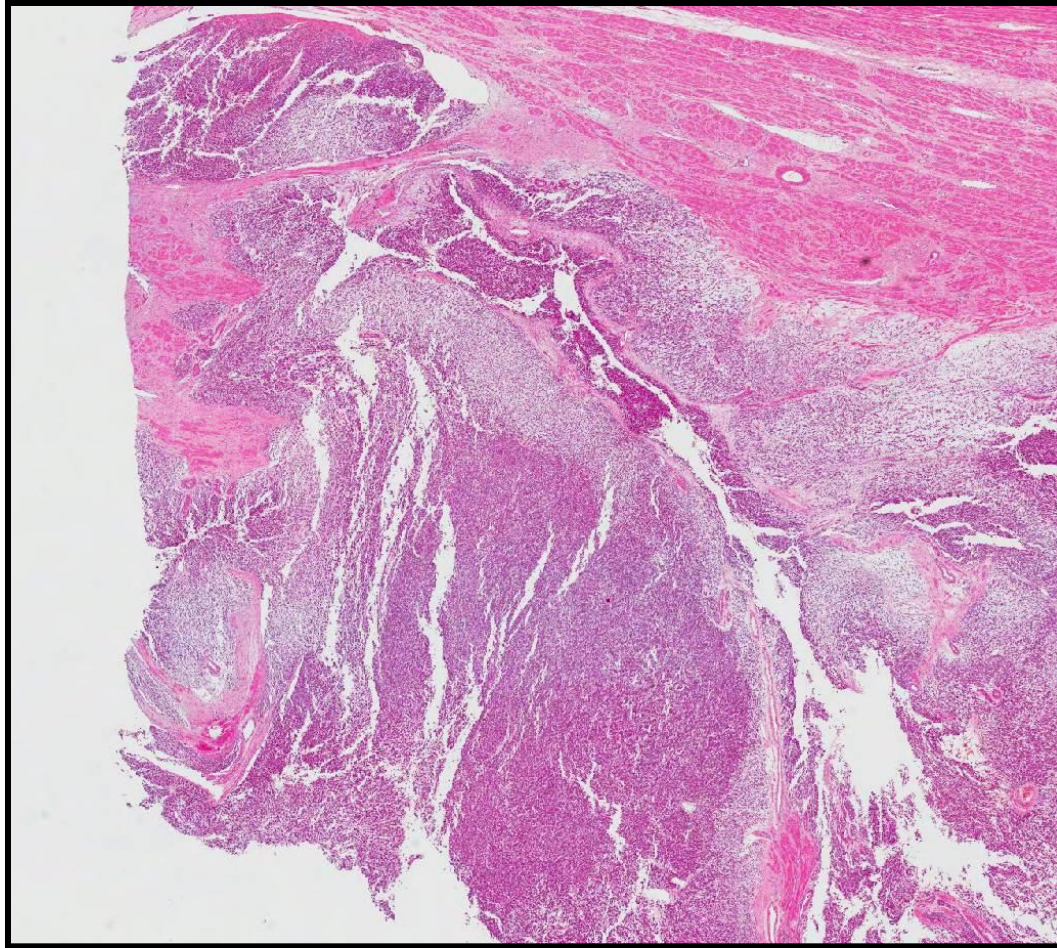
# YWHAE-NUTM2 high grade ESS

- UES (WHO 2003) with uniform nuclear features 50% harbour  $t(10:17)(q22;p13)$  translocation
- NUTM2A/B formerly known as FAM22A/B
- Change of nomenclature- sequence homology to NUT protein (encoded by NUTM1) important in NUT midline carcinoma
- YWHAE-NUTM2 genetic re-arrangements and JAZF1/SUZ12 and EPC1/PHF1 genetic re-arrangements mutually exclusive

# Gross appearance uterus

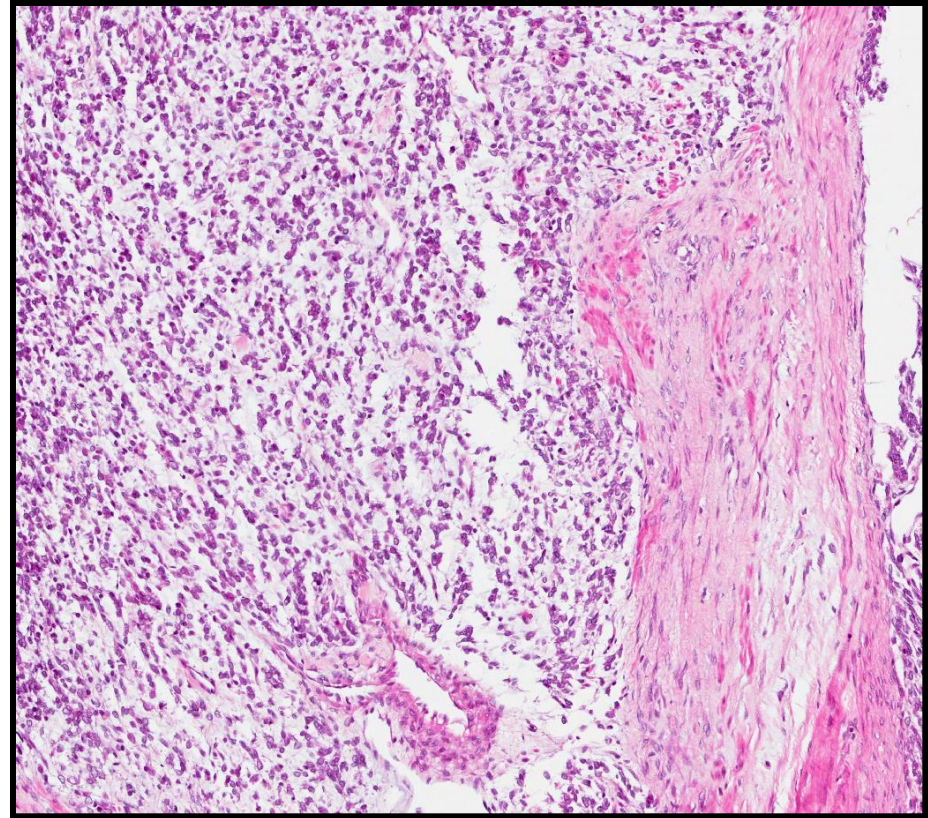
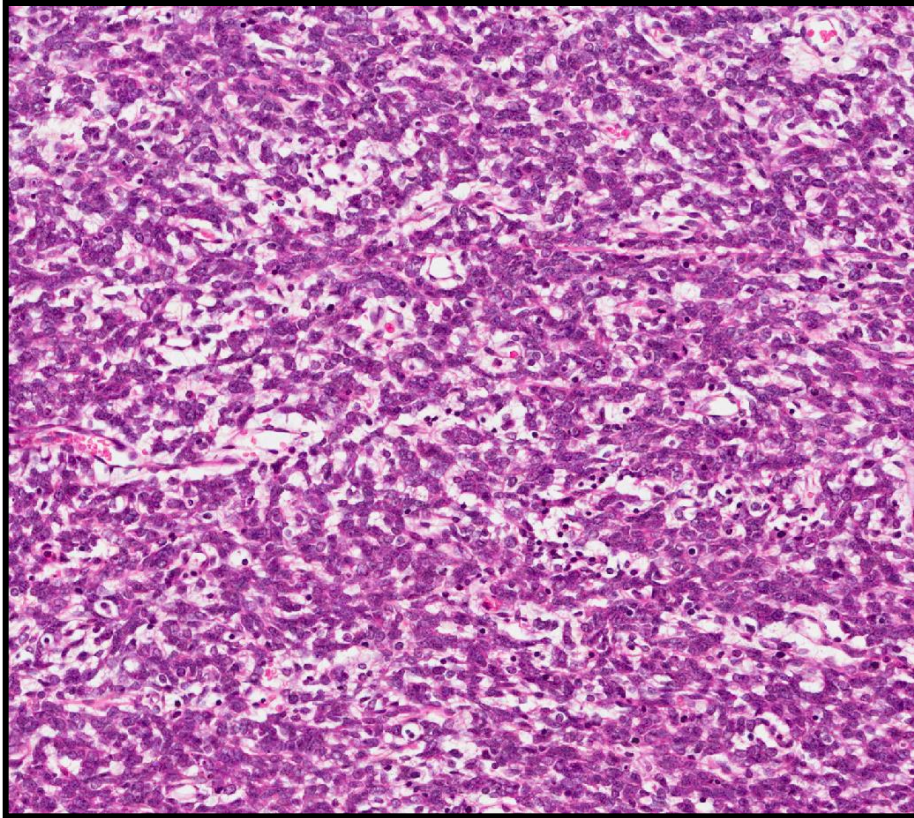


# Histology : Variable cellularity





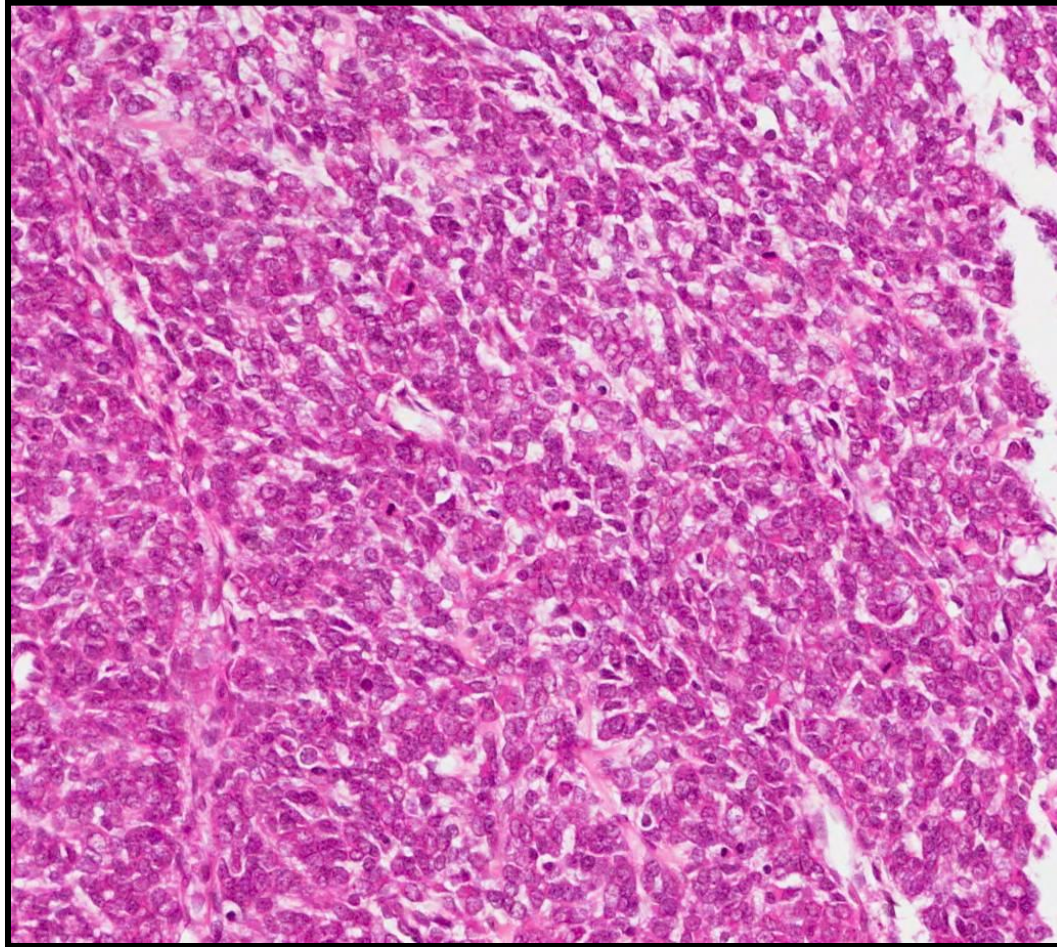
# Dual cell population



Rich vascular network comprising thin wall capillaries



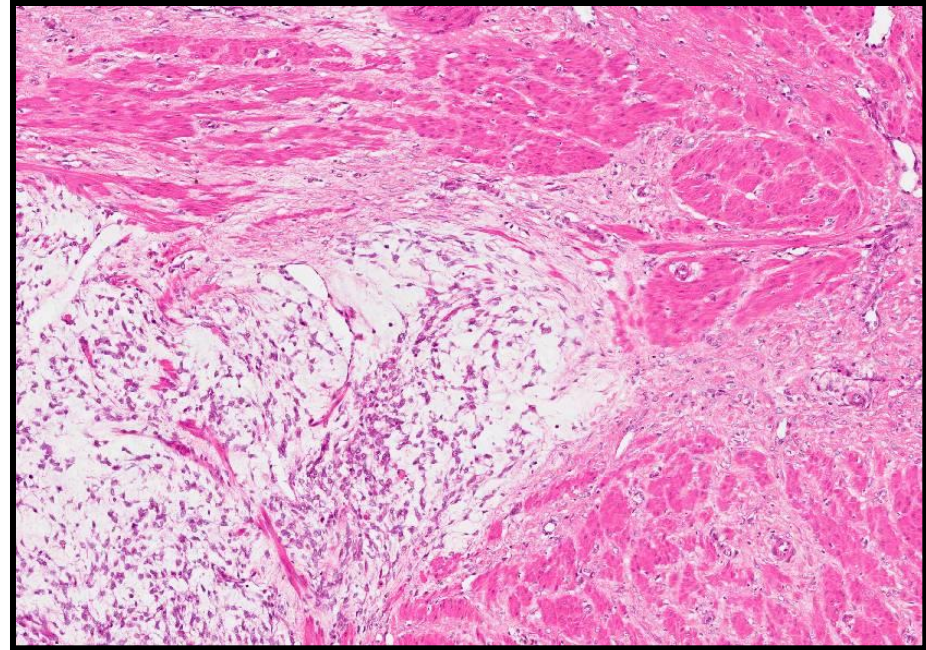
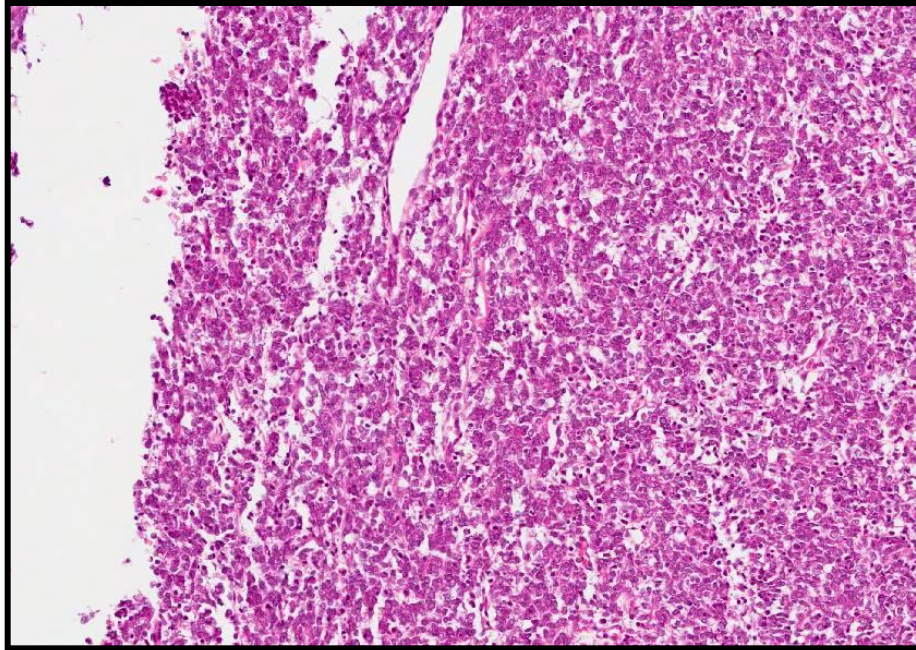
# Multiple mitoses (>10/10HPF)



Irregular nuclear contours but non-pleomorphic



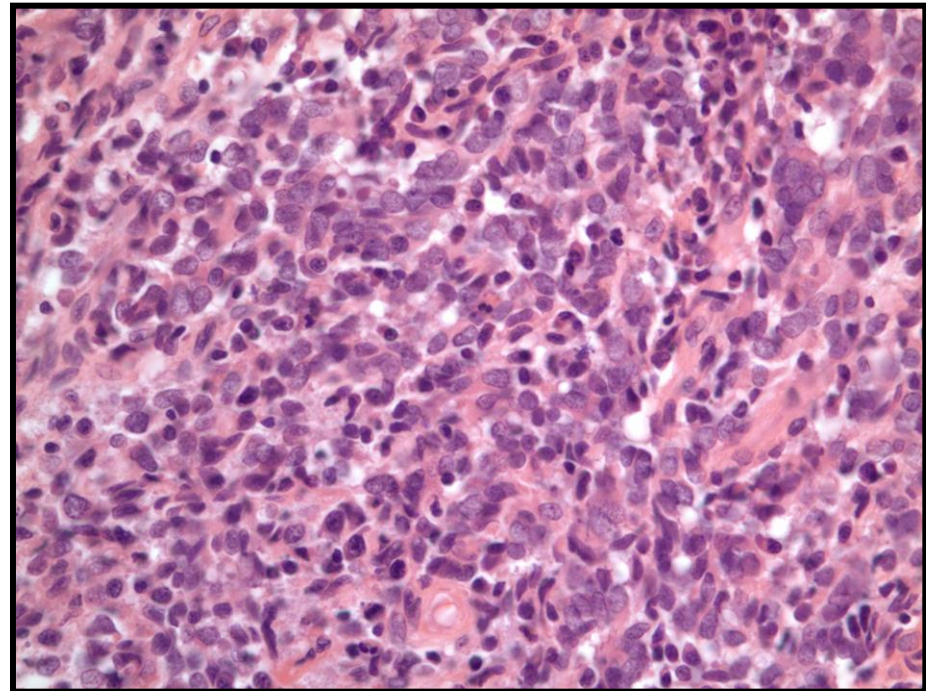
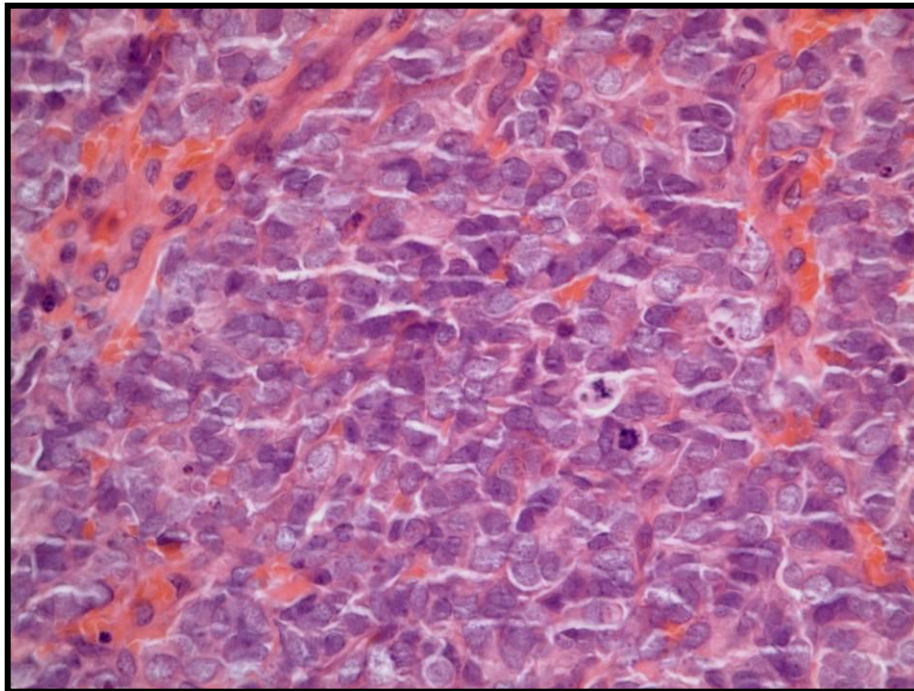
# Myometrial infiltration



Fibromyxoid where tumour permeates myometrium



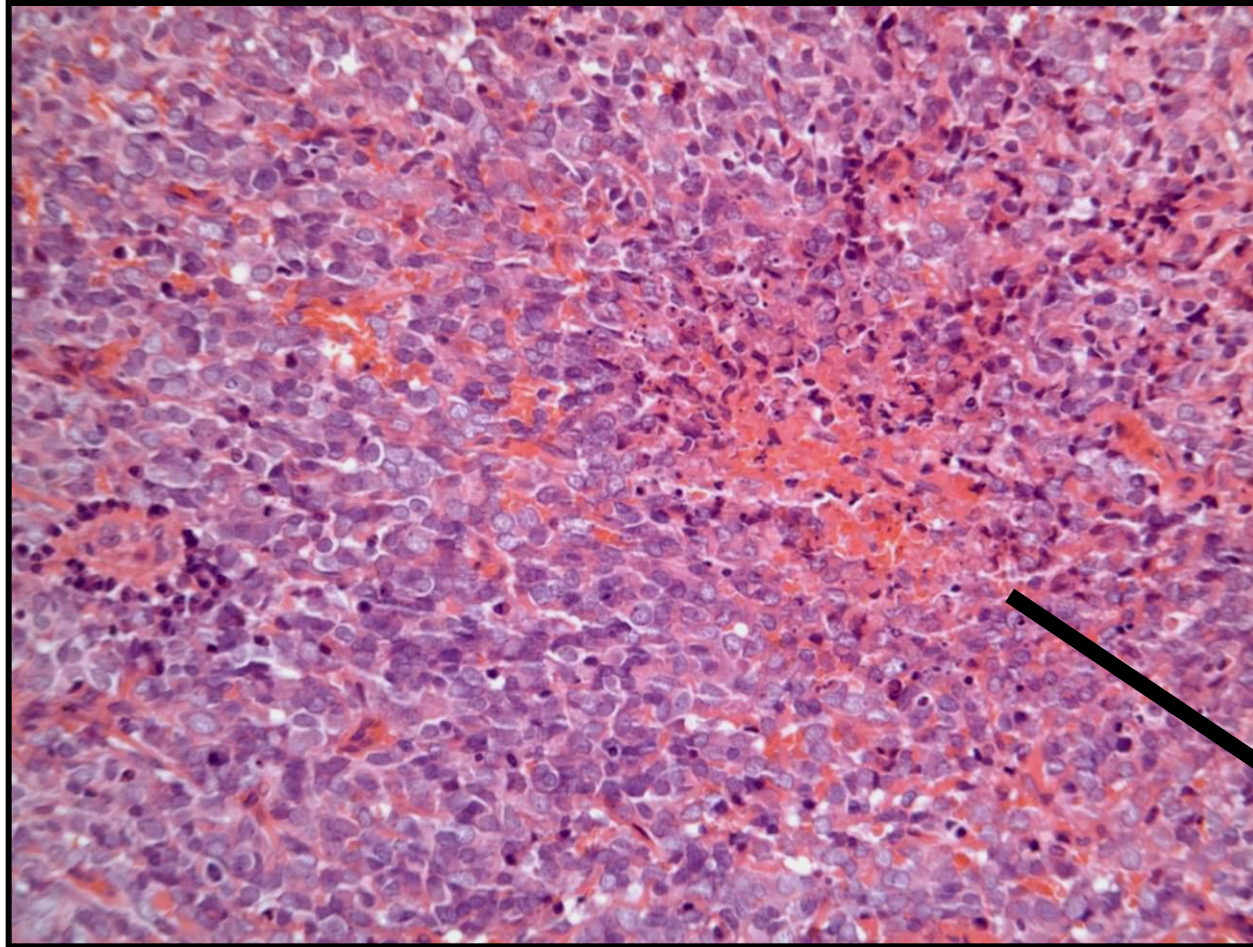
# Cells with round nuclei



Mitoses easily seen, nuclear enlargement 4-6 x size of lymphocyte



# YWHAE-NUTM2 HG-ESS

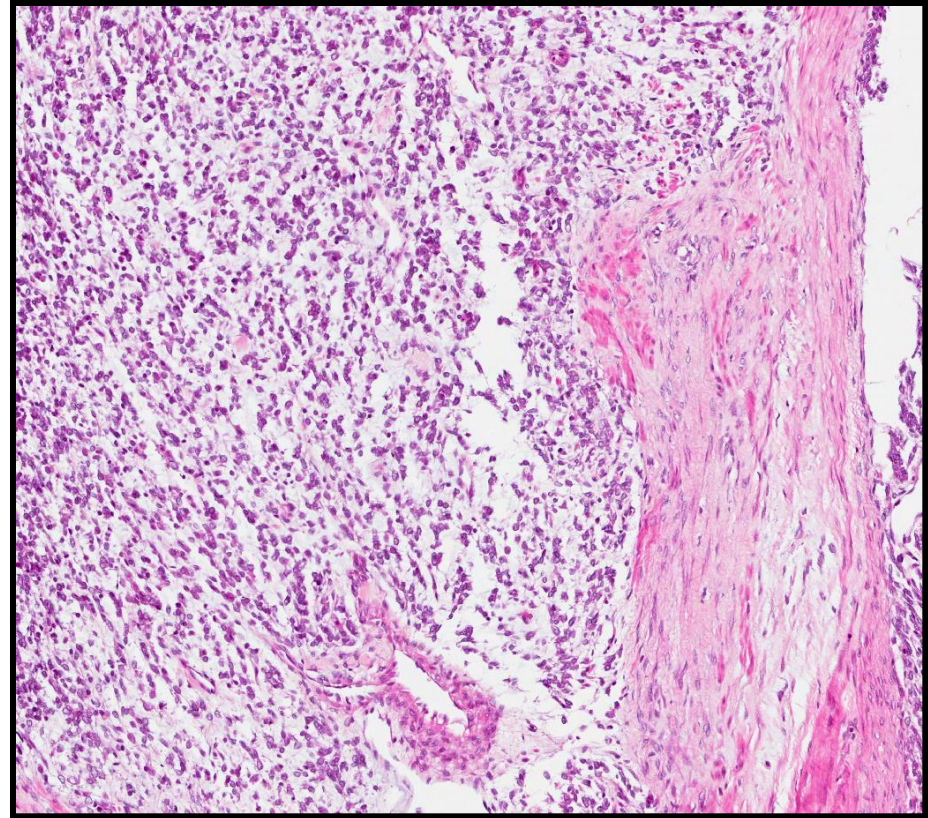
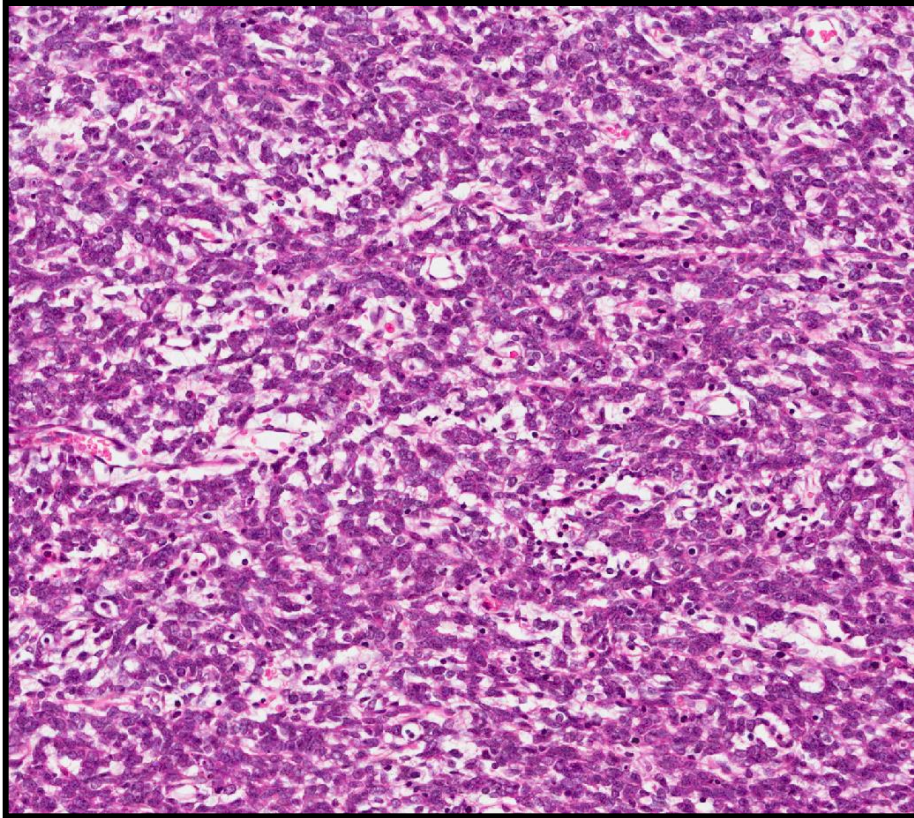


Focal  
necrosis

Small round blue cell tumour



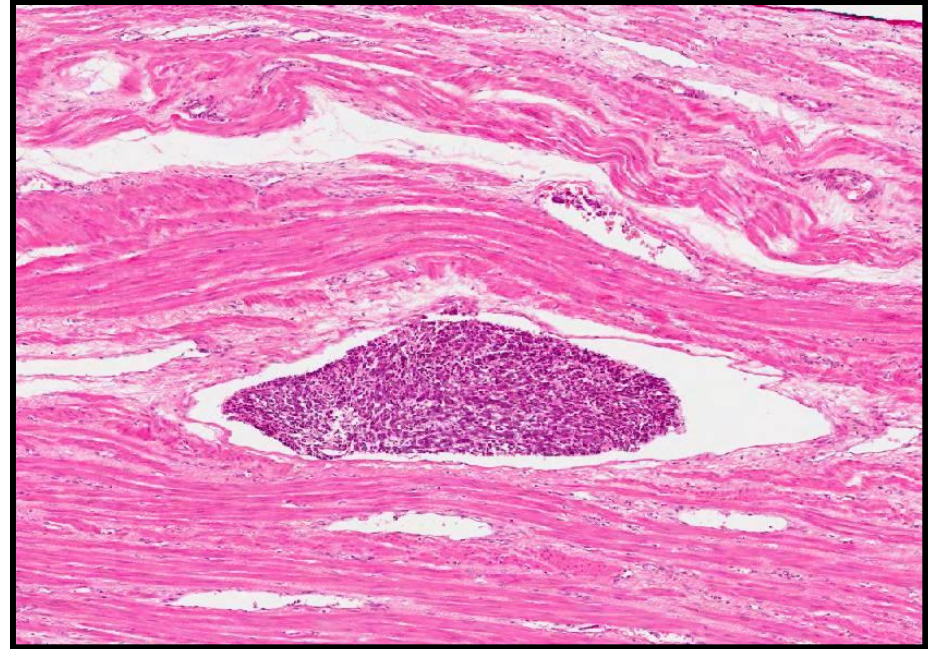
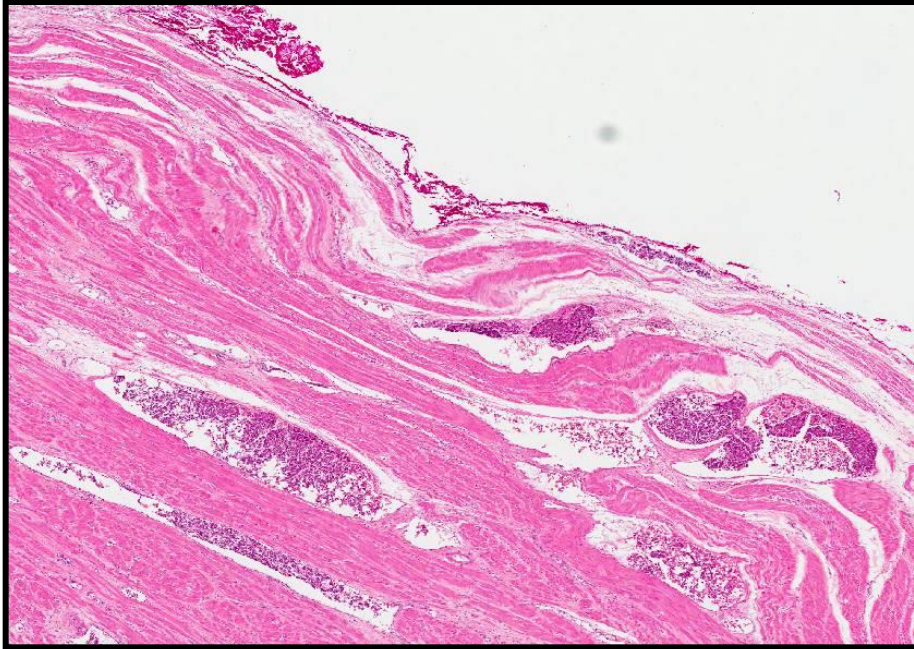
# Dual cell population



Rich vascular network comprising thin wall capillaries



# Vascular permeation



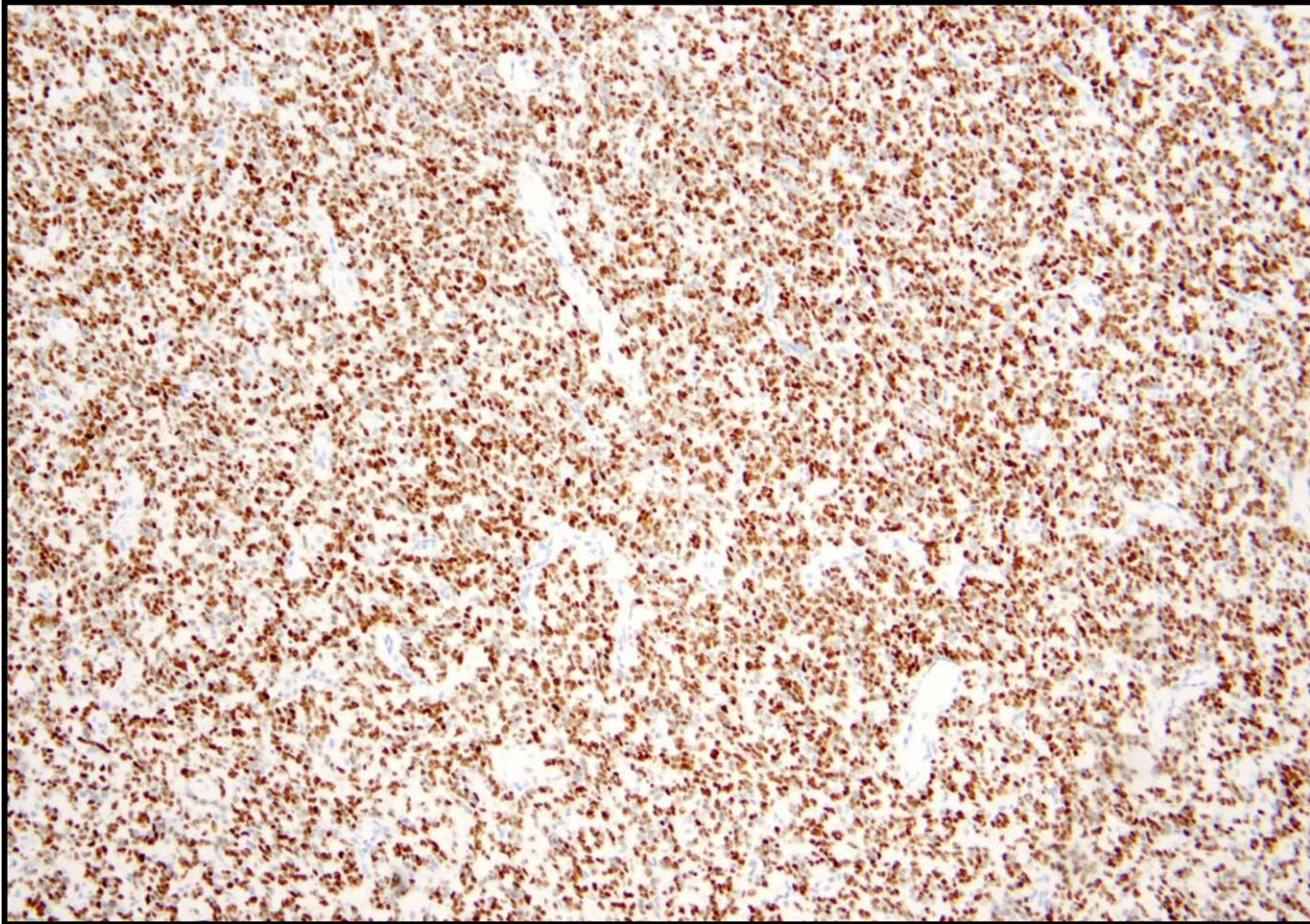
# Cyclin D1 as a Diagnostic Immunomarker for Endometrial Stromal Sarcoma With *YWHAE-FAM22* Rearrangement

*Cheng-Han Lee, MD, PhD,\*† Rola H. Ali, MD,\*† Marjan Rouzbahman, MD,‡  
Adrian Marino-Enriquez, MD,§ Meijun Zhu, PhD,§ Xiangqian Guo, PhD,|| Alayne L. Brunner, PhD,||  
Sarah Chiang, MD,¶ Samuel Leung, MSc,\*† Nataliya Nelnyk, MSc,# David G. Huntsman, MD,#  
C. Blake Gilks, MD,\*† Torsten O. Nielsen, MD, PhD,\*† Paola Dal Cin, PhD,§  
Matt van de Rijn, MD, PhD,|| Esther Oliva, MD,¶ Jonathan A. Fletcher, MD,§ and Marisa R. Nucci, MD,§*

[Am J Surg Pathol.](#) 2012 Oct;36(10):1562-70.



# Cyclin D 1 diffuse positive

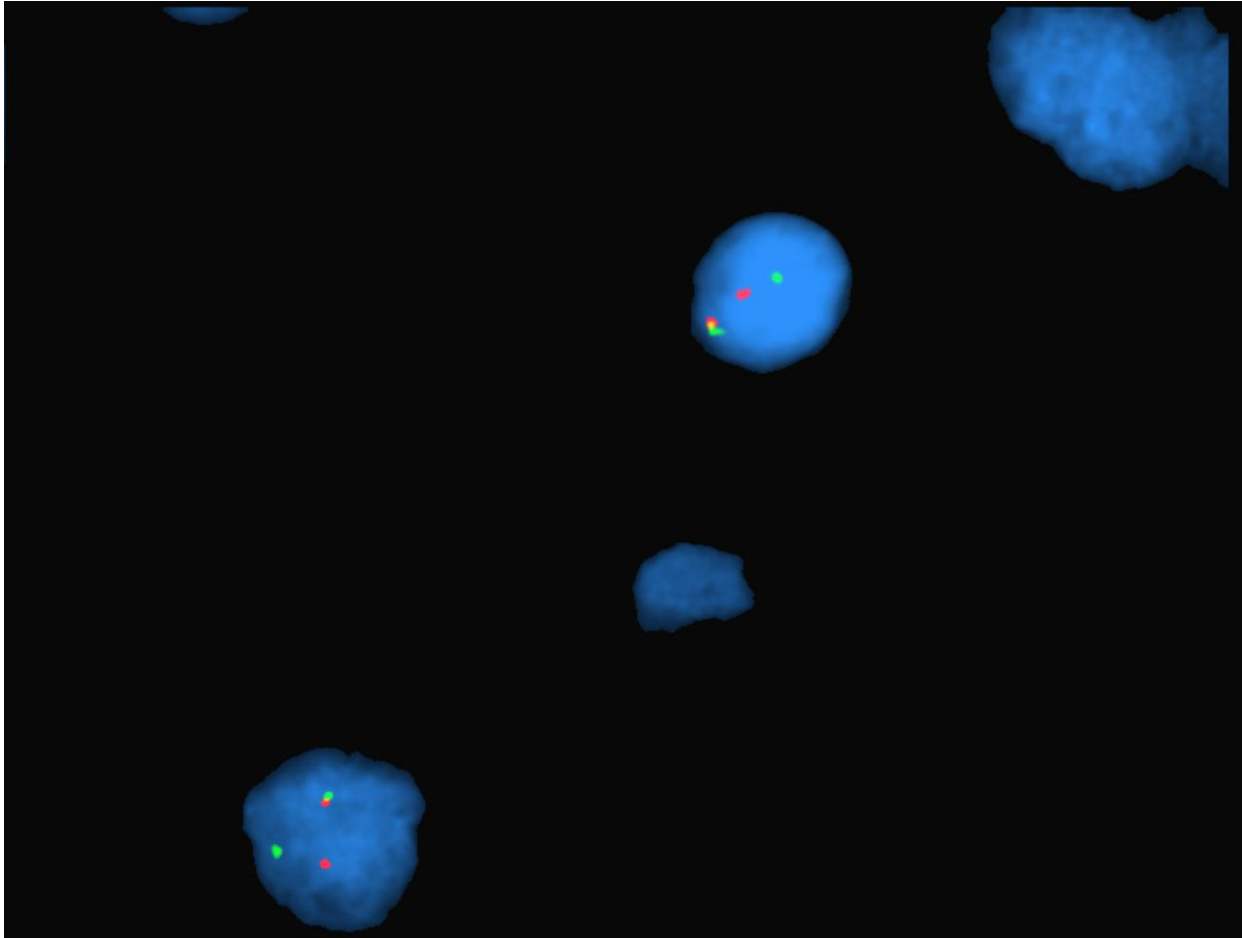


Courtesy Dr Esther Oliva

# HG-ESS (YWHAE-NUTM2)

- 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

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



YWHAE-NUTM2 ESS courtesy Drs Lee and Oliva



# Undifferentiated Uterine sarcoma (WHO 2014)

## Definition:

- A tumour arising in the endometrium or myometrium, lacking any resemblance to proliferative –phase endometrial stroma, with high-grade cytological features and with 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 (2014)

- Why replace UES with UUS?
- Not all UES arise from the endometrium WHO 2014 acknowledges this
- More accurate terminology UUS
- No specific lines of mesenchymal differentiation
- **Diagnosis of exclusion**

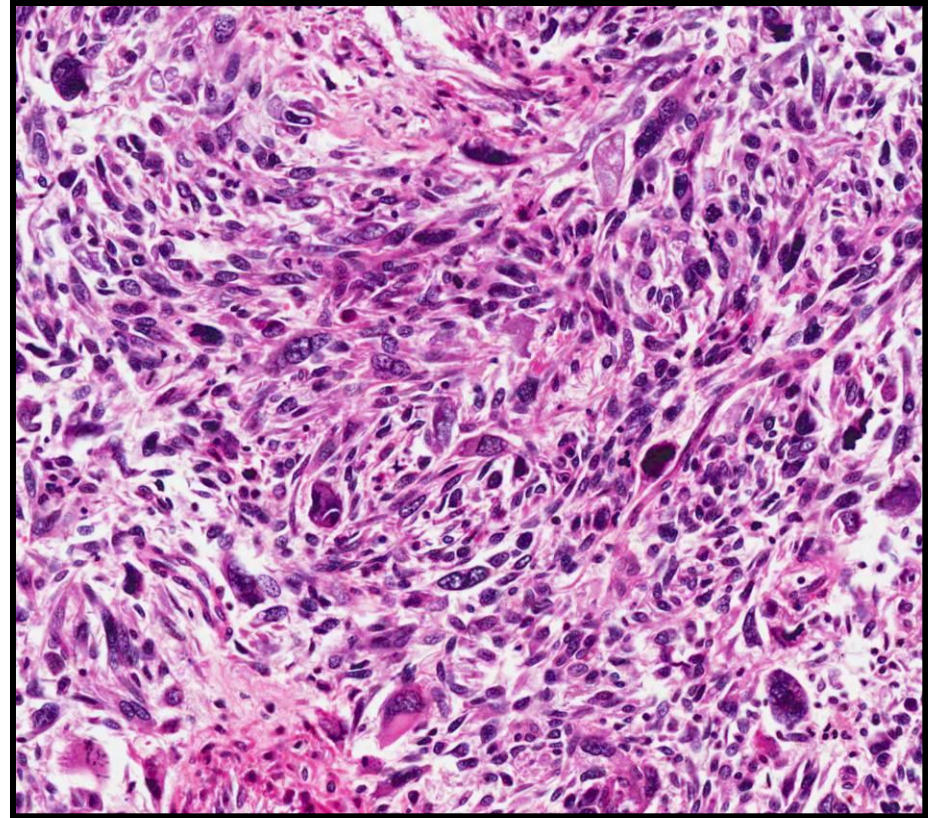
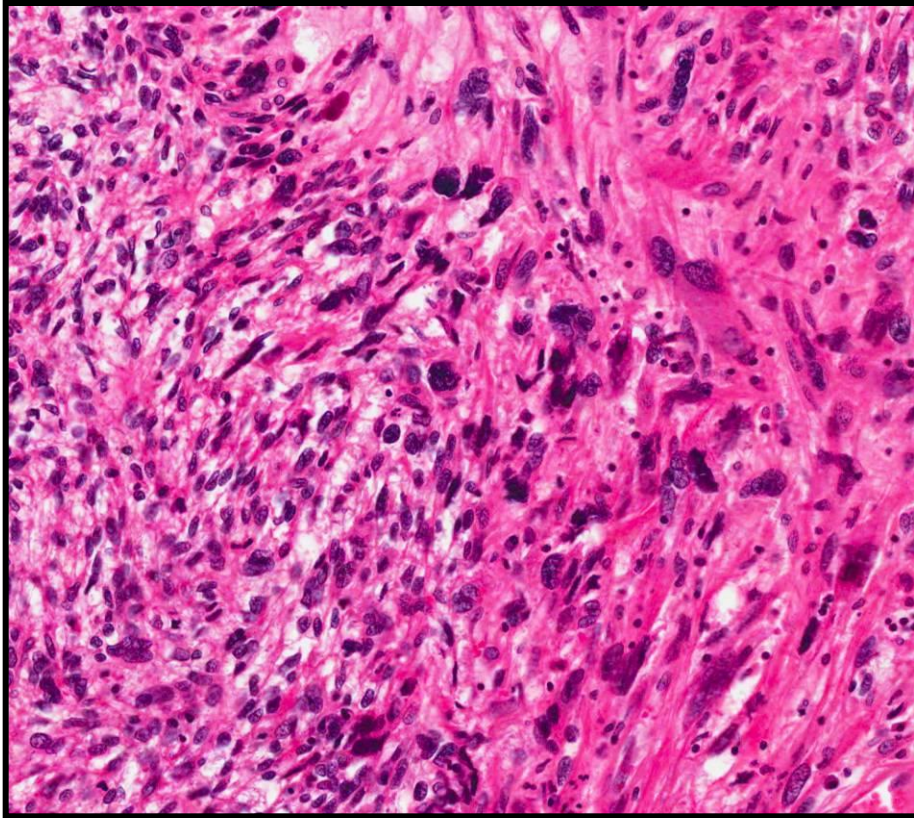
# Histologic features of Undifferentiated Uterine Sarcoma (UUS)

- Heterogeneous group of sarcomas 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)
  - High mitotic activity and necrosis

Subset of UUS harbour missense TP53 mutations



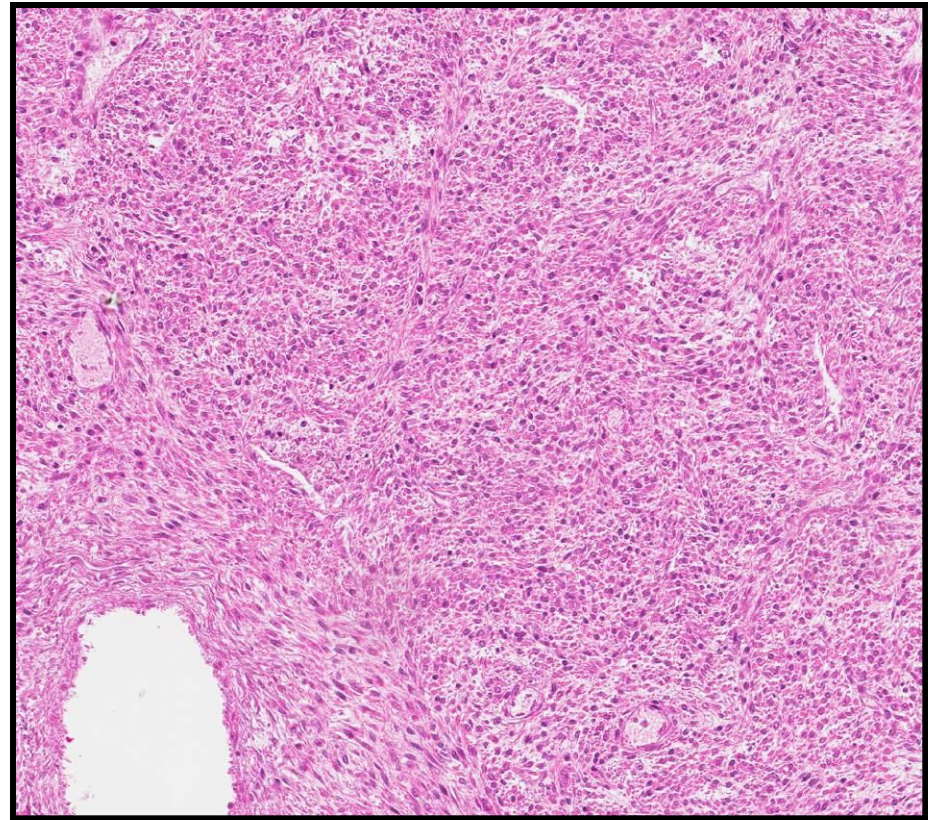
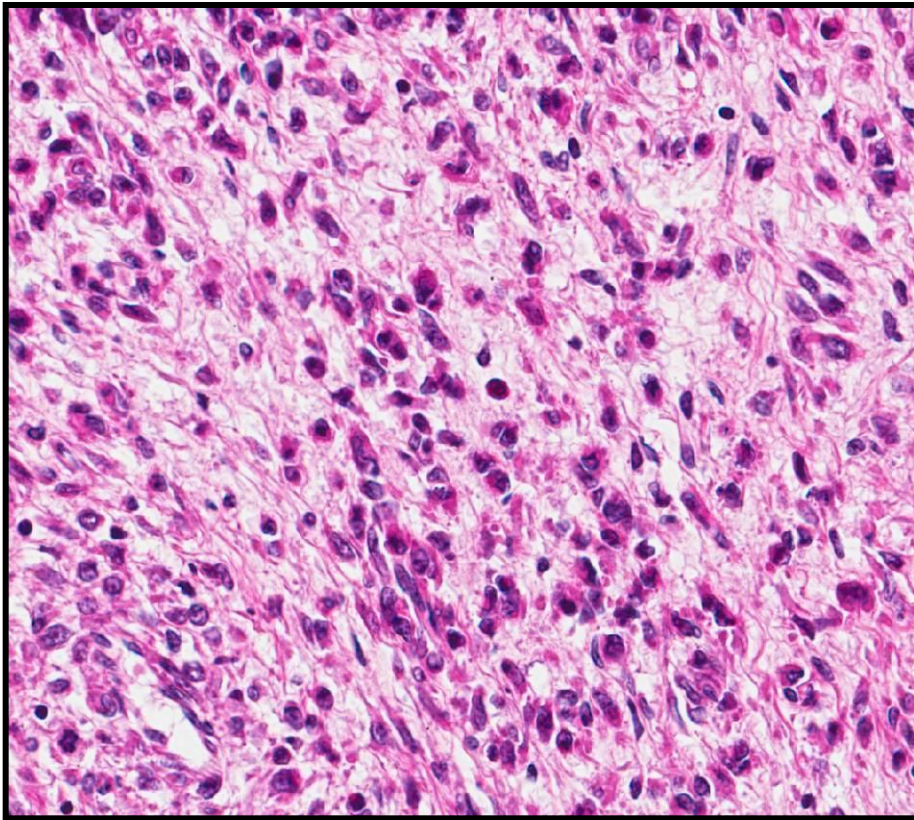
# DDx leiomyosarcoma



Marked diffuse cytologic atypia



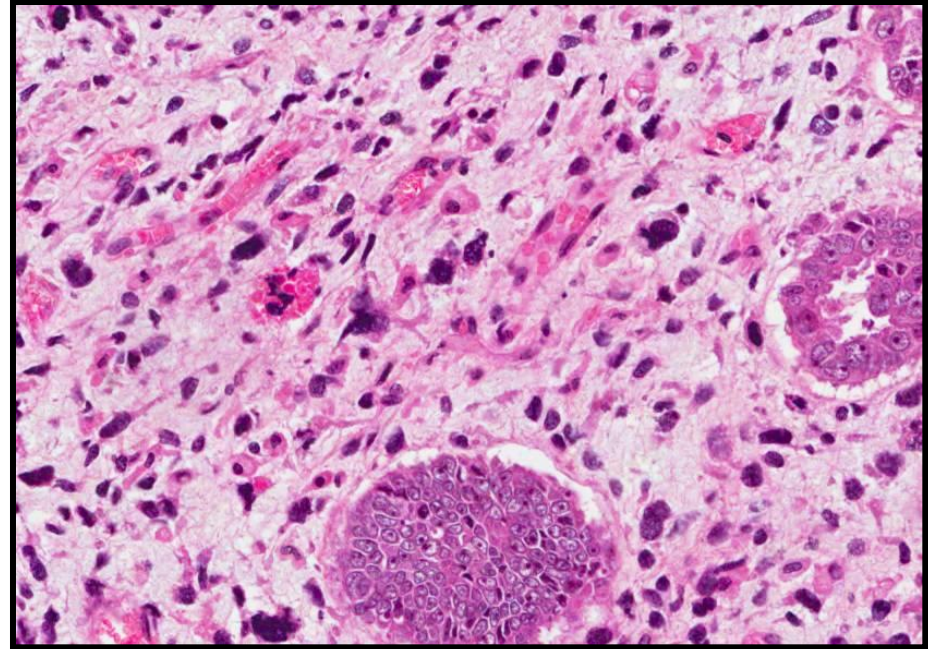
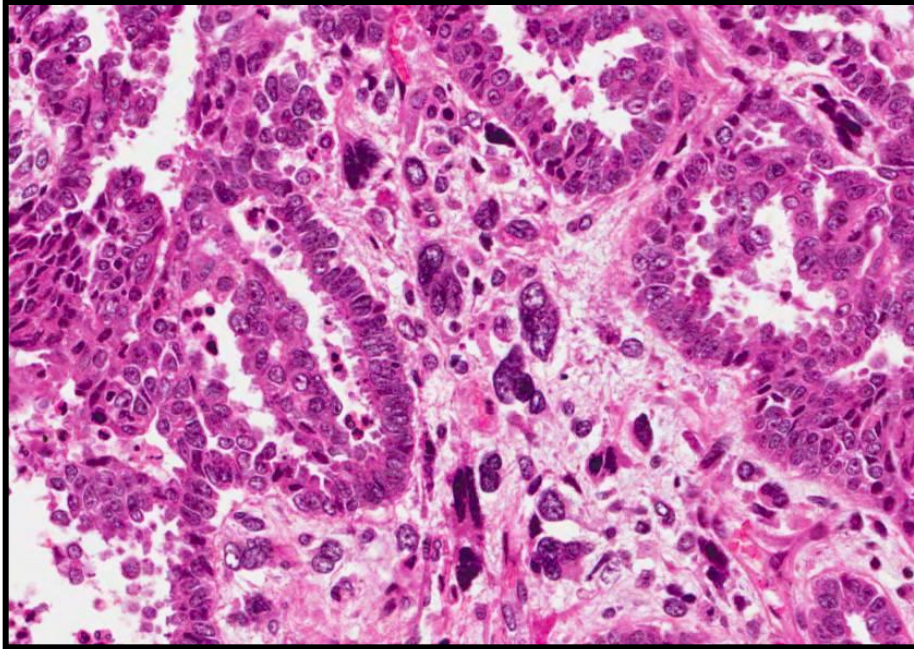
# DDx Leiomyosarcoma



Increased cellularity, coagulative necrosis with ghost outlines of cells



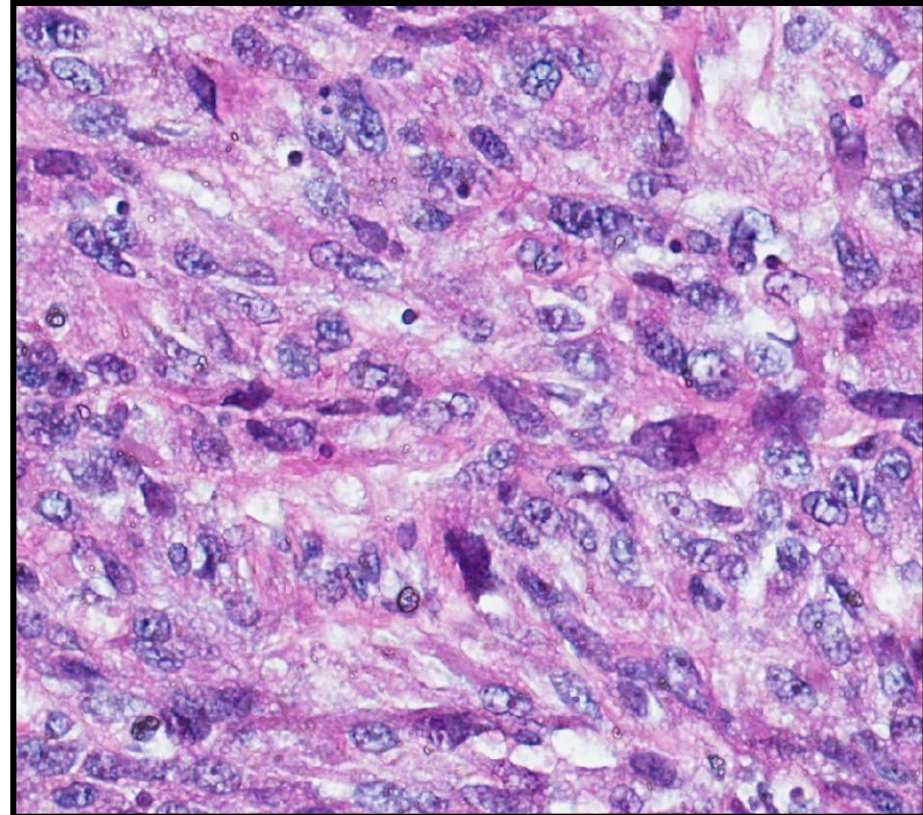
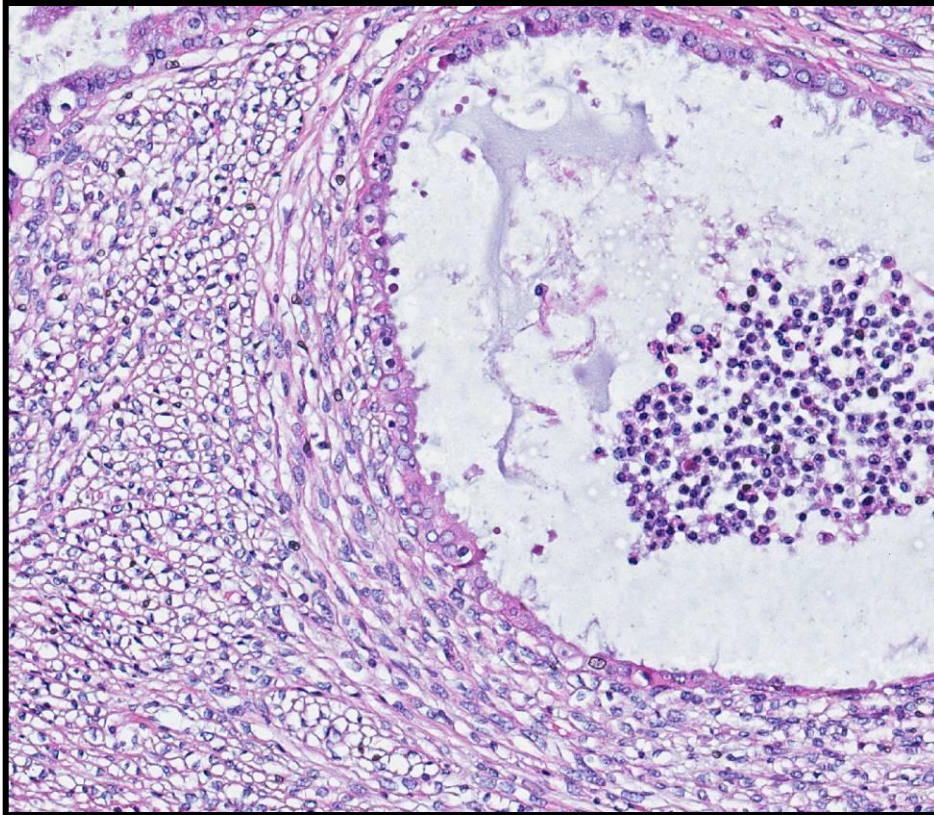
# DDx Carcinosarcoma



With rhabdomyoblasts-heterologous differentiation

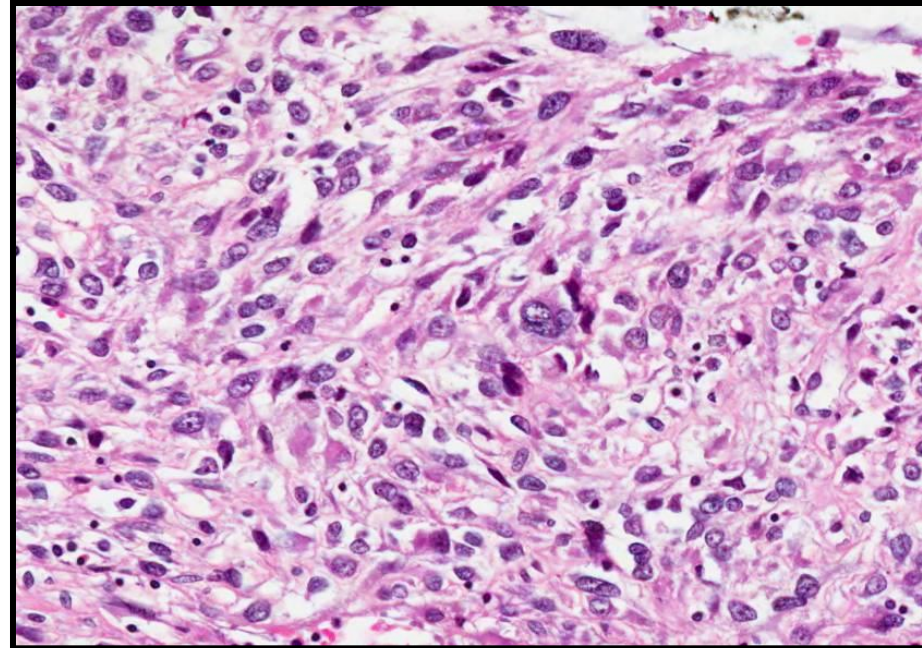
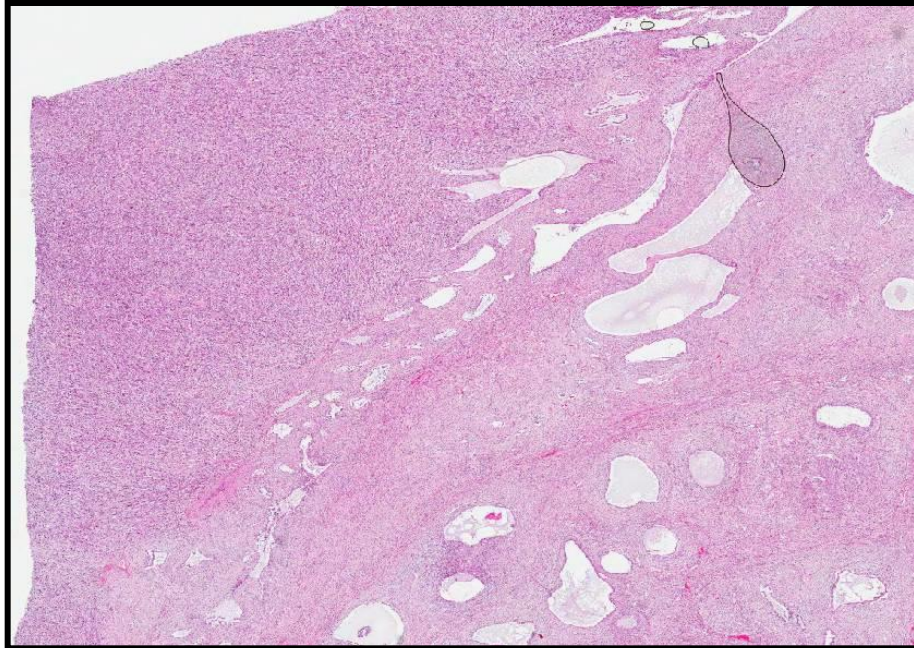


# DDx : Adenosarcoma with sarcomatous overgrowth



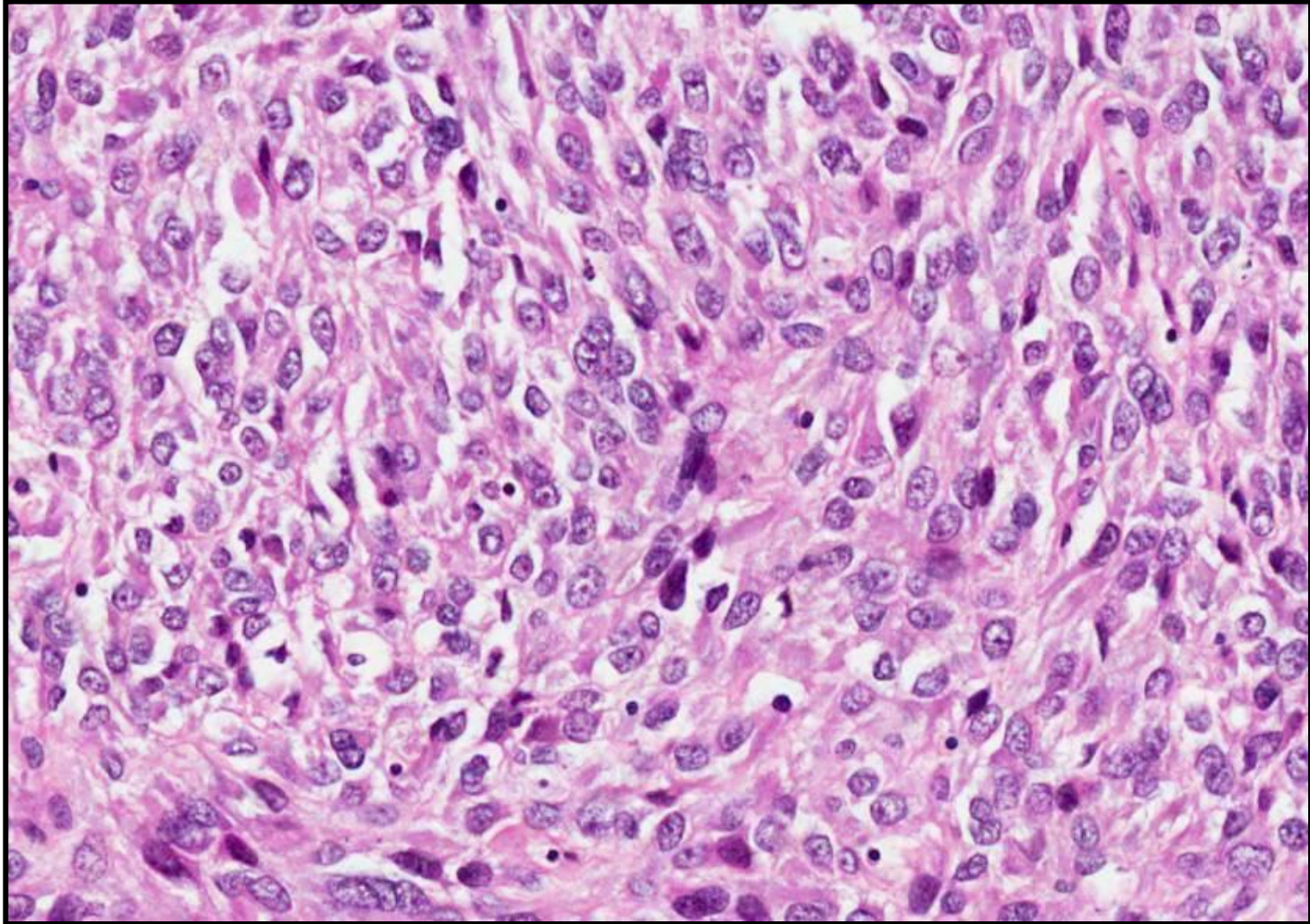


# Adenosarcoma with sarcomatous overgrowth



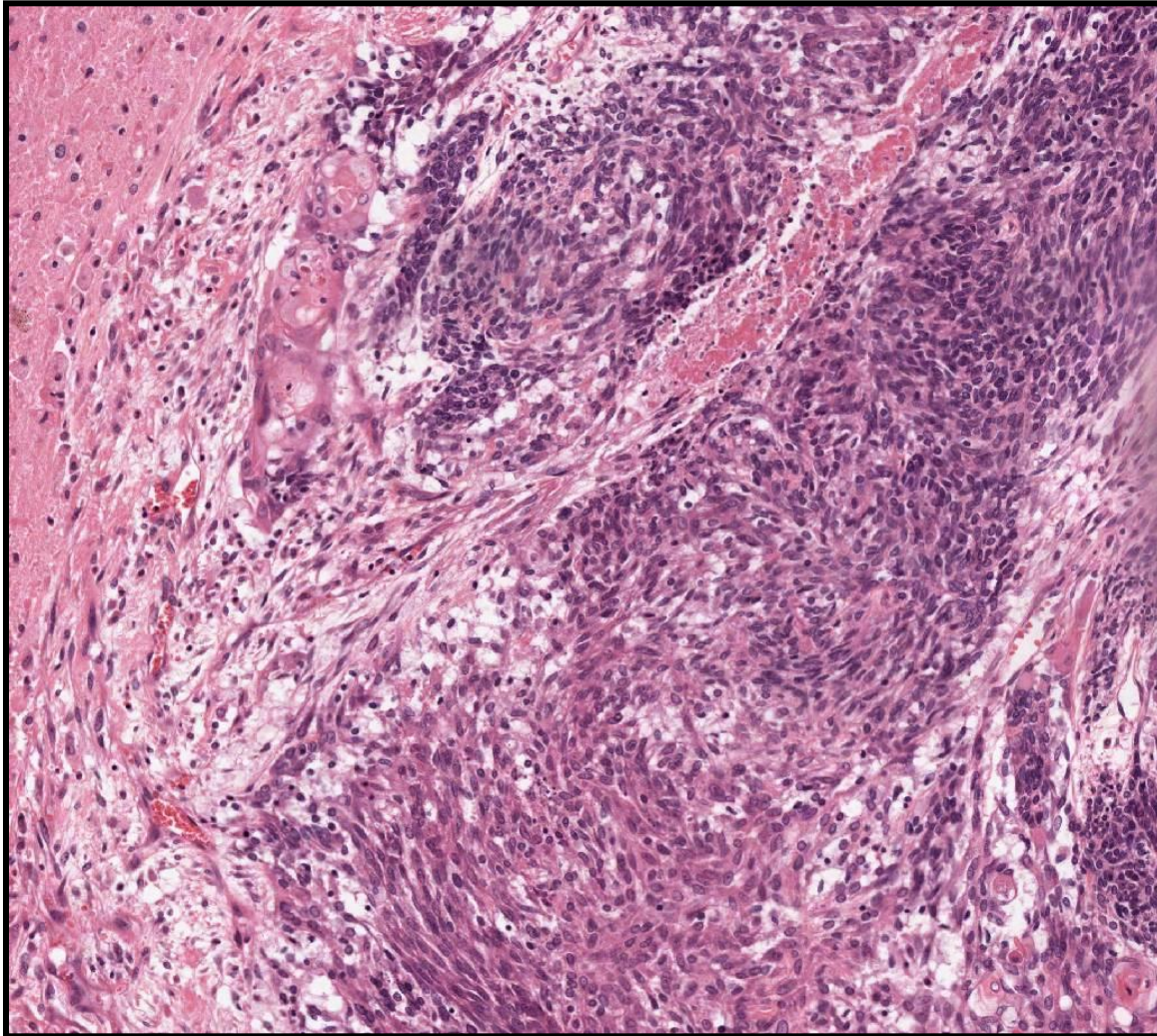


# Sarcomatous overgrowth in adenosarcoma



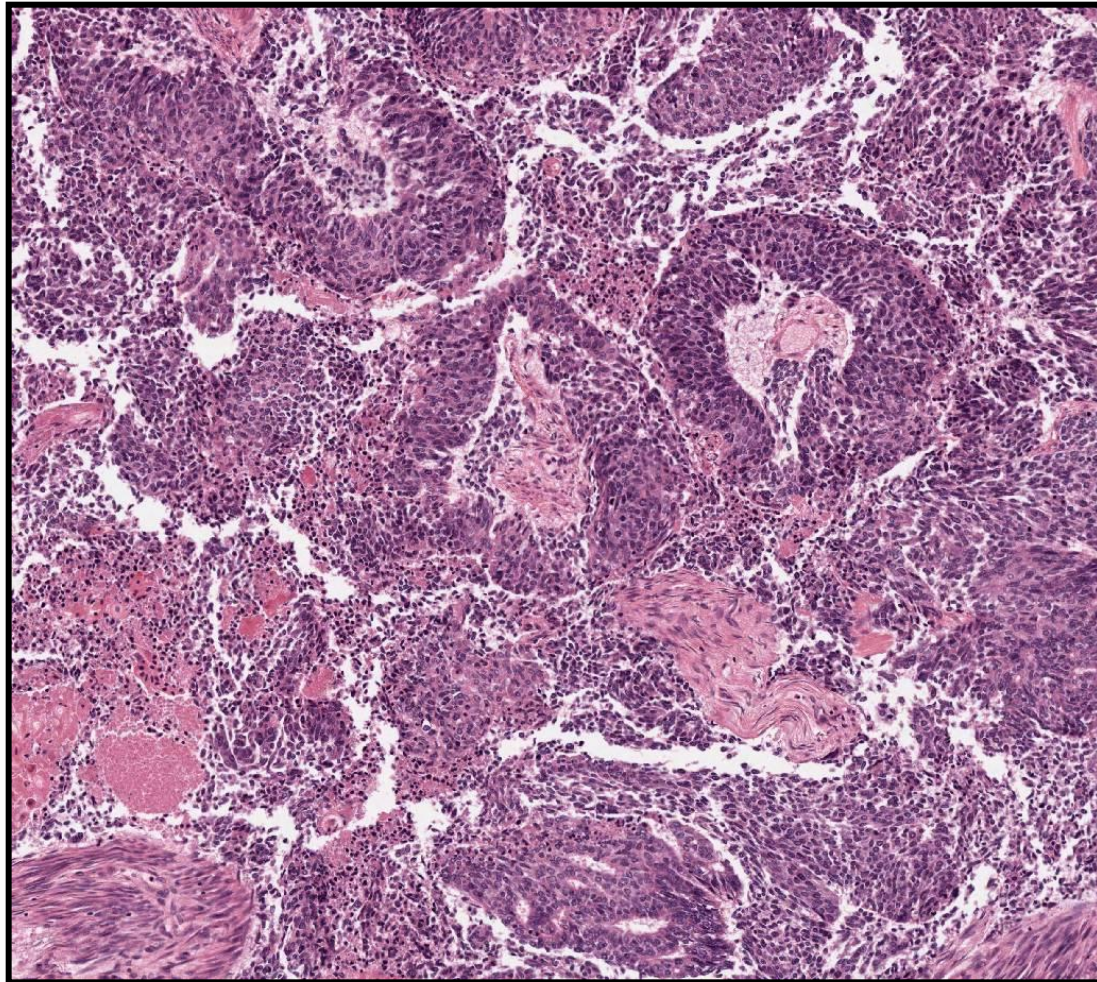


# DDx Undifferentiated carcinoma





# DDx Undifferentiated carcinoma



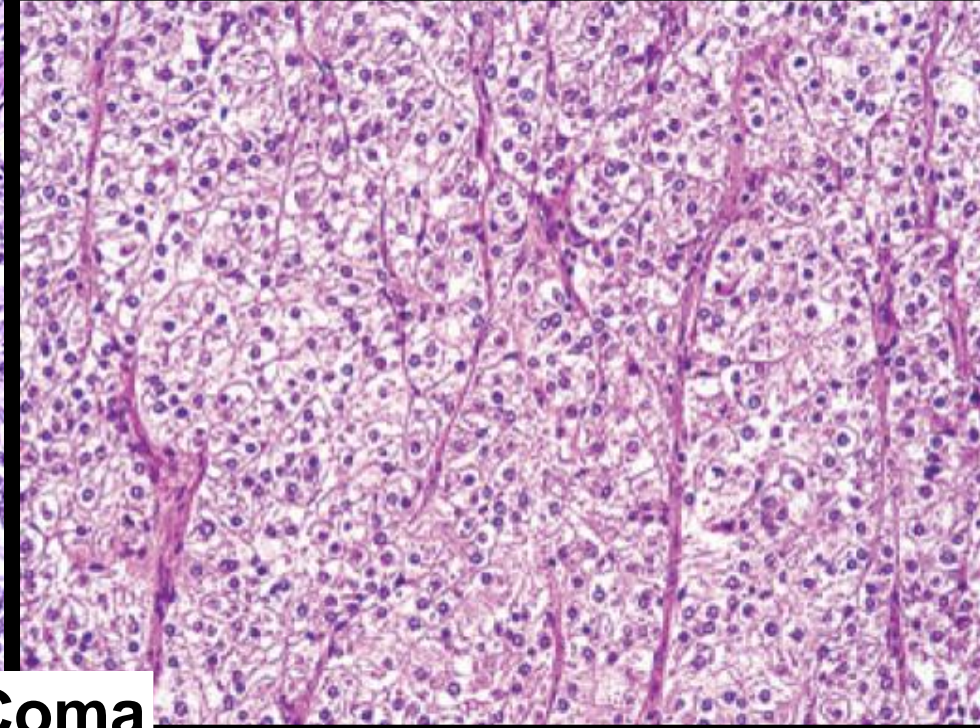
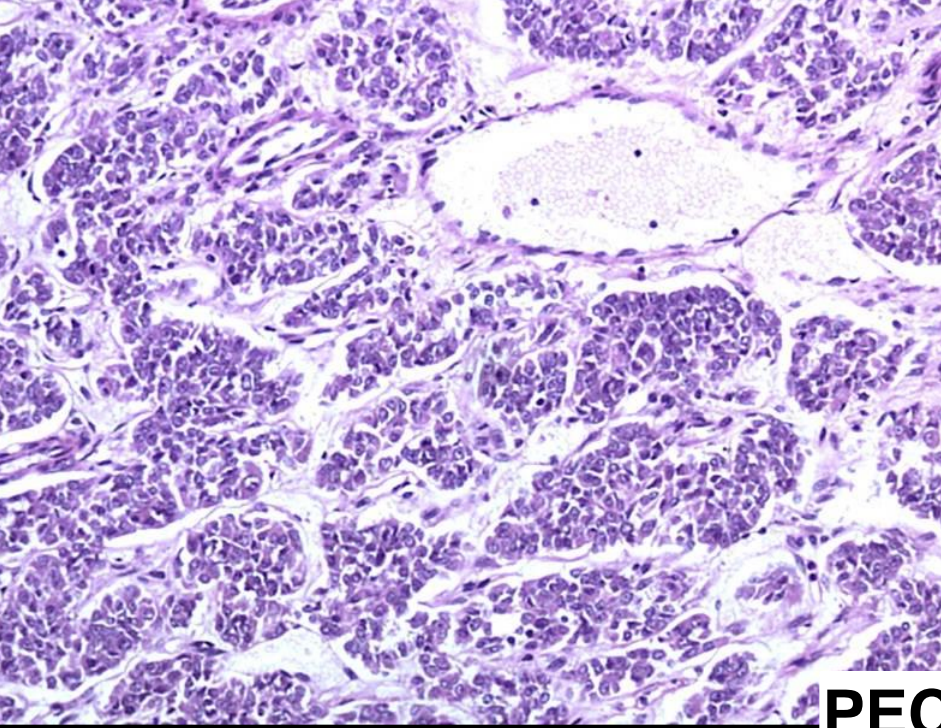
Loss of MMR proteins may be seen



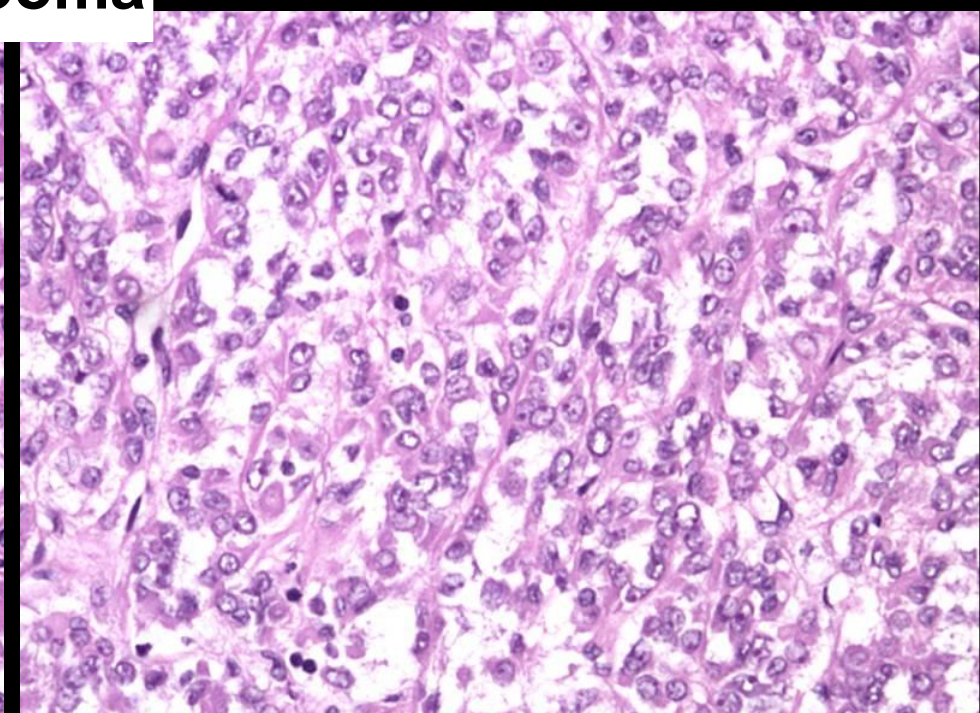
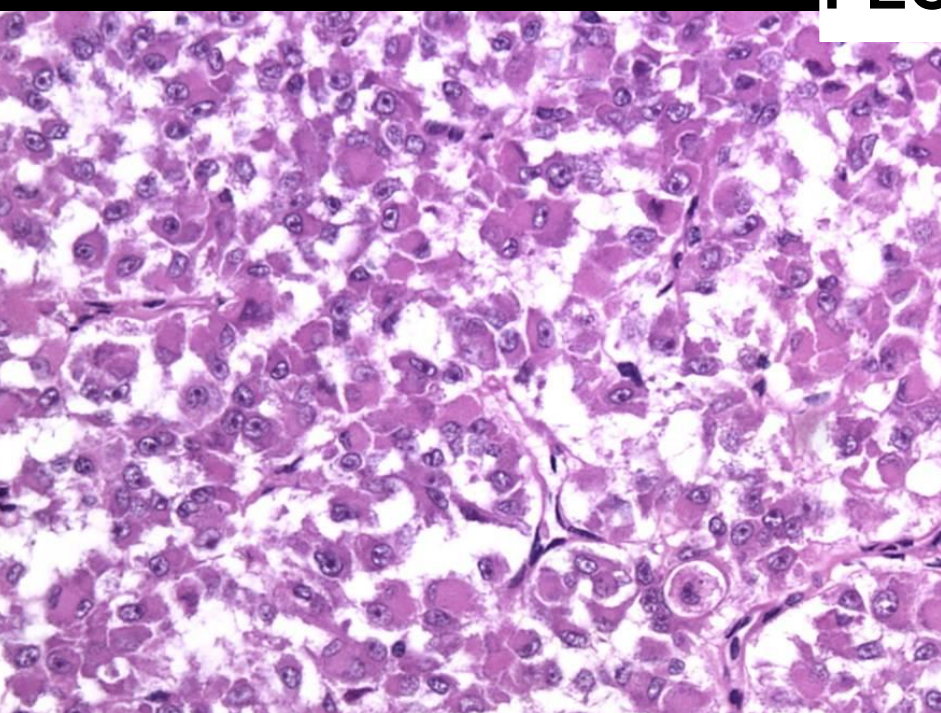
# Immunohistochemistry of UUS

- CD10 may be positive NOT- ESS
- Hormone receptors may be positive.
- Focal SMA + (need panel of smooth muscle markers to dx LMS)
- Consider malignant PEComa
- Focal keratin or EMA consider undifferentiated or de-differentiated endometrial carcinoma





**PEComa**





# 2014 WHO Classification-LGESS

- Low-grade ESS (JAZF1 LGESS and classic ESS without genetic re-arrangement)-
- Same histology and immunophenotype
  - (Cyclin D1<10%) or negative
  - CD10 Strong diffuse
  - ER strong diffuse
  - PR strong diffuse
- Presentation : usually with stage I disease (resectable)
- Prognosis : excellent (small risk of late recurrence -10-20%)
- Rx : anti-oestrogenic therapy useful in disease control (aromatase inhibitors)

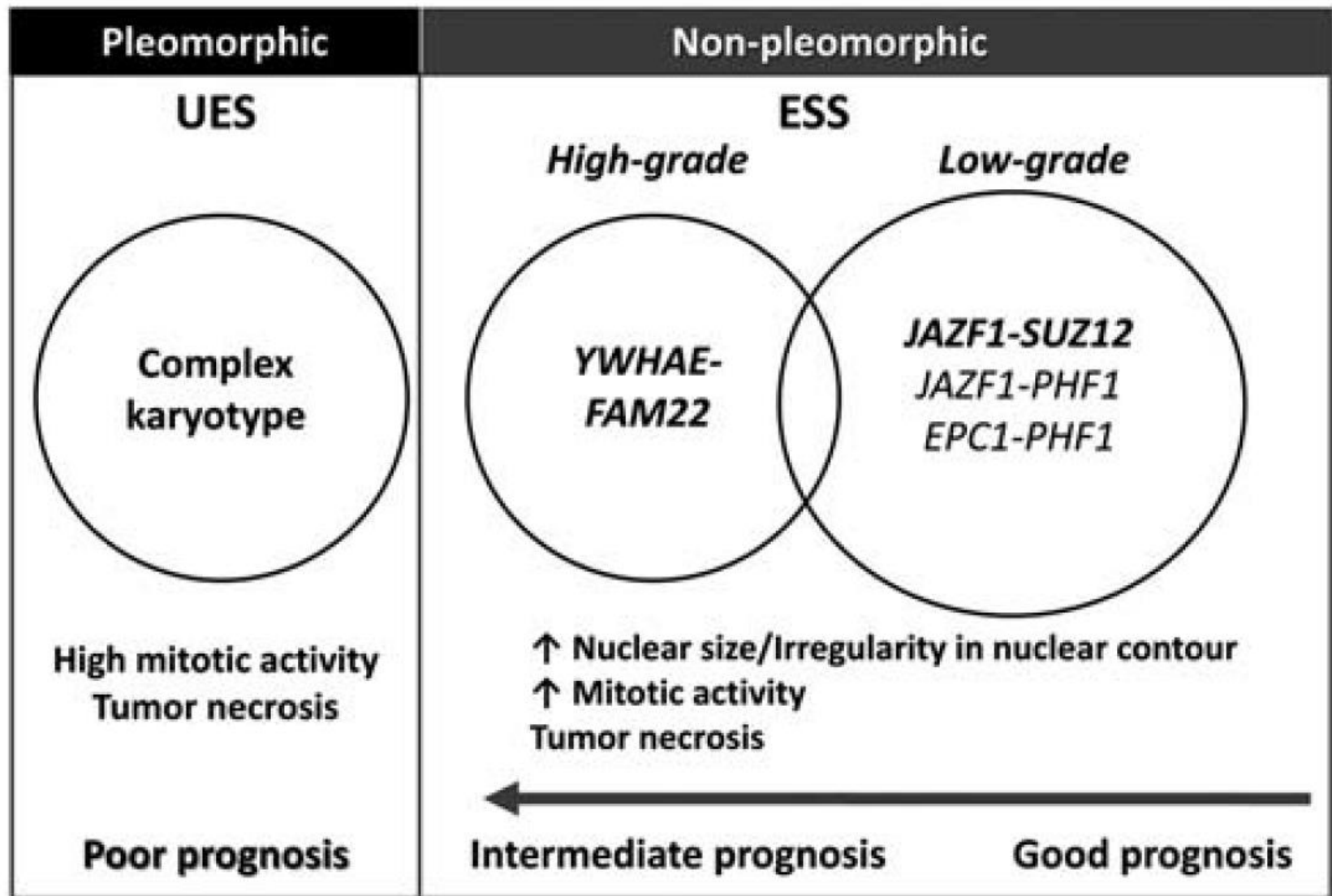
# YWHAE-NUTM2 ESS

- Presentation : advanced disease (stage 2-4)
- Treatment : surgery but rapid recurrence recognised (few months to years)
- Cyclin D1 strong diffuse positive >70% cells
- CD10, ER and PR classically negative in high grade component). Negative for epithelial markers.
- Anti-oestrogenic therapy (no value)
- Some long term survivors stage 2 or higher have had survival benefit with adjuvant Rx
  - Adjuvant chemotherapy
  - Radiation therapy



# UUS

- May present at high stage
- Dismal prognosis for patients with stage 2 or greater
- Immunohistochemistry : Variably positive with immunohistochemical markers used for mesenchymal tumour diagnosis (no consistency)
- Subset with uniform nuclei +ve for Cyclin D1 focal ER, PR or CD10 staining may be seen (exclude YWHAE-NUTM2 high grade ESS)
- Mnx : Non-responsive to conventional chemotherapy or radiation Rx



**FIGURE 7.** Proposed classification for pure uterine sarcomas.



# Staging LMS and ESS

FIGO staging for uterine sarcomas (2009).

Stage	Definition
-------	------------

(1) *Leiomyosarcomas and endometrial stromal sarcomas<sup>a</sup>*

- |      |  |
|------|--|
| 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.

Int J Gynecol Obstet 104,179





# DDx- rare but consider.....

- Uterus in pelvis
- Pelvis also site of other soft tissue tumours
- Is tumour Uterine in origin?
  - Mixed tumours (carcinosarcoma or adenosarcoma) (1block/cm)
  - Generous sampling (endometrium)- older people
- Is it arising from outwith the uterus
  - Dedifferentiated liposarcoma
  - PEComa (rarely from within uterus)
  - GIST (gastro-intestinal stromal tumour)
  - Peripheral nerve sheath tumour
  - Low-grade fibromyxoid sarcoma

# High grade sarcoma ( not mixed tumour)

- Once carcinosarcoma and adenosarcoma with sarcomatous overgrowth excluded:
- Pleomorphic Uterine sarcoma
  - UUS, leiomyosarcoma, rare heterologous sarcomas (pleomorphic rhabdomyosarcoma)
- Monomorphic Uterine sarcoma
  - ESS, leiomyosarcoma or IVL, dedifferentiated or undifferentiated endometrial carcinoma
  - PEComa :(HMB45, Melan A, S100, desmin, SMA, h-caldesmon)-mTOR inhibitors (recent studies suggested response)
  - Ewing's sarcoma : Cyclin D1 +ve, CD 99, FLI-1



# DDX

- Tumour

- morphologically low grade ESS
- Growth pattern low grade ESS
- smooth muscle differentiation

- Options?

- Low grade ESS (JAZF1 LGESS or ESS without demonstrable genetic arrangement) – FISH or RT-PCR for genetic fusions
- Uterine leiomyoma with intravascular leiomyomatosis
- Note unlikely to be HGESS no documentation of associated smooth muscle differentiation with YWHAE-NUTM2 ESS

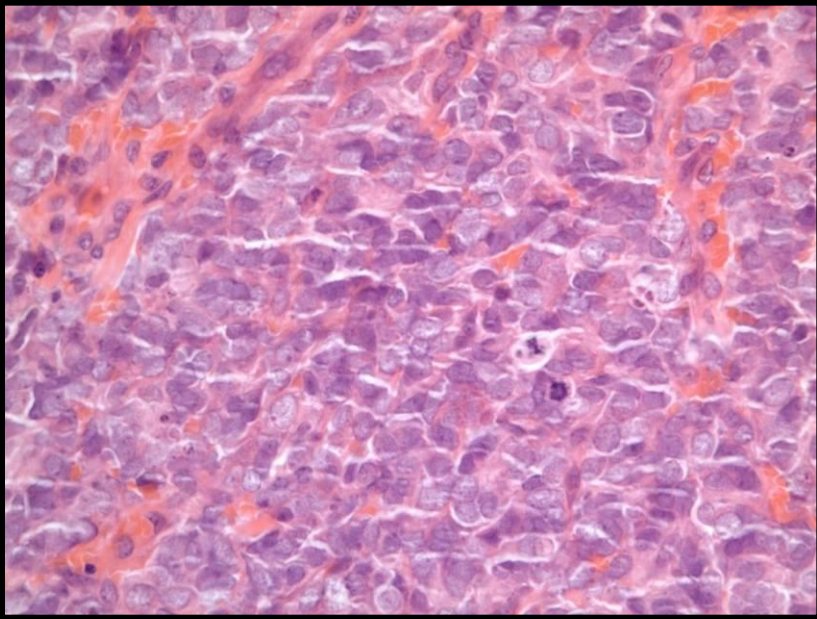
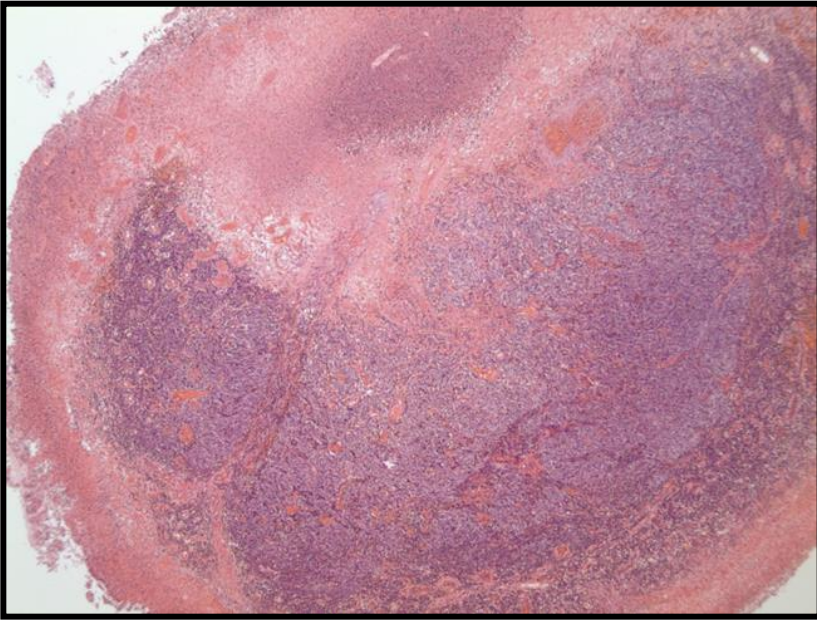
# De-differentiated ESS

- Biphasic tumour
  - Monomorphic low grade component (ovoid cells)
  - High grade component (round cells)
- De-differentiated ESS (lacks cyclin D1 positivity)
  - Unlike YWHAE- NUTM2 ESS

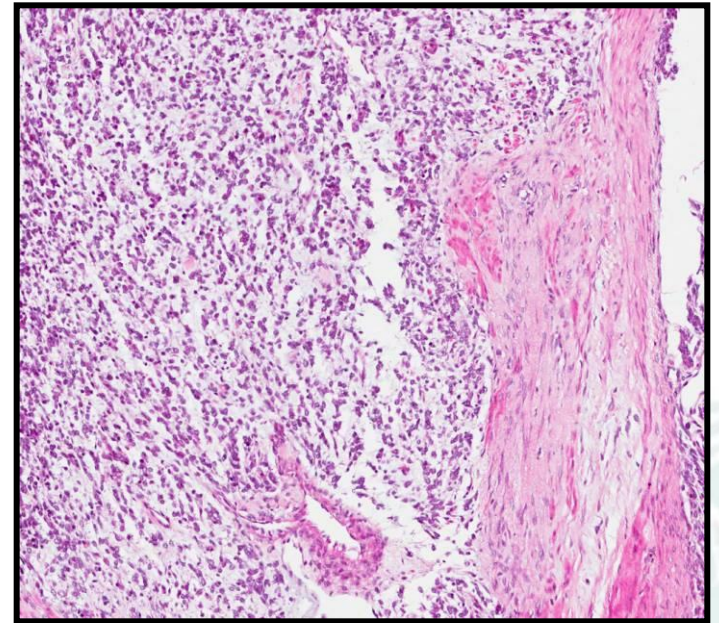
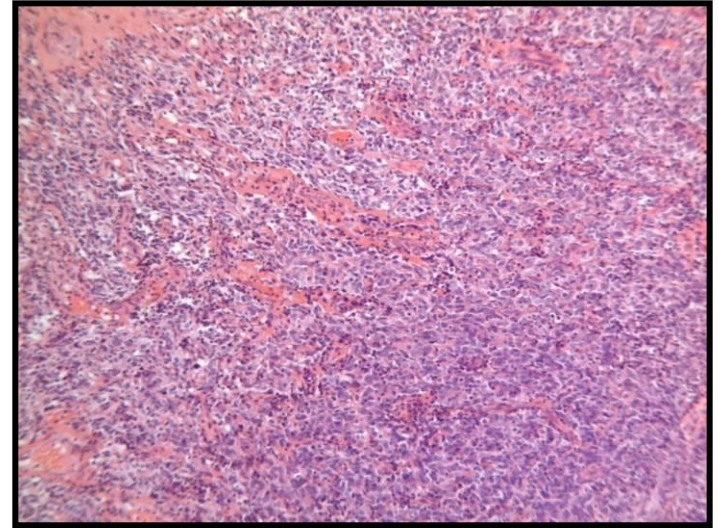
# Diagnosis of Uterine sarcoma

- Need hysterectomy specimen
- Patience
- Very generous sampling
- Small biopsies may not be representative!





Small round blue cell tumour



Spindle cell component  
fibromyxoid stroma