



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)

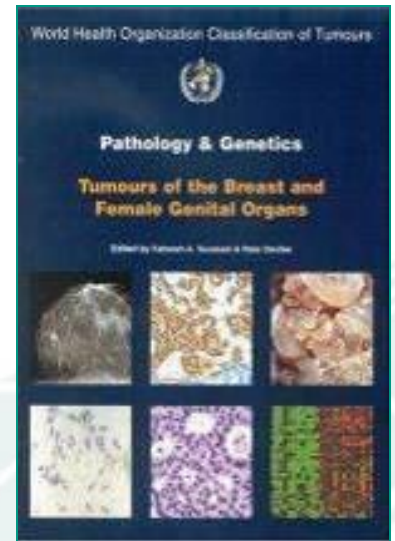
- Recognised 3 categories:
 - Low grade ESS
 - High Grade ESS
 - Undifferentiated Sarcoma
- Made case: importance that tumour must morphologically resemble stromal cells of proliferative endometrium

ESS

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

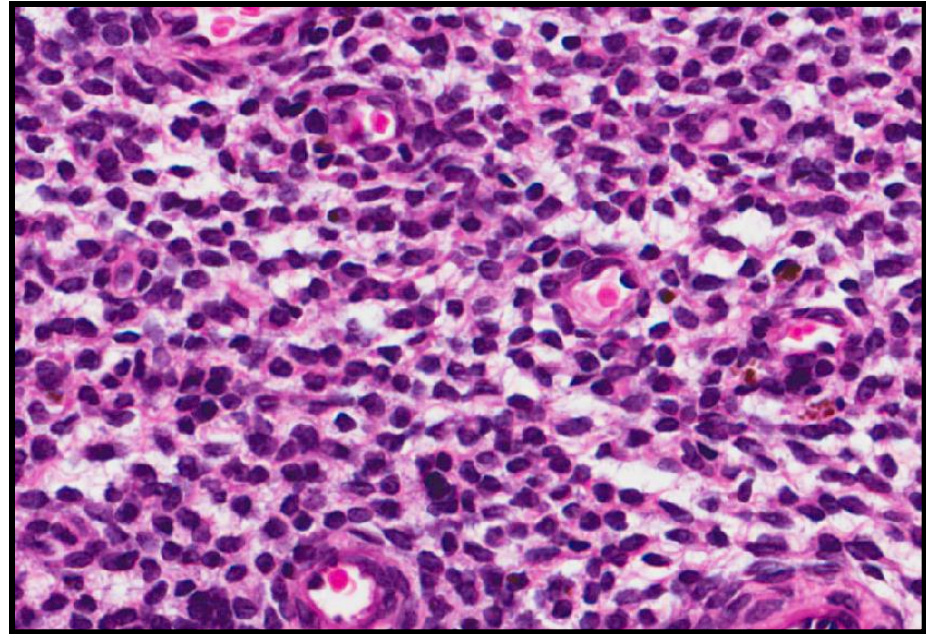
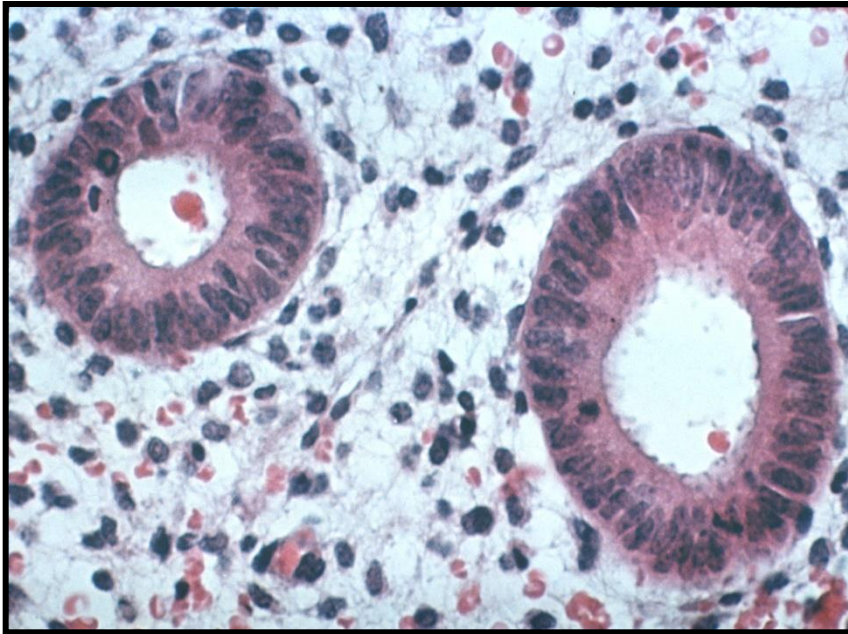
Prognosis

	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

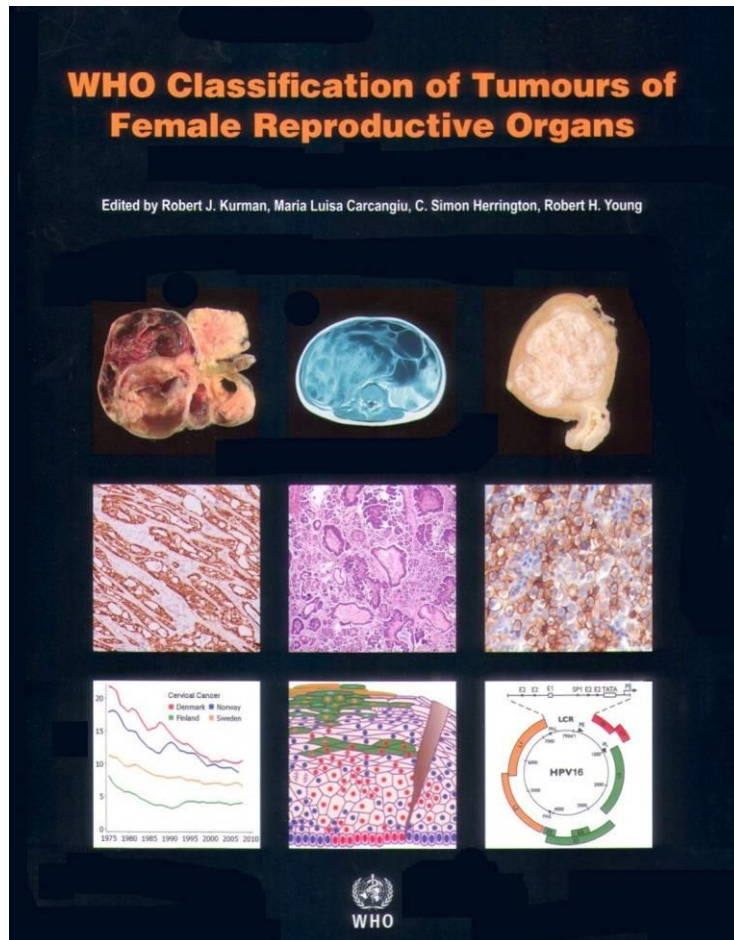
The Grey zone

- 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

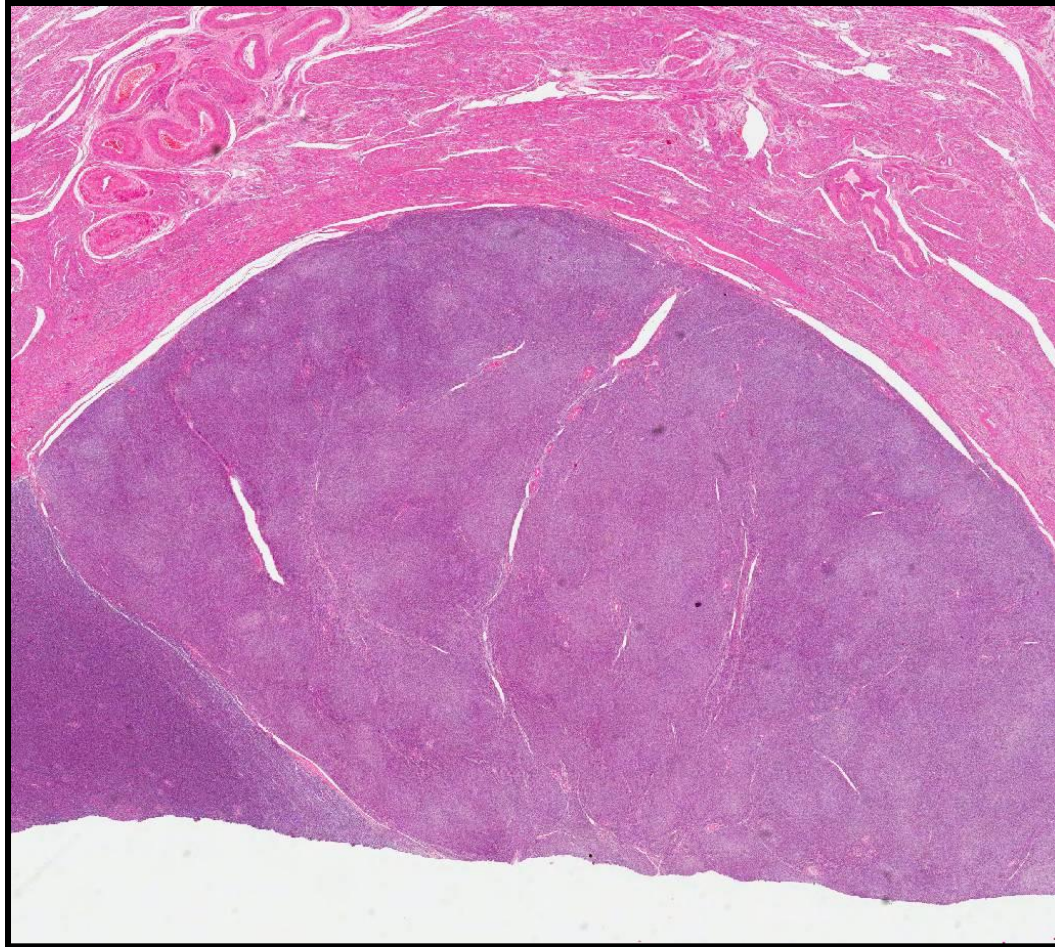
ESN (Stromal nodule)

- 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

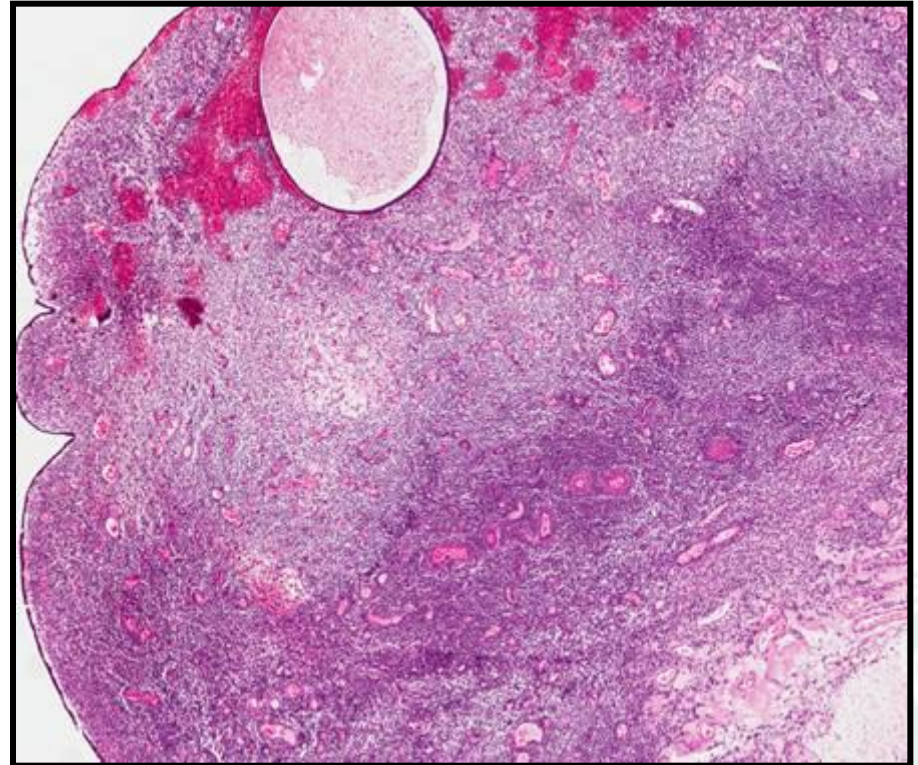
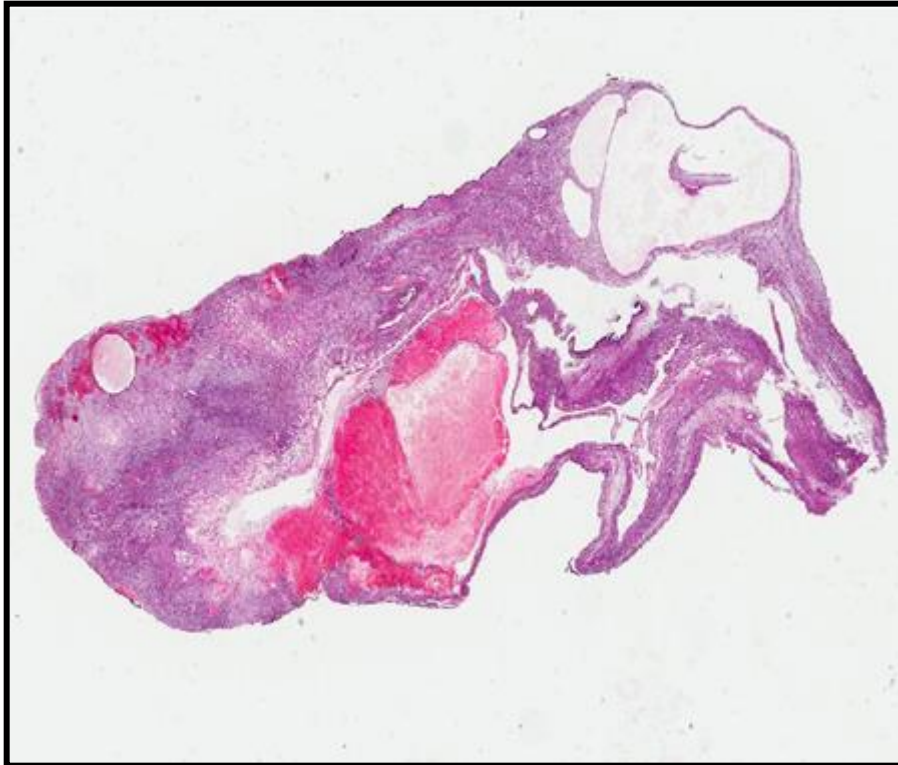
- Grossly fleshy yellow/tan
- Histology
 - Cellular
 - Hyalinised
 - Cysts (34%)
 - Infarct type necrosis (68%)
- Up to 3mm focal irregularity allowed (Tavasoli and Norris 2002)
 - < 3 in number
 - Lobulated or finger-like projections into adjacent myometrium
 - Endometrial Stromal tumour with limited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

Endometrial stromal nodule



ES neoplasm "endo polyp"

Note base not identified. Diagnosis cannot be made

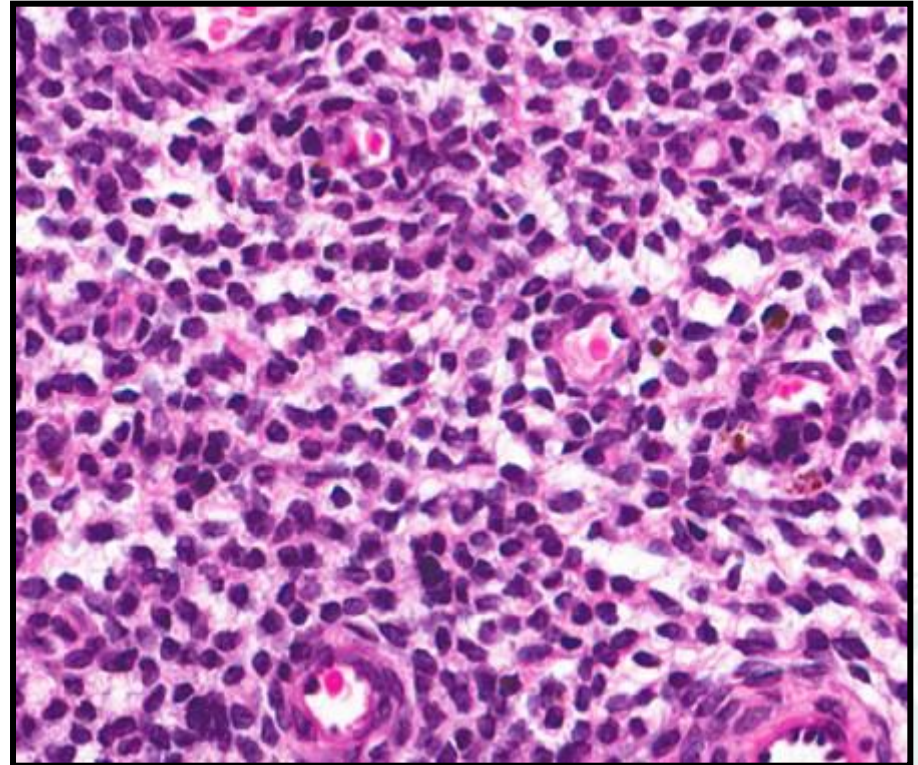
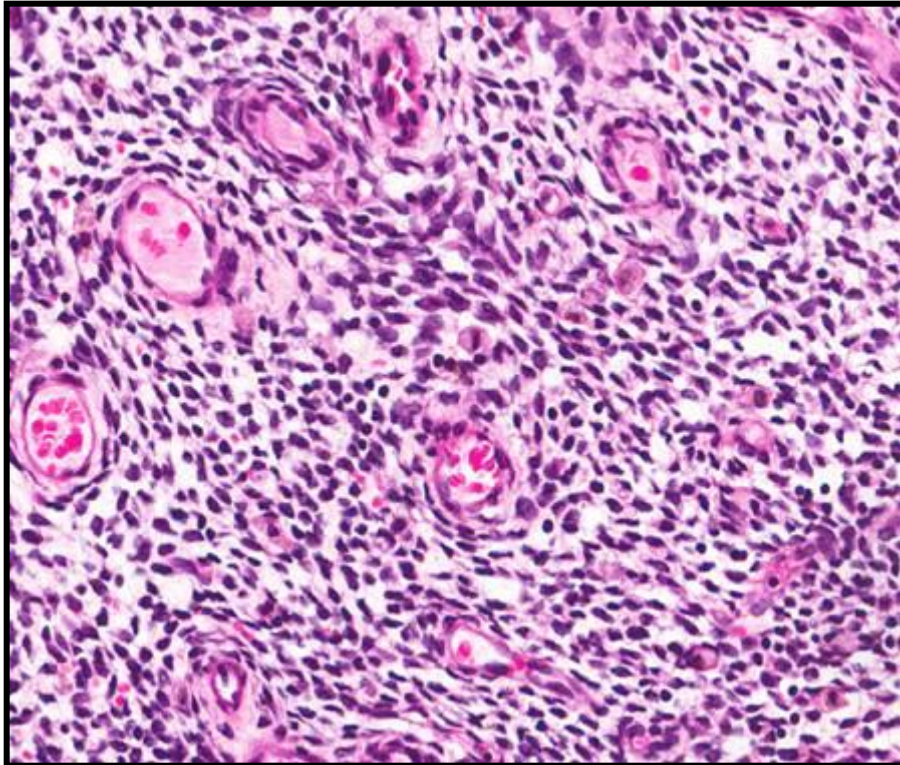


Cellular polypoid lesion no glands as part of lesion

ESN vs ESS

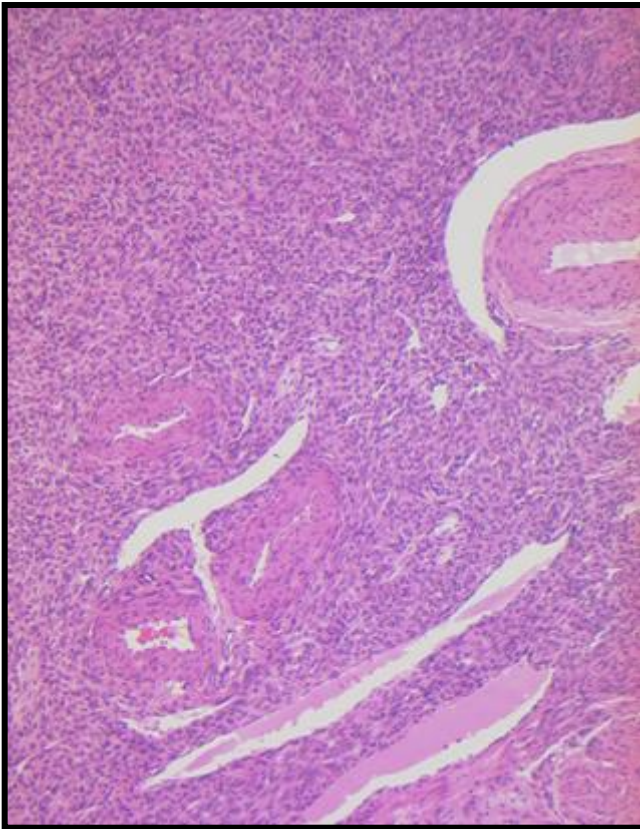
- Cannot be differentiated on curettage material unless entire lesion represented in curettage material
- Infiltrative margins/vascular invasion (required)
- Hysterectomy
- **EXAMINE PERIPHERY CAREFULLY.**

HP endo "polyp"



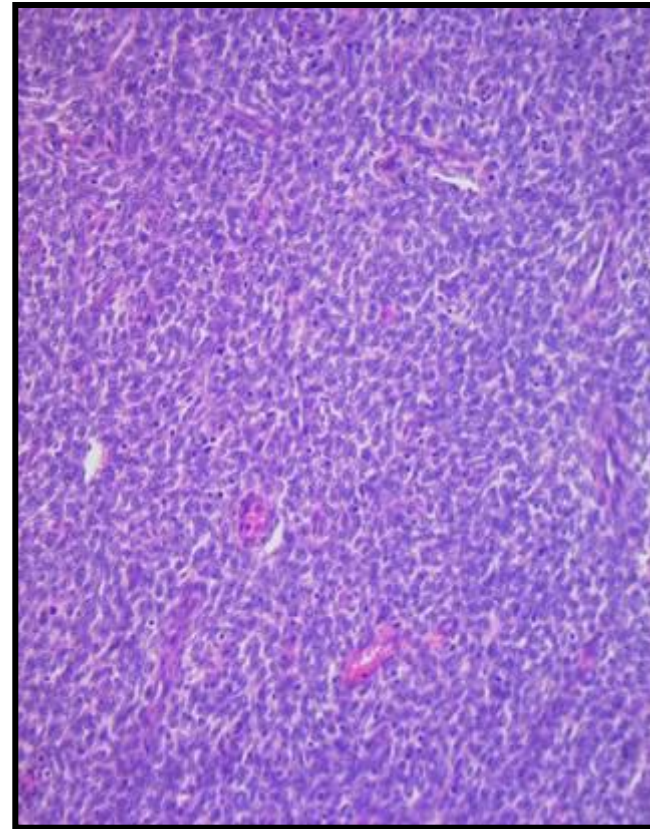
Need hysterectomy to make a definitive diagnosis

Stromal nodule vs. HC leiomyoma



Cellular leiomyoma

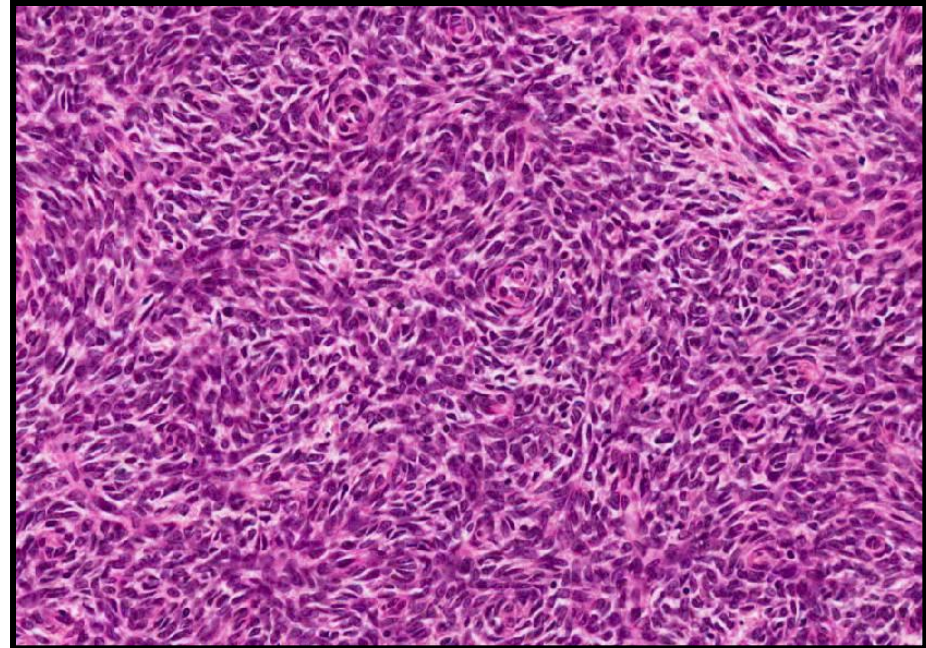
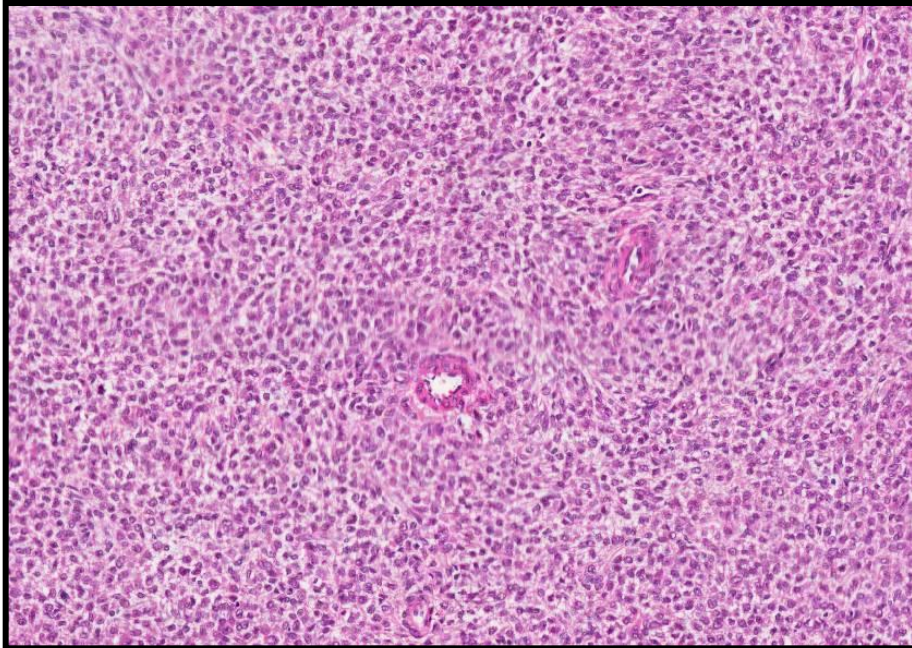
Fascicular growth



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

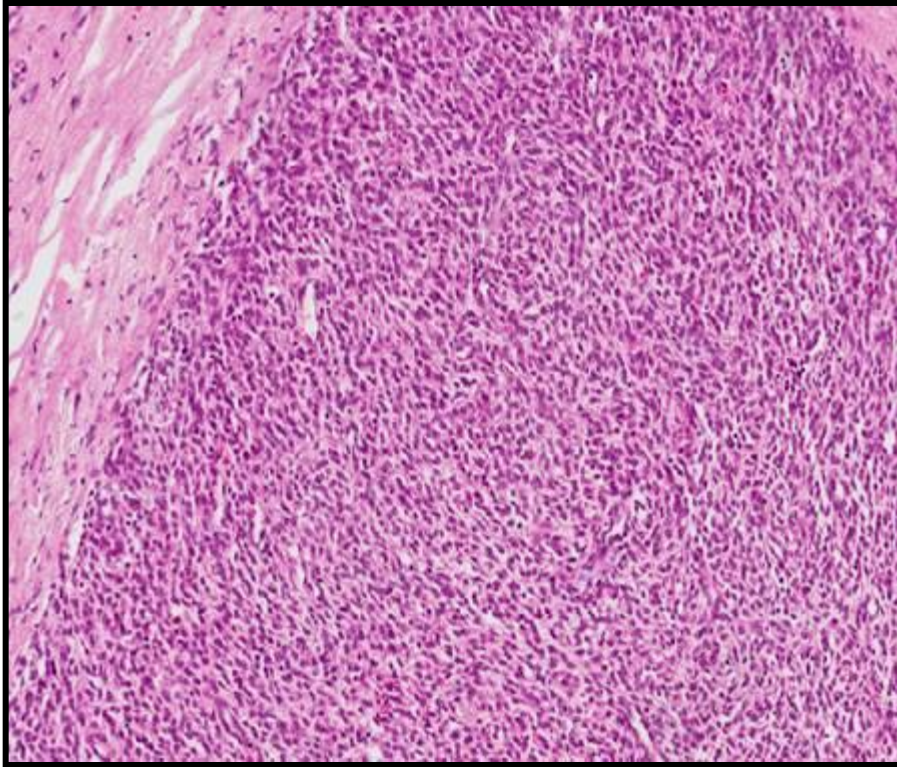


Endometrial stromal sarcoma



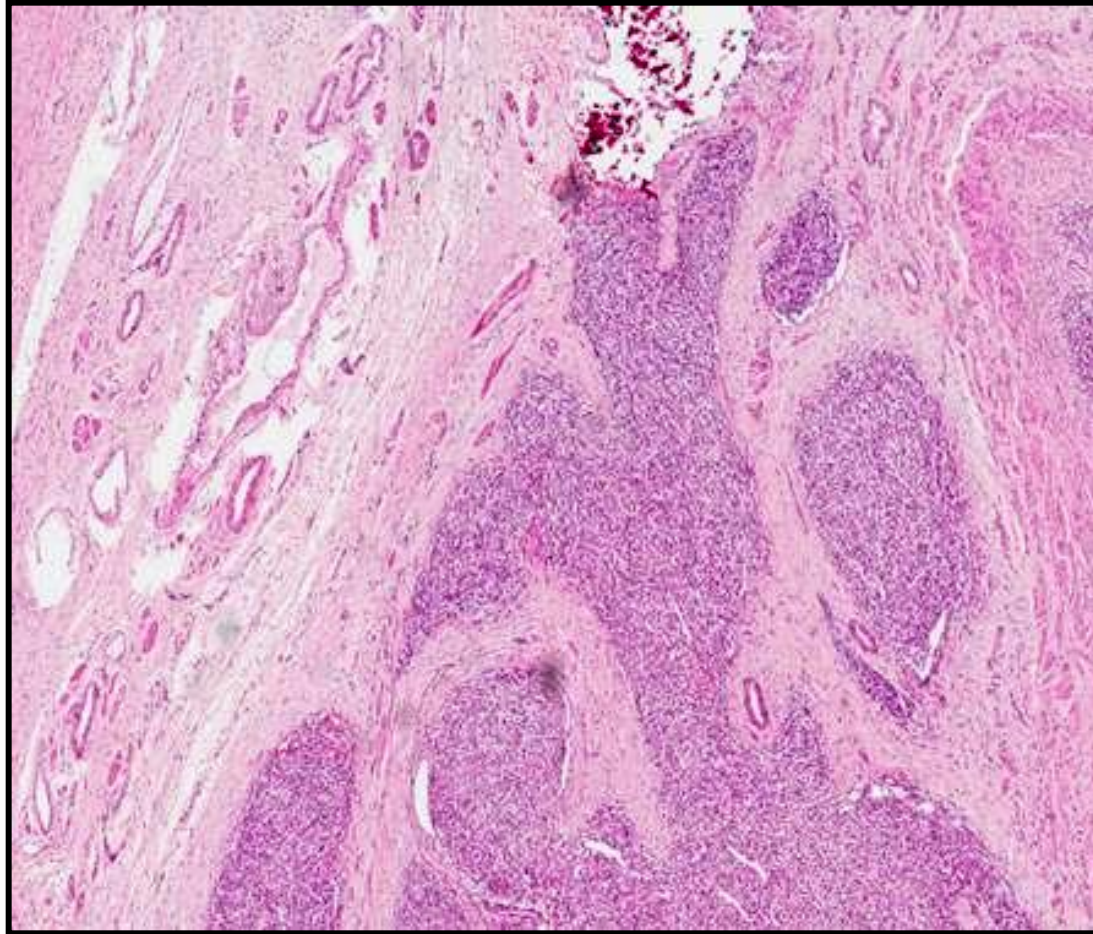
Cystic change

LG Endometrial Stromal Sarcoma-cells



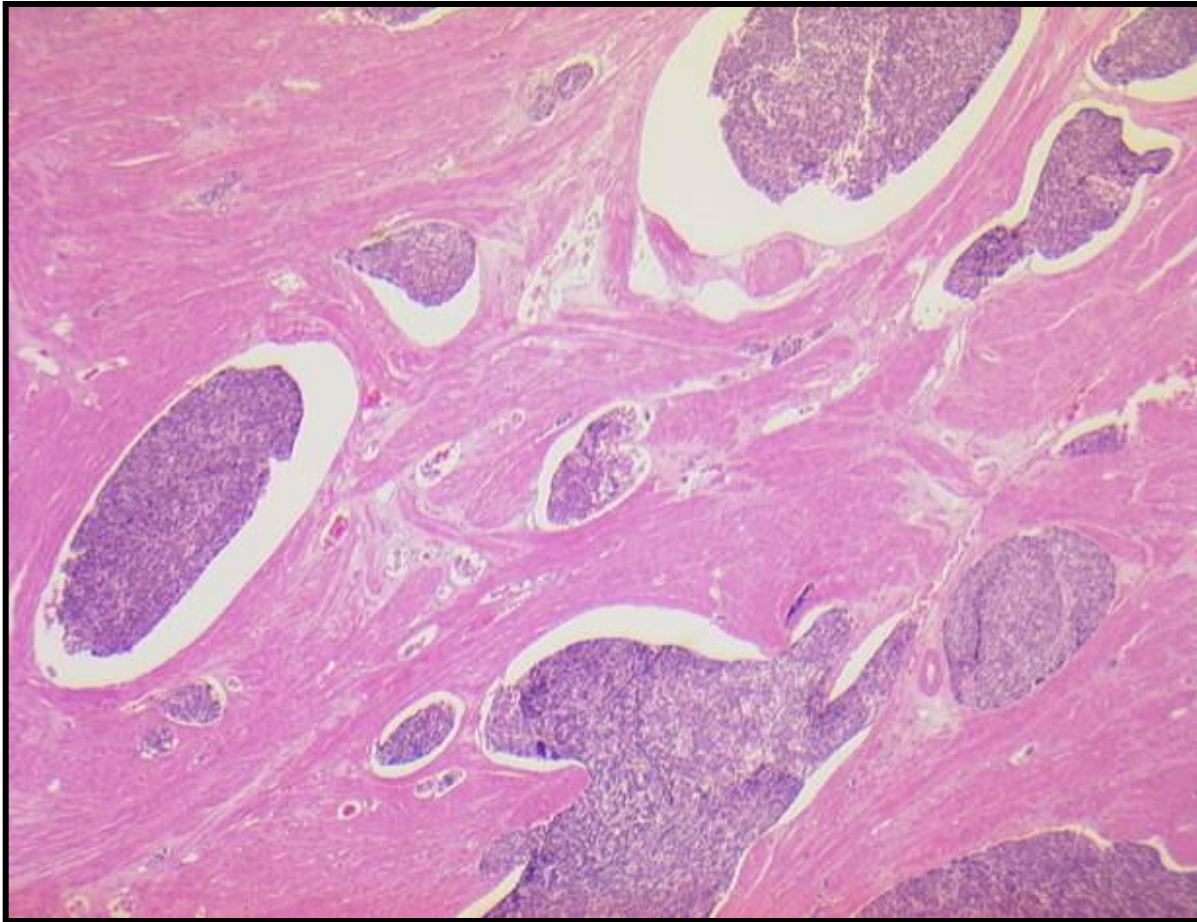
- Proliferation of small, round to oval monomorphic cells
- Scant cytoplasm
- Nuclei have smooth contours (round to oval in shape)

ESS



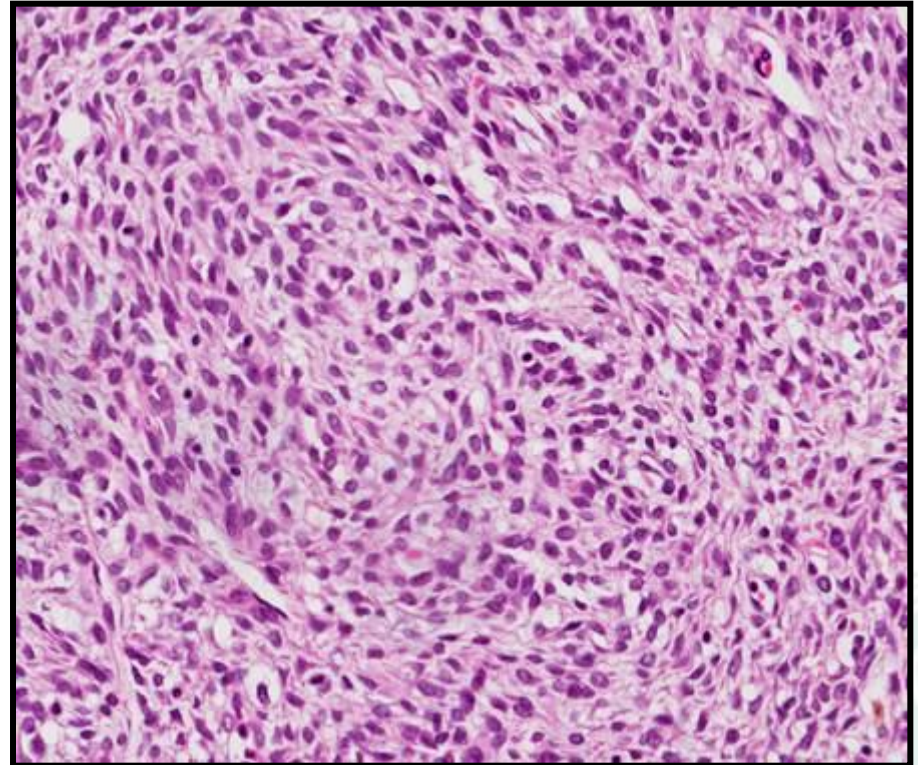
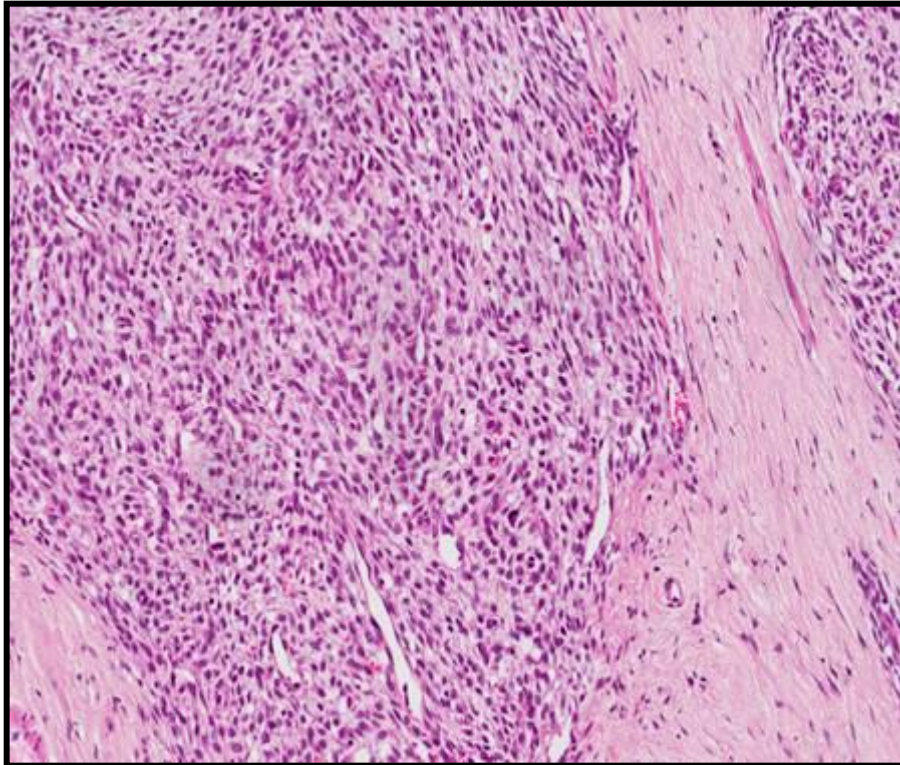
Finger like myometrial permeation

ESS- lymphovascular permeation



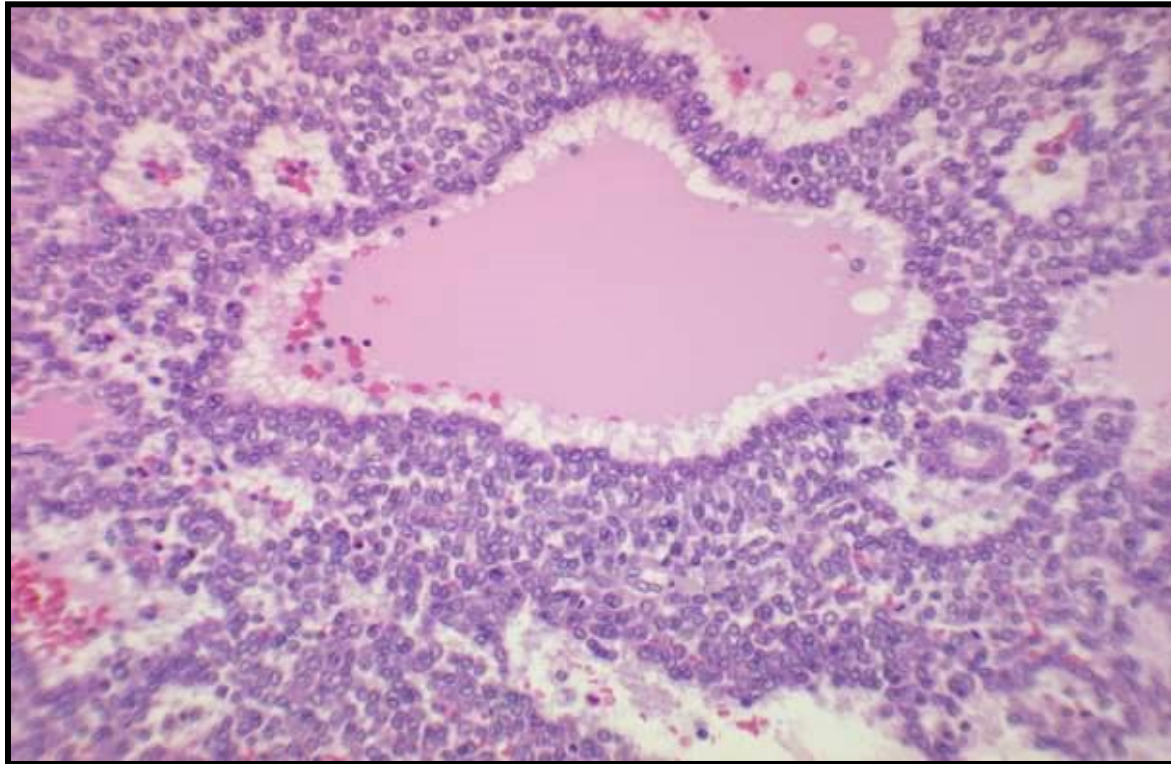
Lymphovascular permeation - conspicuous feature

ESS "low grade"



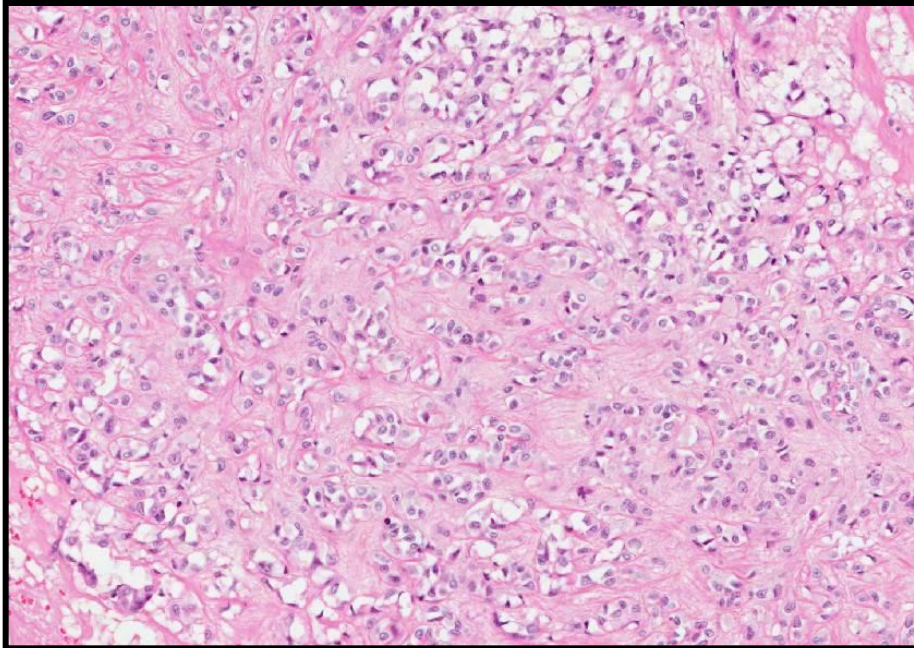
Stroma resembles proliferative phase stroma

Endometrial stromal sarcoma

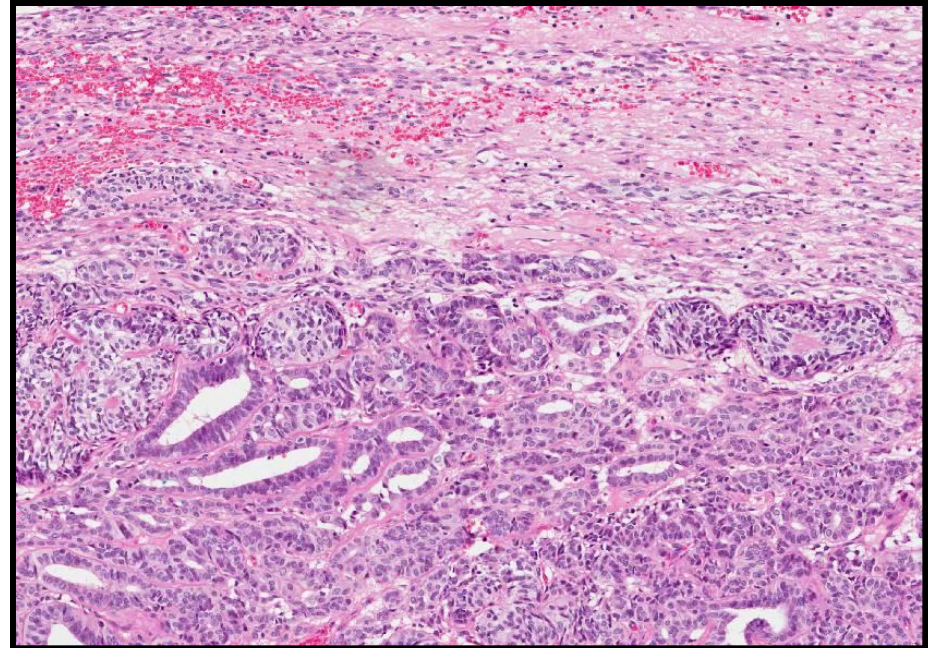


Cystic change

ESS

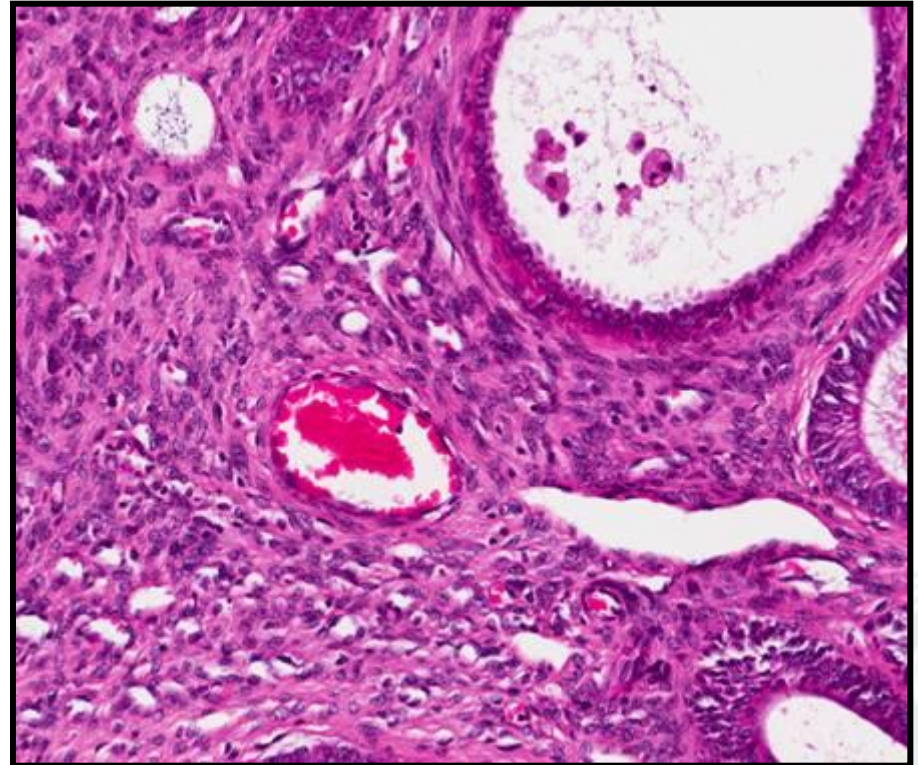
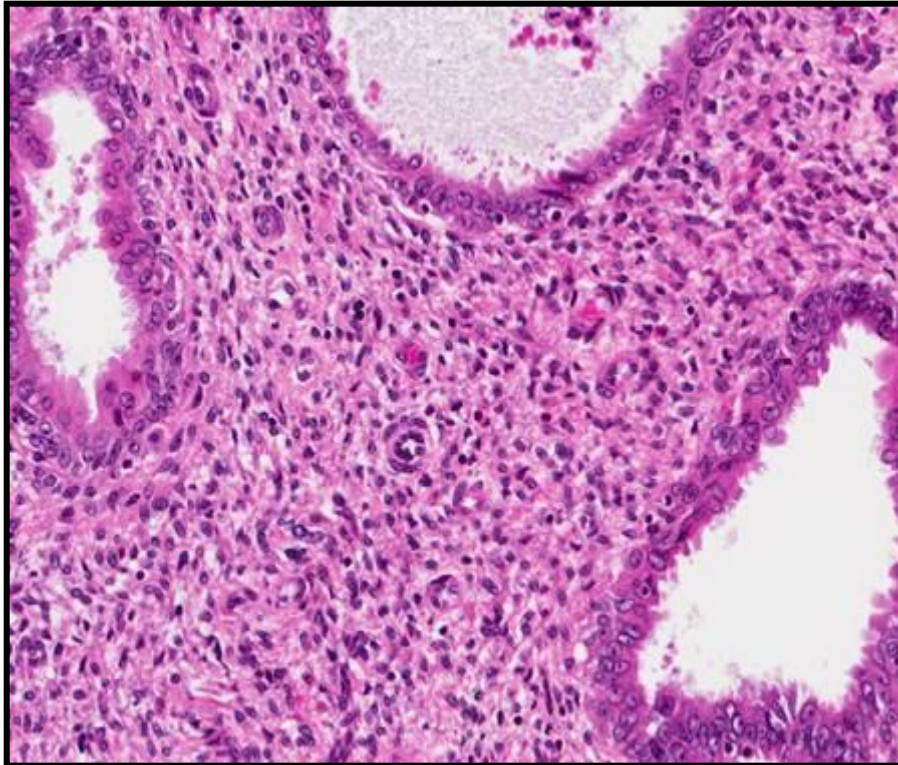


Extensive hyalinisation



Glandular differentiation

ESS with glandular differentiation

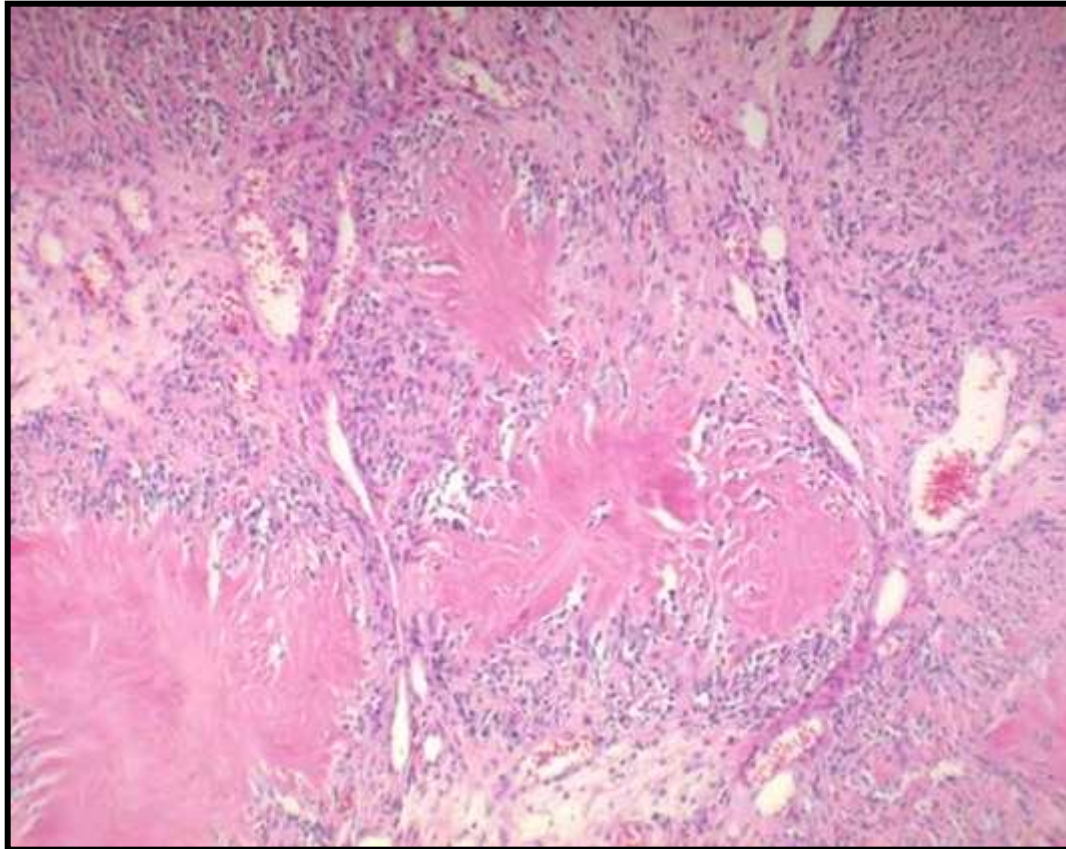


Marked stromal cellularity with familiar small calibre arterioles

ESS with glandular differentiation

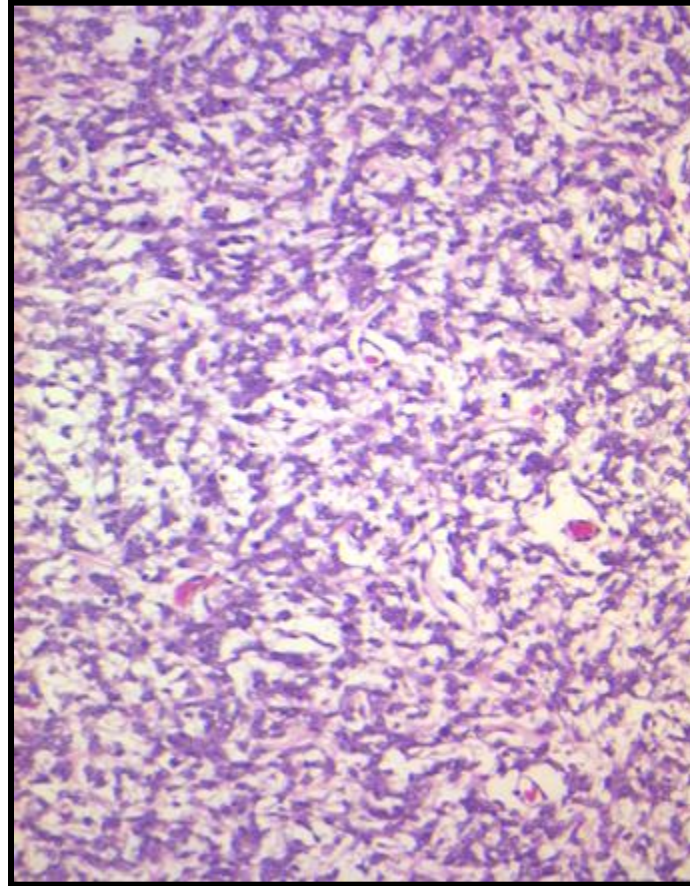
- Clement PB, Scully RE. Endometrial stromal sarcomas of the uterus with extensive endometrioid glandular differentiation: a report of three cases that caused problems in differential diagnosis. *Int J Gynecol Pathol.* 1992 Jul.;11(3):163–173.
- McCluggage WG, Ganesan R, Herrington CS. Endometrial stromal 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

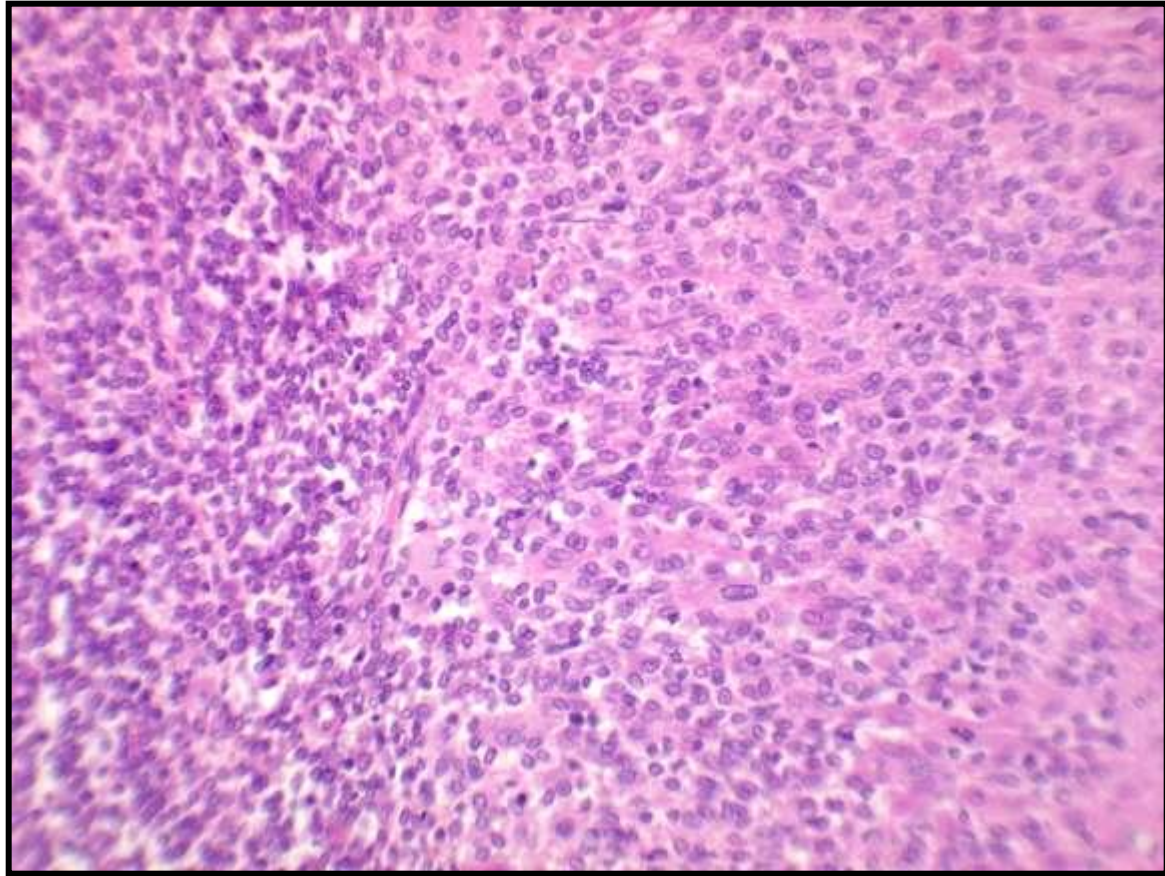


“star-burst” pattern of hyalinisation
suggests SM differentiation

Myxoid differentiation

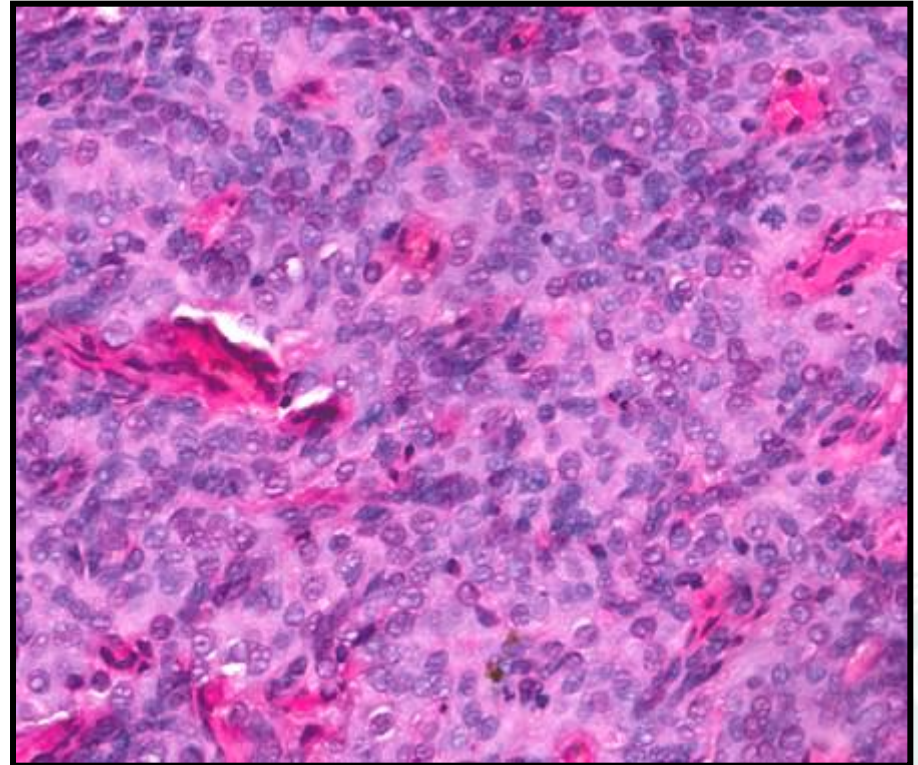
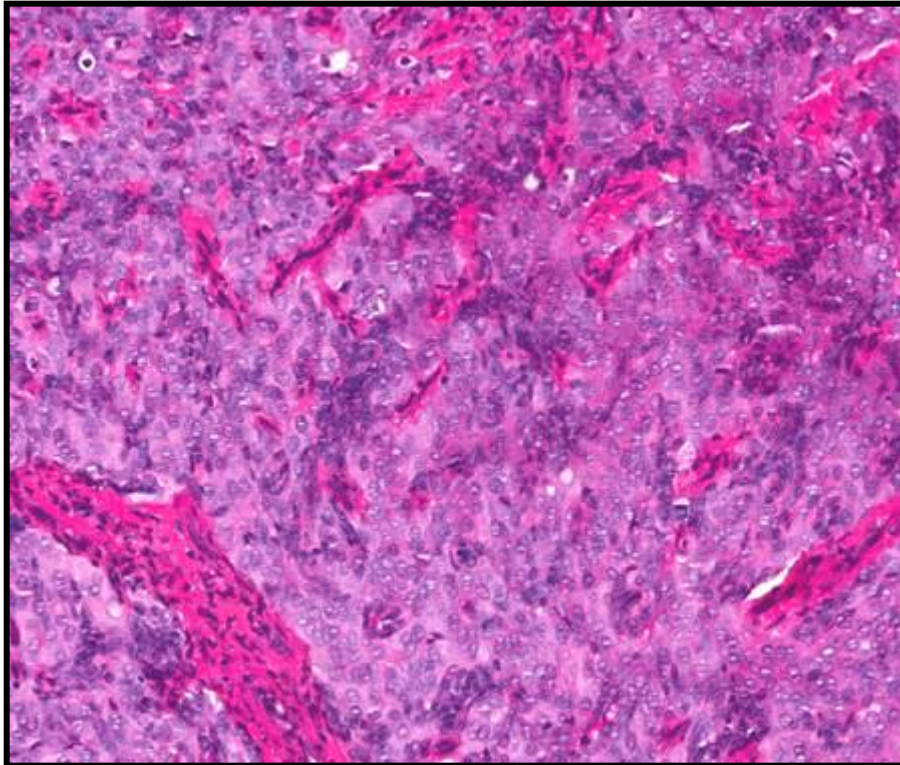


ESS with SM differentiation



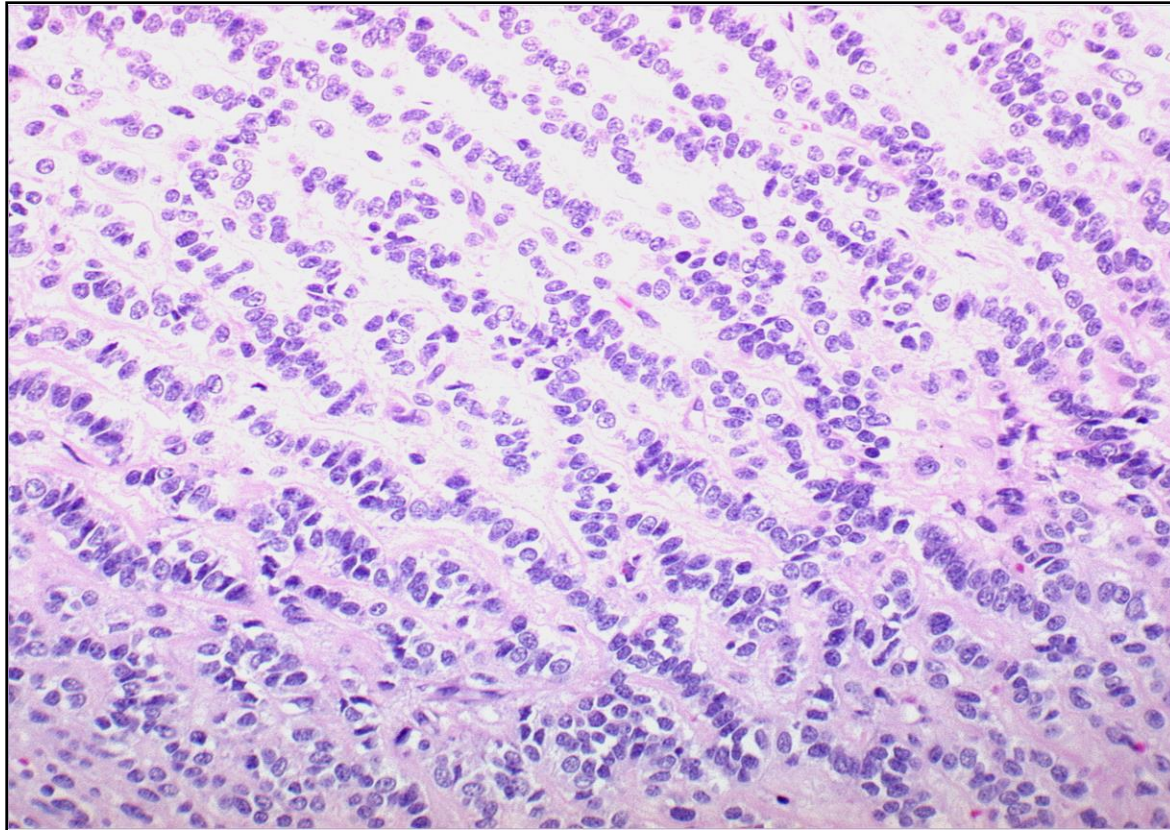
Dual cell population

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

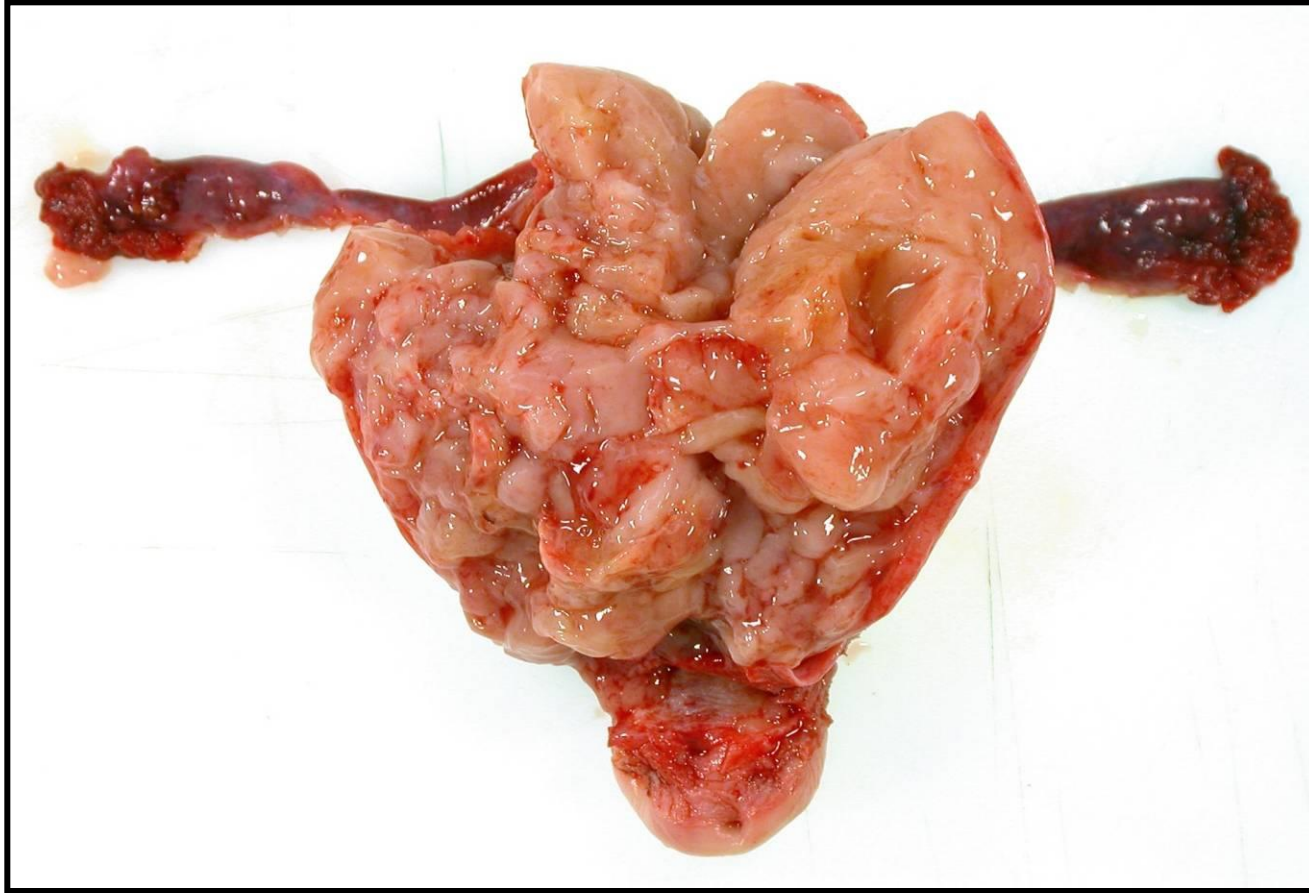
Cheng-Han Lee, MD, PhD,† Adrian Mariño-Enriquez, MD,* Wenbin Ou, PhD,* Meijun Zhu, PhD,* Rola H. Ali, MD,† Sarah Chiang, MD,‡ Frédéric Amant, MD,§ C. Blake Gilks, MD,† Matt van de Rijn, MD, PhD,|| Esther Oliva, MD,‡ Maria Debiec-Rychter, MD,¶ Paola Dal Cin, PhD,* Jonathan A. Fletcher, MD,* and Marisa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

Am J Surg Pathol 2012; 36, 641-653

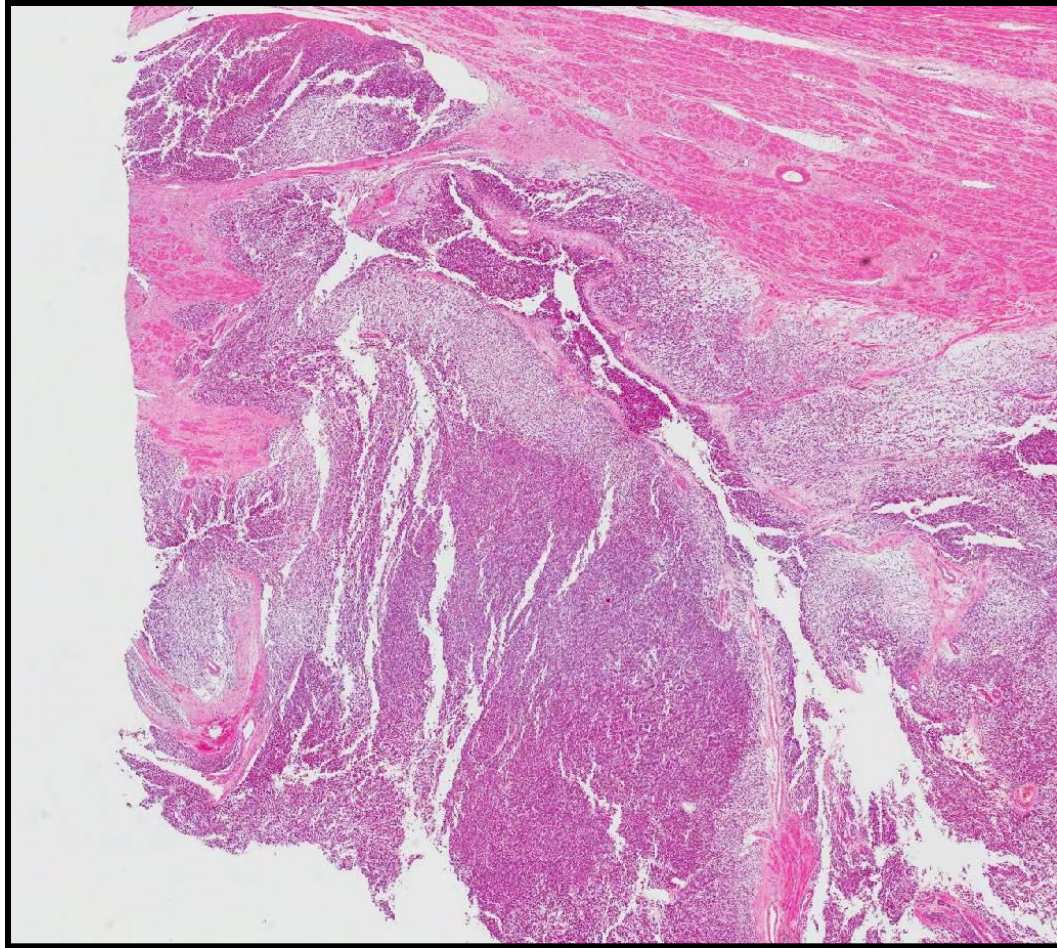
YWHAE-NUTM2 high grade ESS

- 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

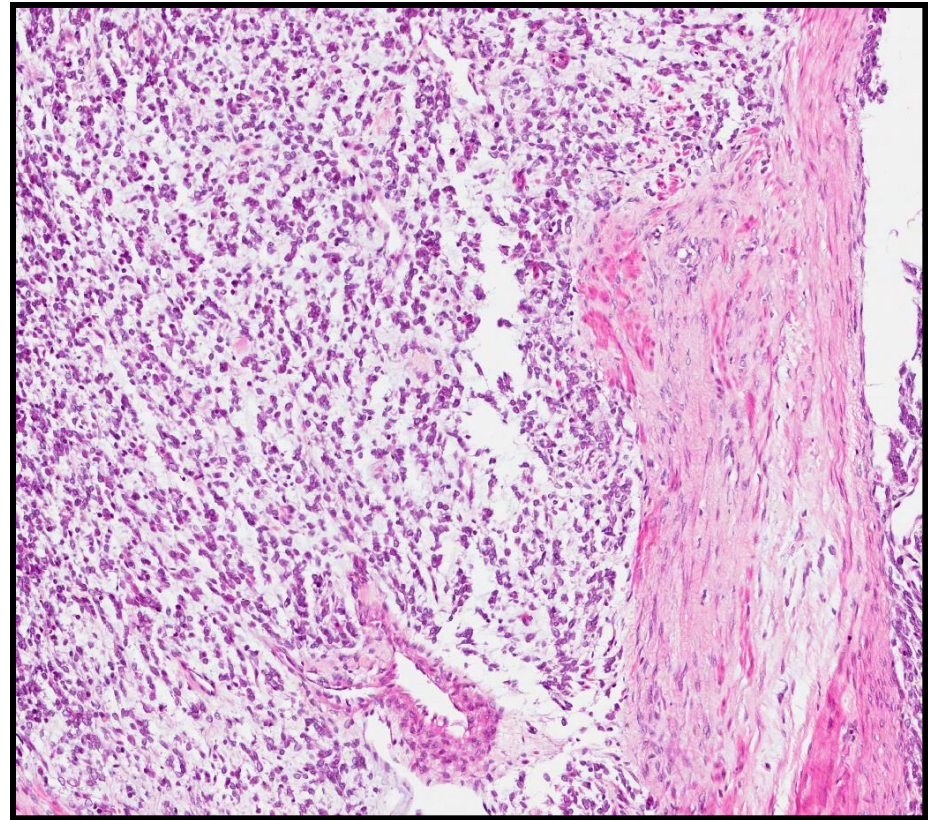
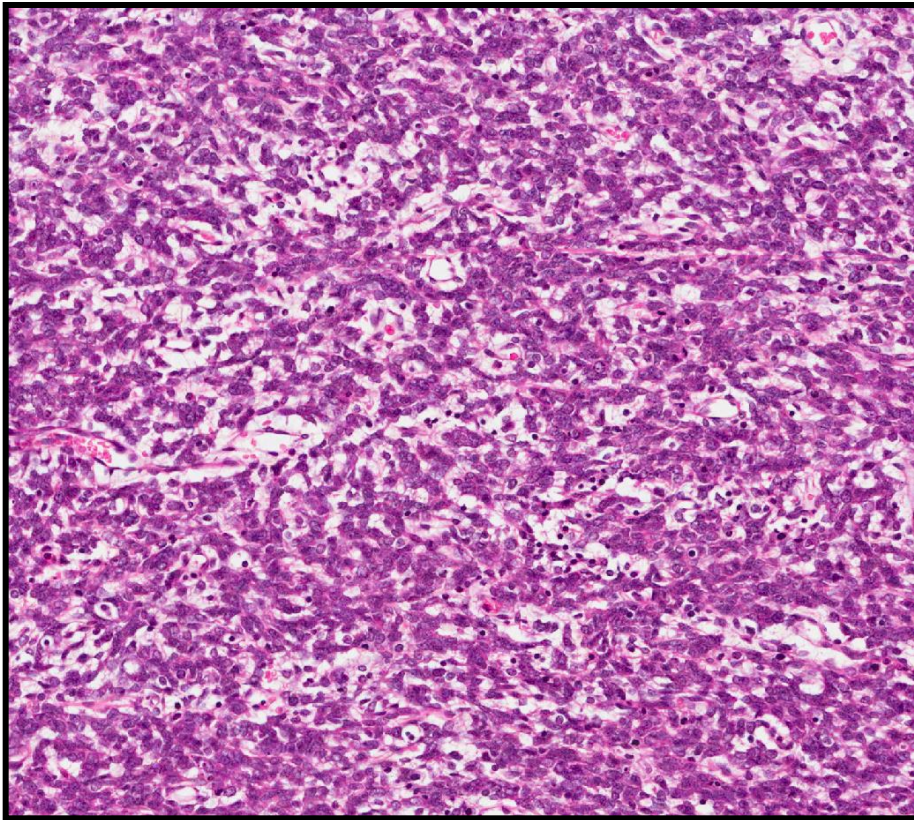
Gross appearance uterus



Histology : Variable cellularity

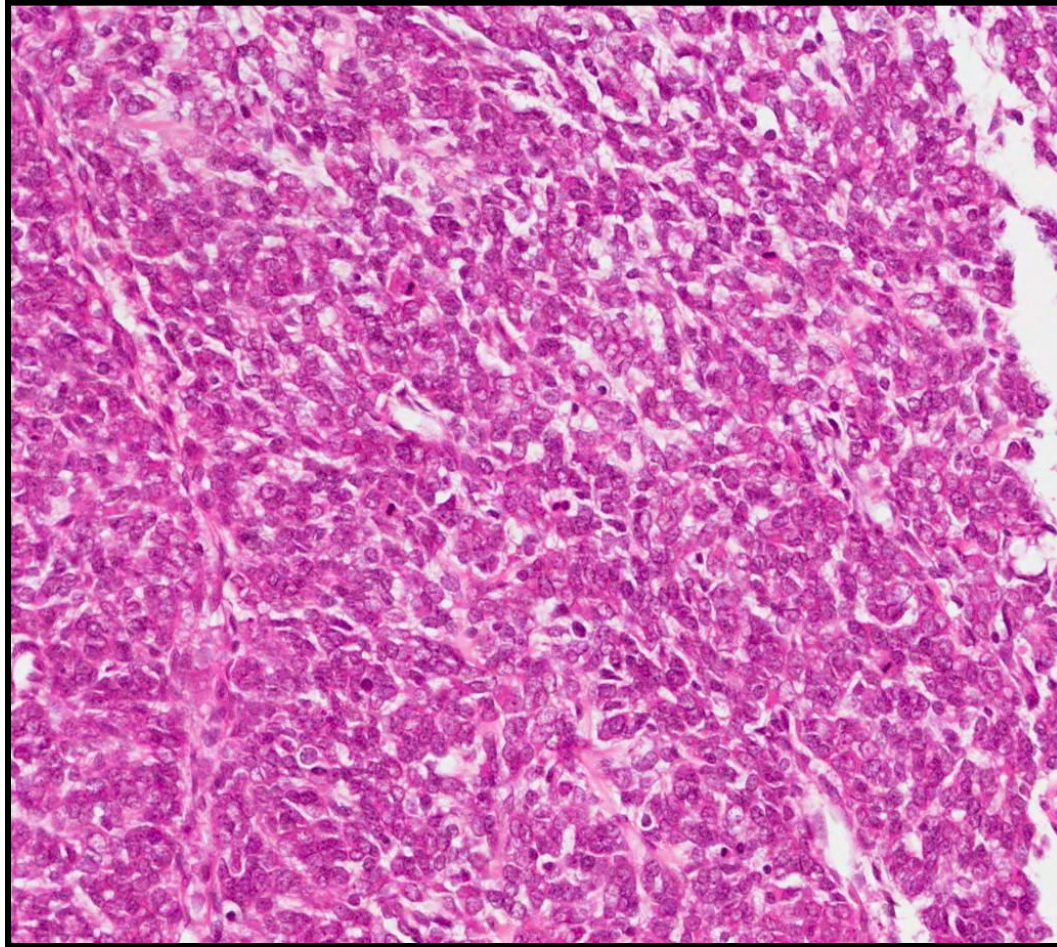


Dual cell population



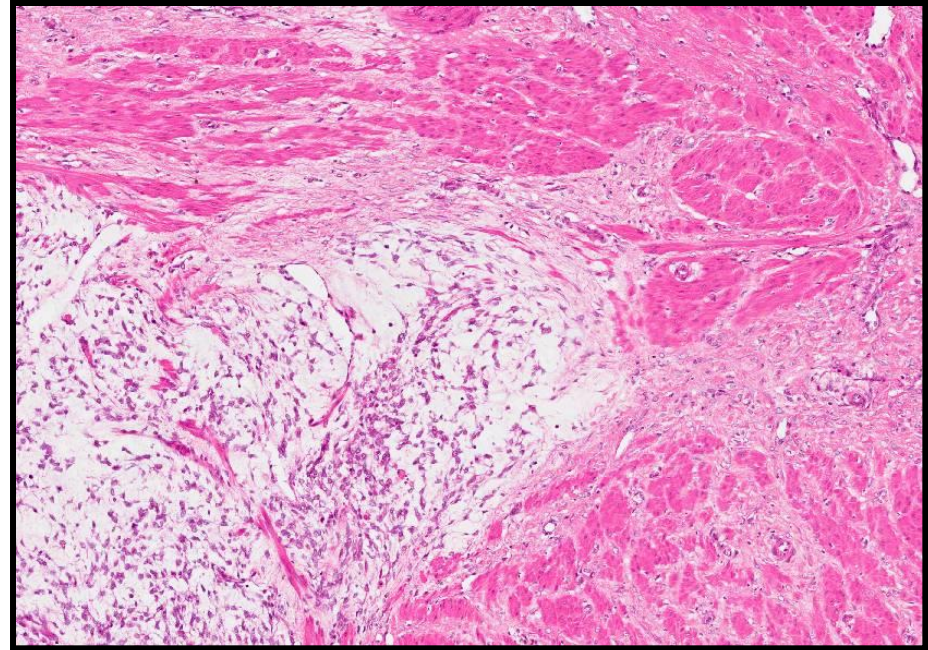
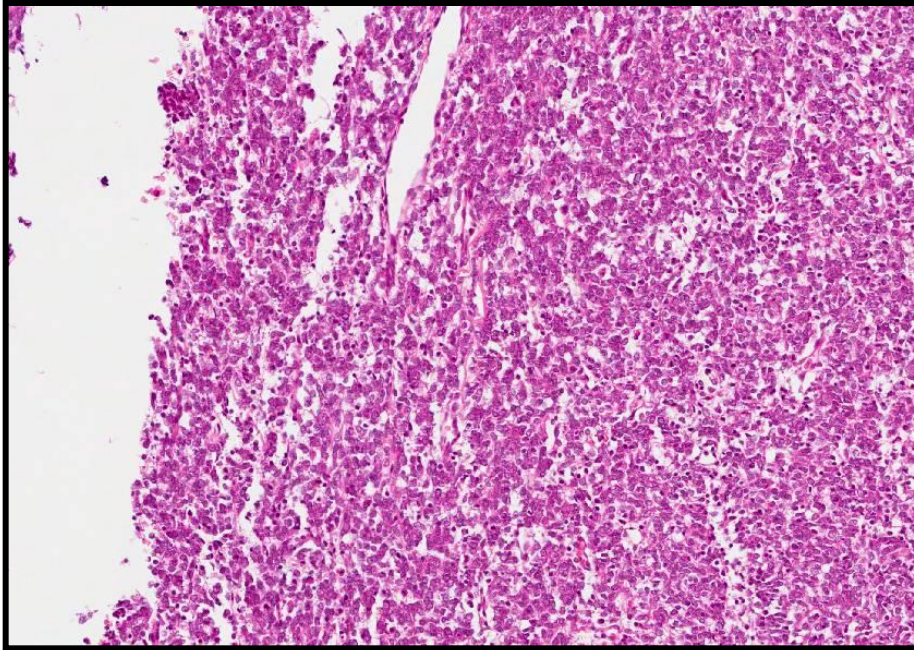
Rich vascular network comprising thin wall capillaries

Multiple mitoses (>10/10HPF)



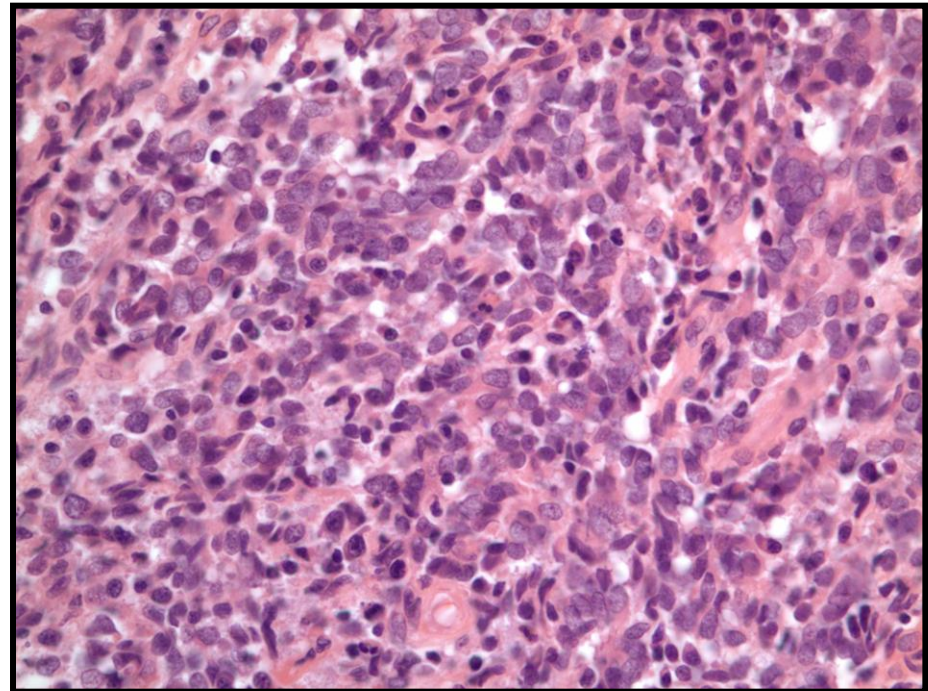
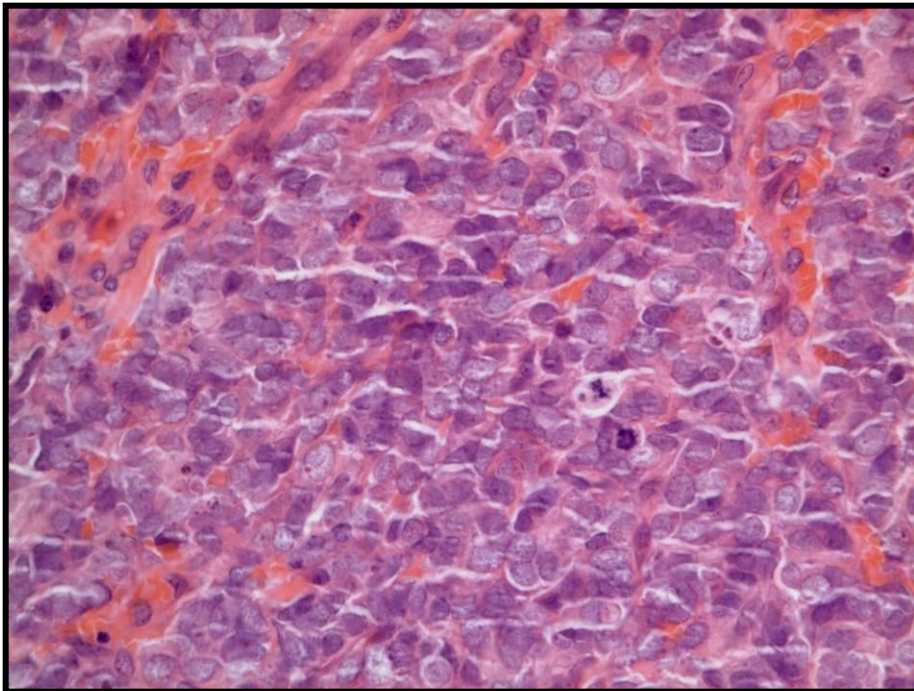
Irregular nuclear contours but non-pleomorphic

Myometrial infiltration



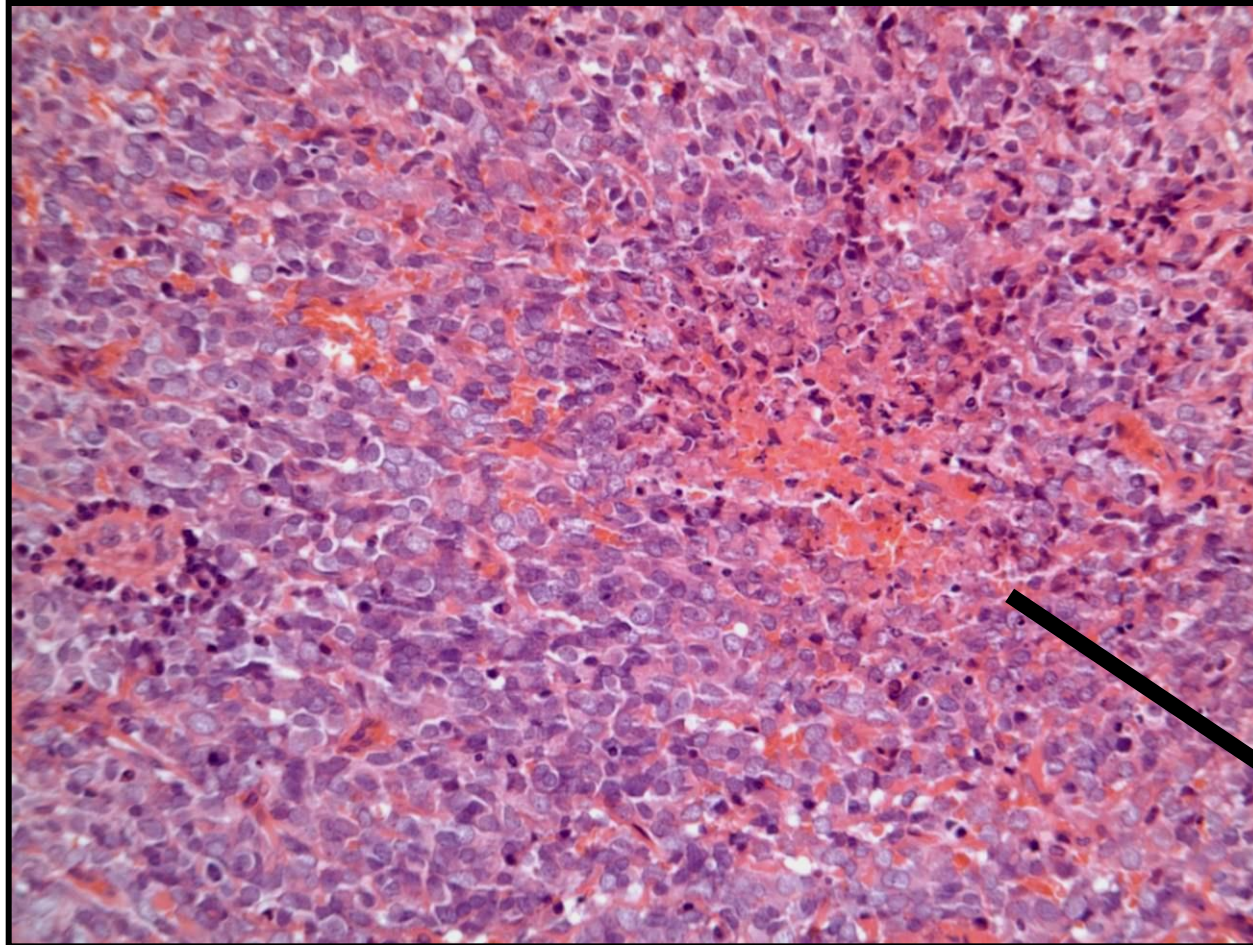
Fibromyxoid where tumour permeates myometrium

Cells with round nuclei



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

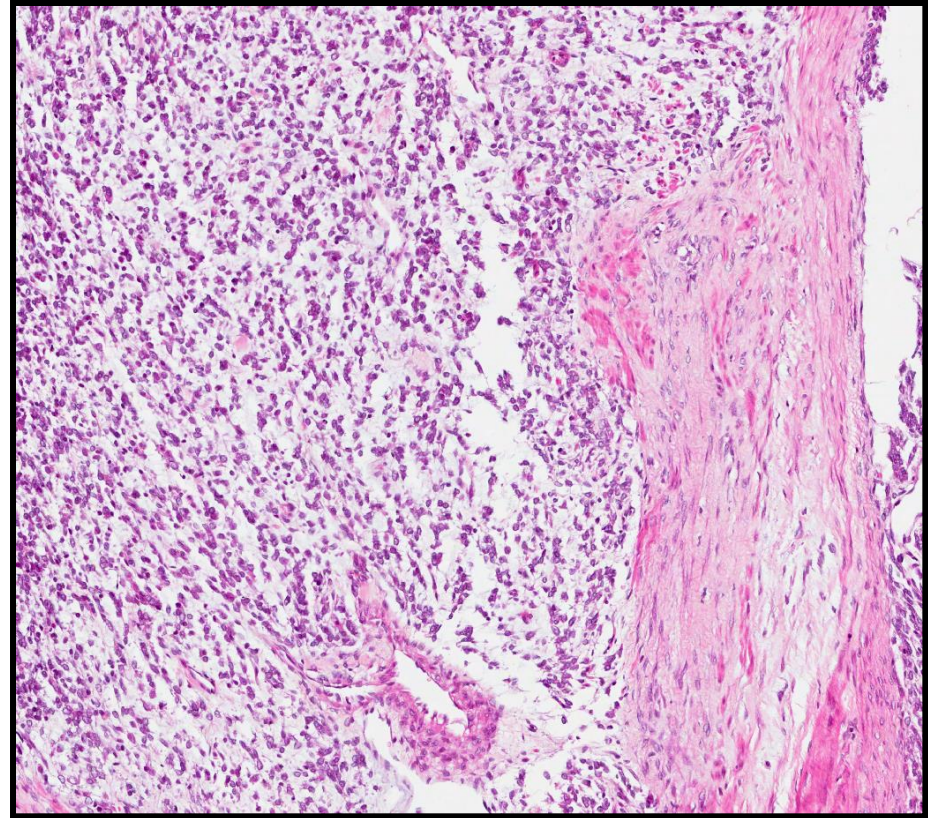
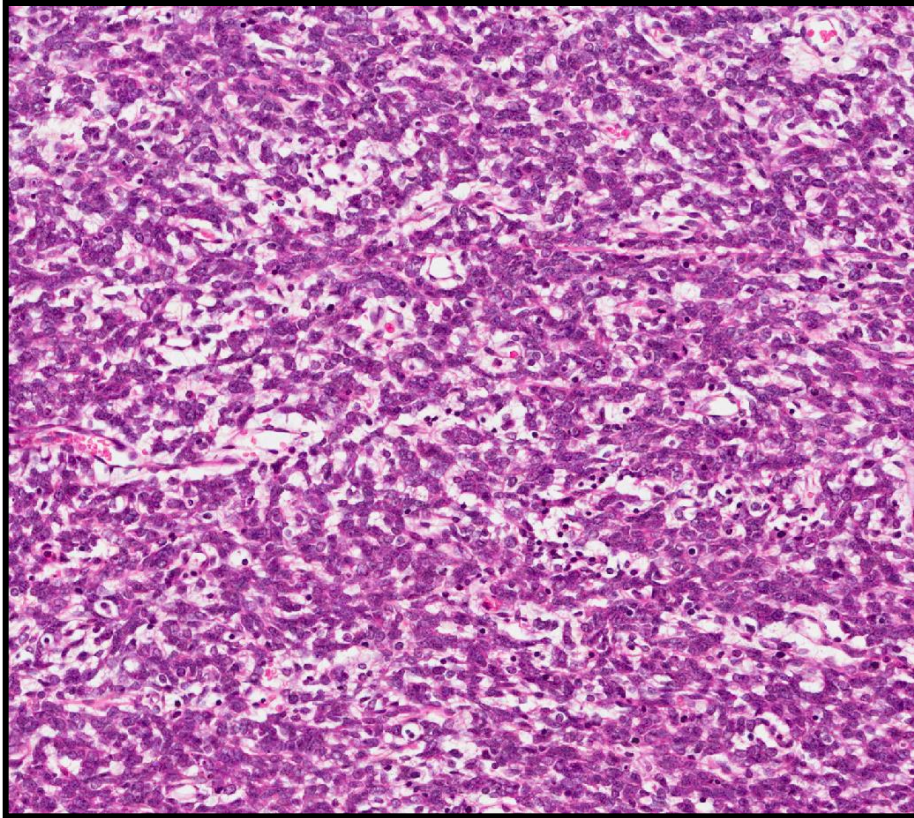
YWHAE-NUTM2 HG-ESS



→ Focal
necrosis

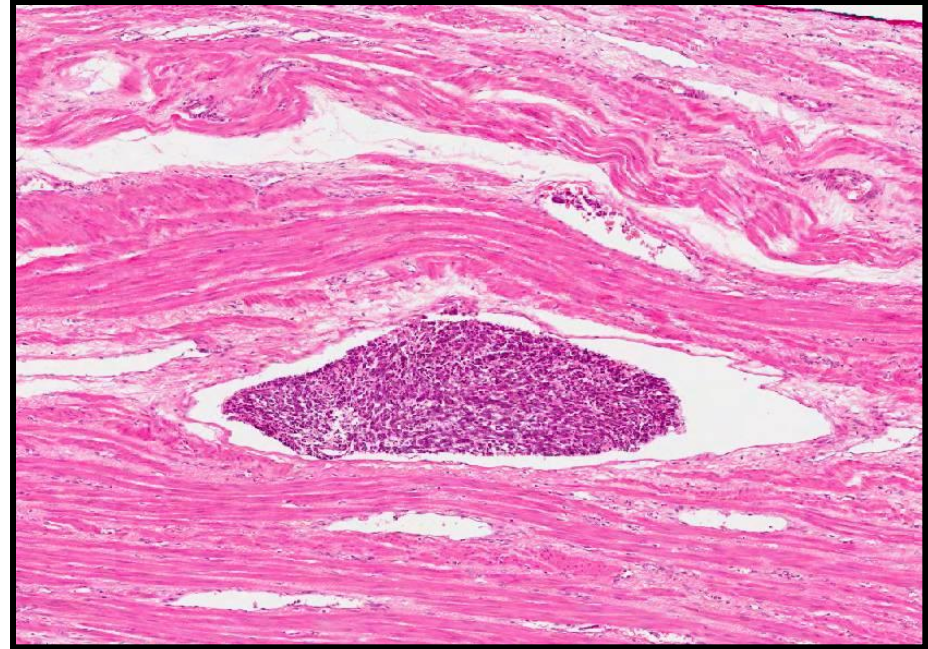
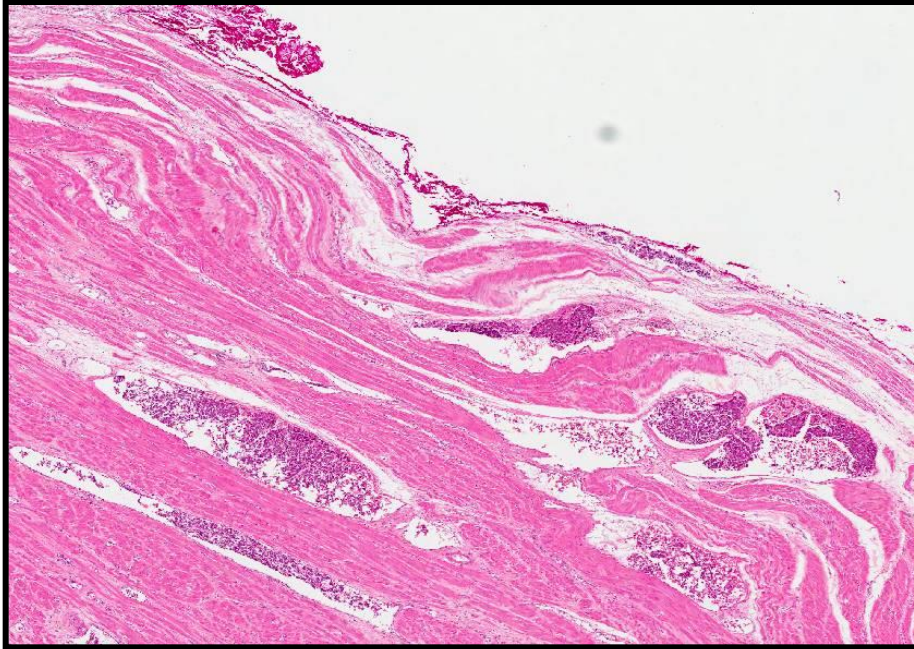
Small round blue cell tumour

Dual cell population



Rich vascular network comprising thin wall capillaries

Vascular permeation

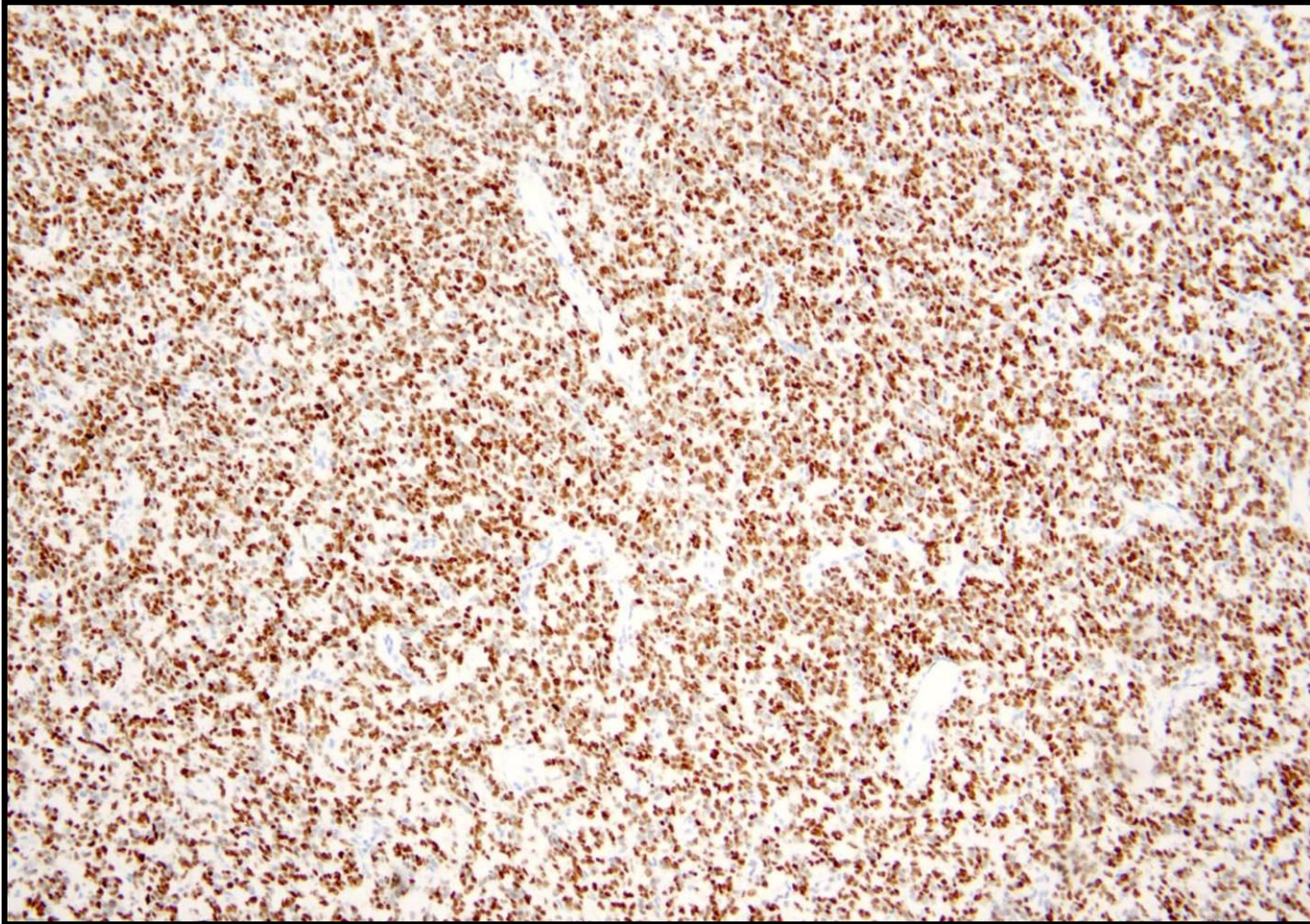


Cyclin D1 as a Diagnostic Immunomarker for Endometrial Stromal Sarcoma With *YWHAE-FAM22* Rearrangement

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

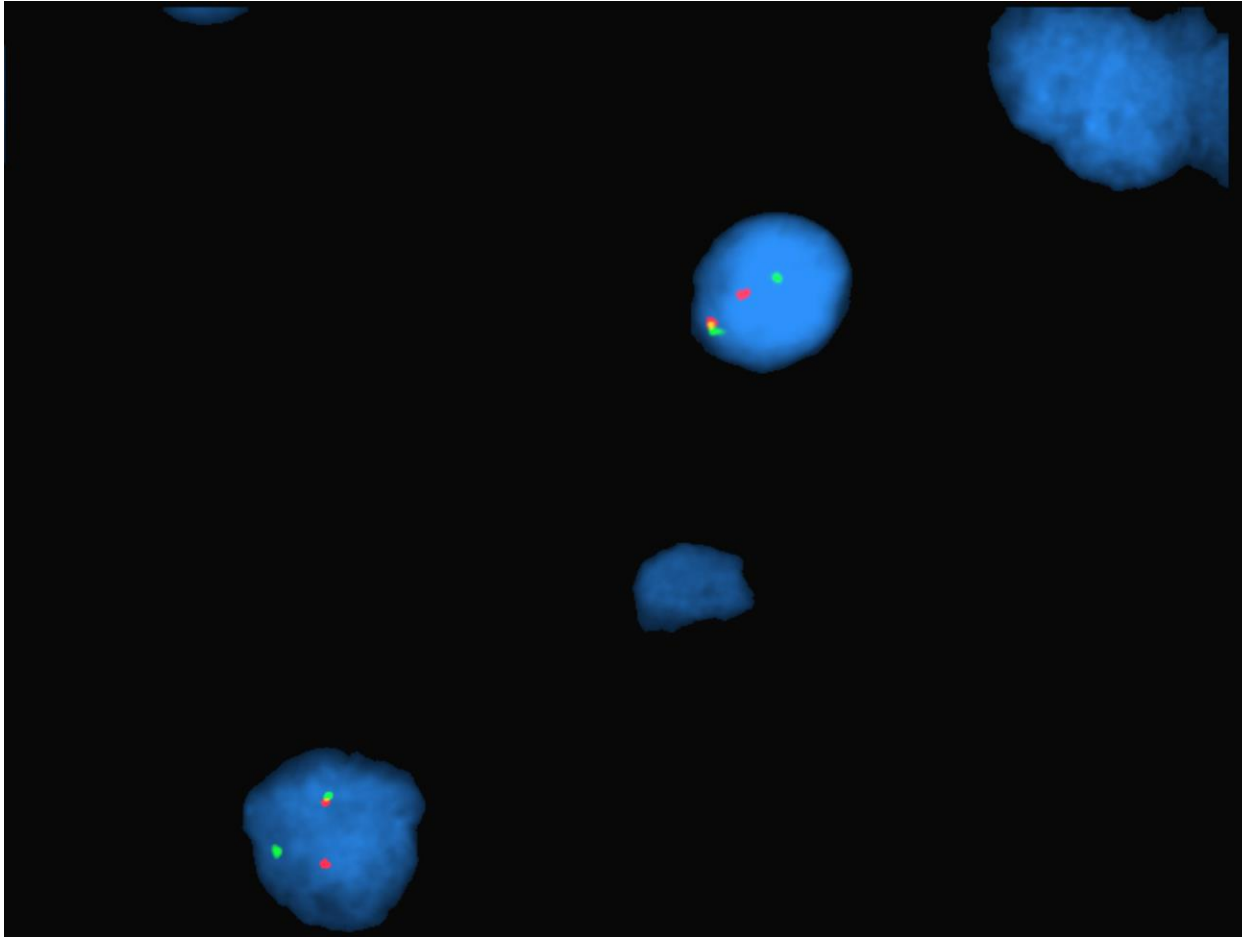


Courtesy Dr Esther Oliva

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)

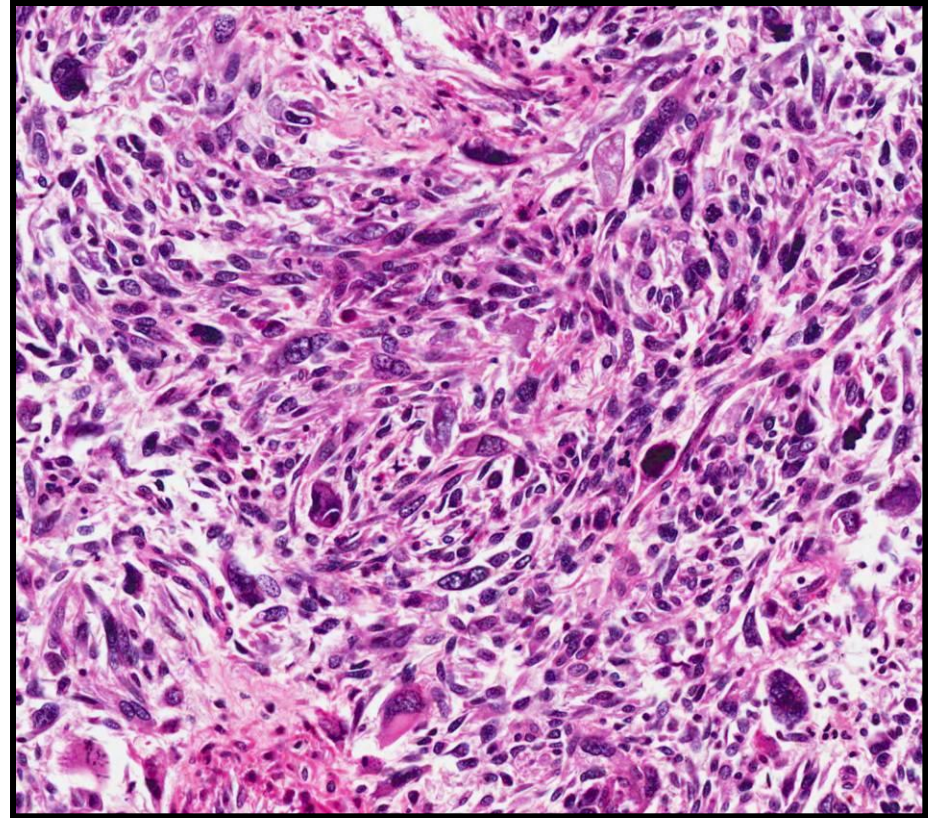
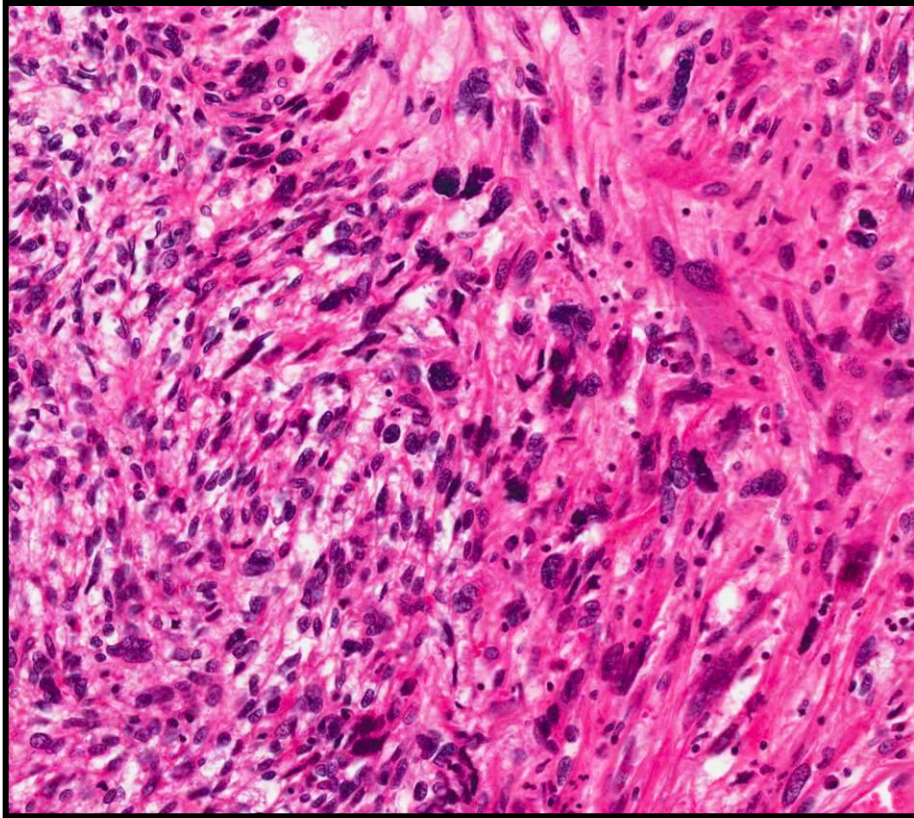
- Why replace UES with UUS?
- Not all UES arise from the endometrium WHO 2014 acknowledges this
- More accurate terminology UUS
- No specific lines of mesenchymal differentiation
- **Diagnosis of exclusion**

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

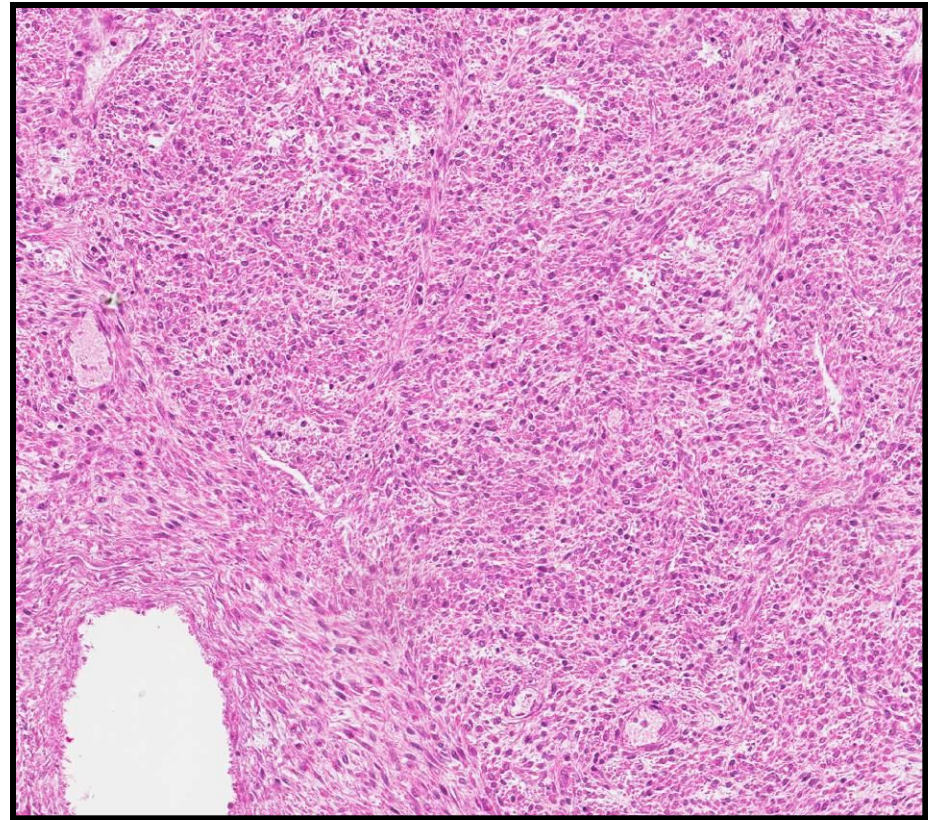
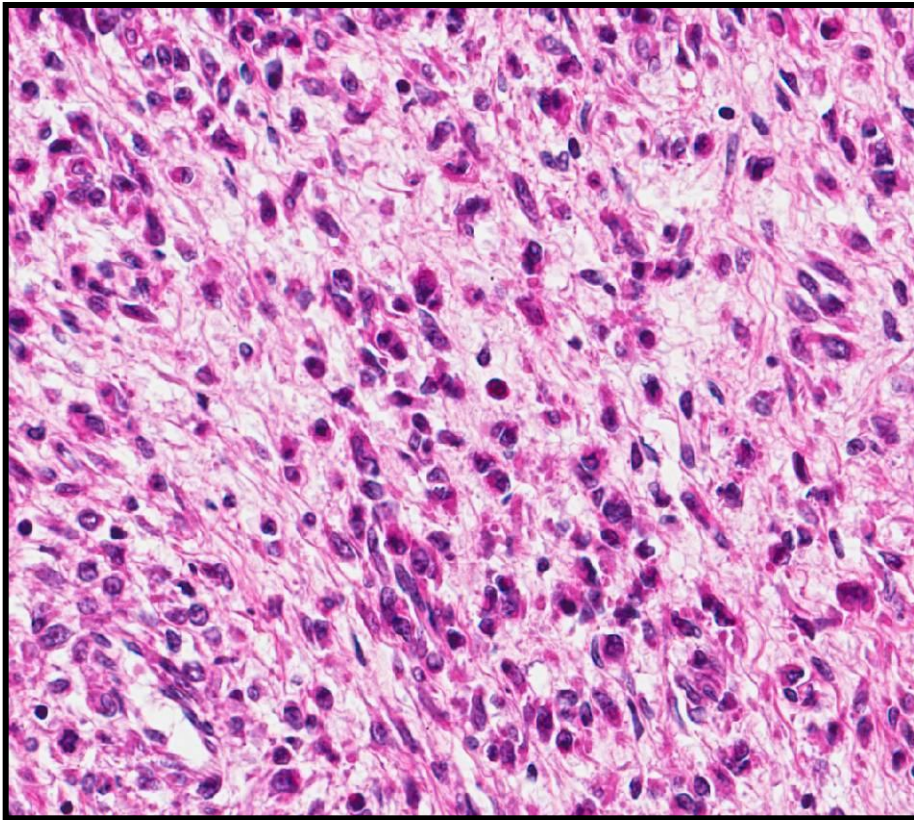
Subset of UUS harbour missense TP53 mutations

DDx leiomyosarcoma



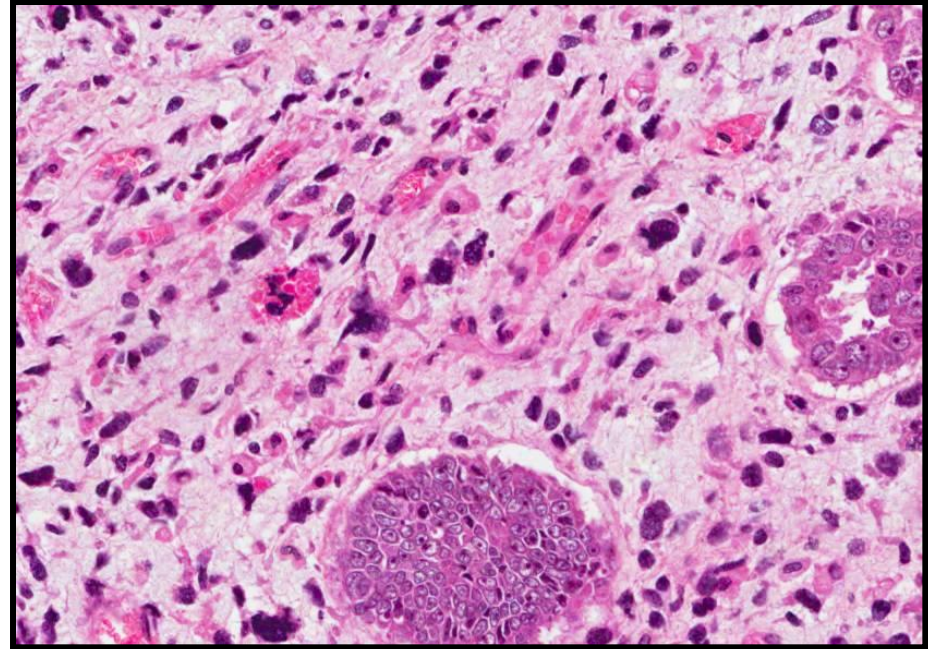
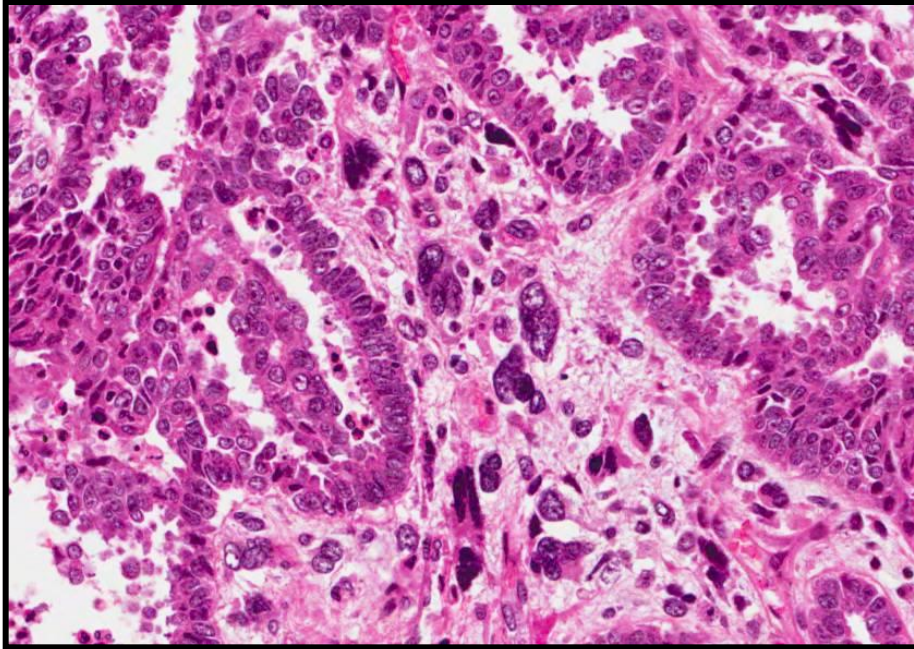
Marked diffuse cytologic atypia

DDx Leiomyosarcoma



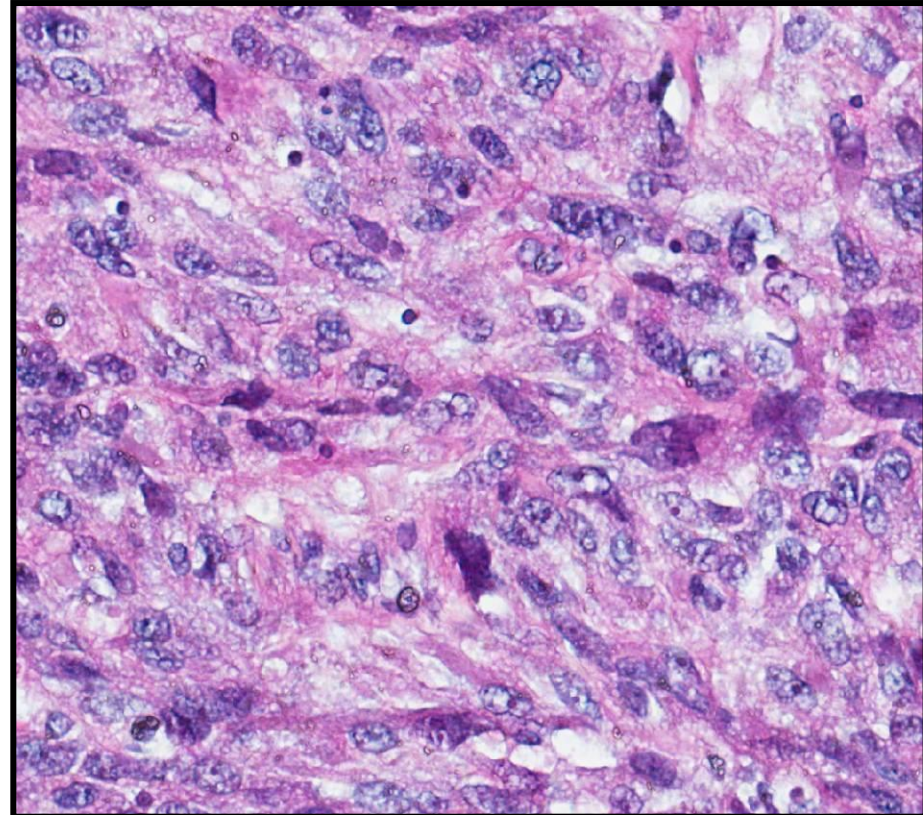
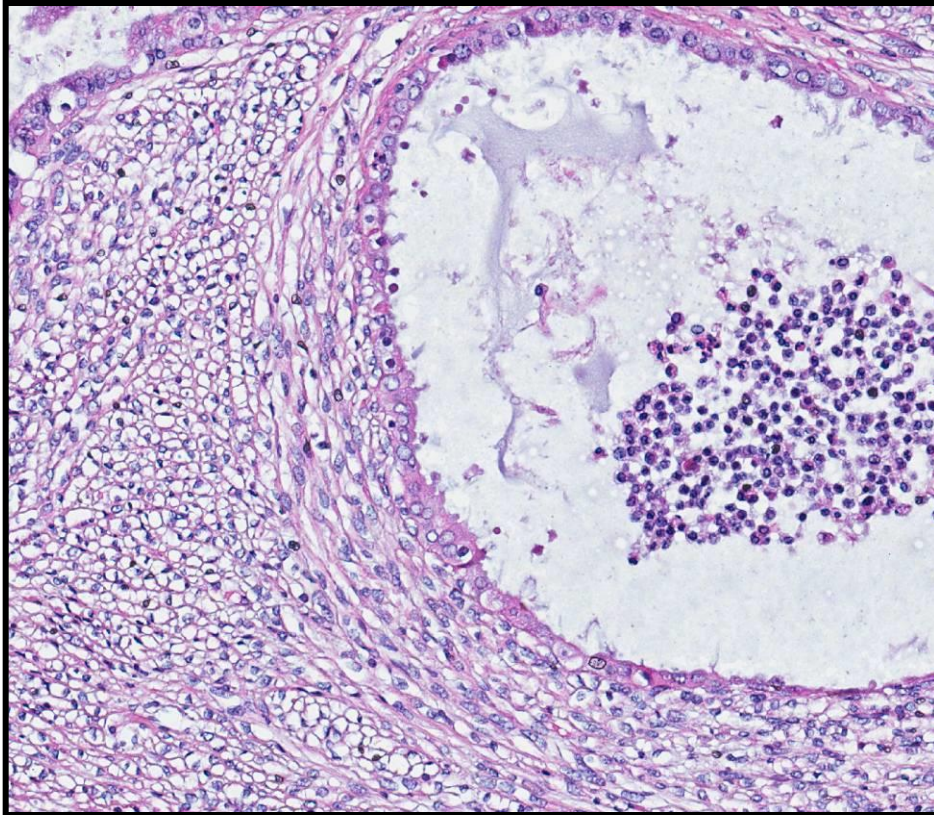
Increased cellularity, coagulative necrosis with ghost outlines of cells

DDx Carcinosarcoma

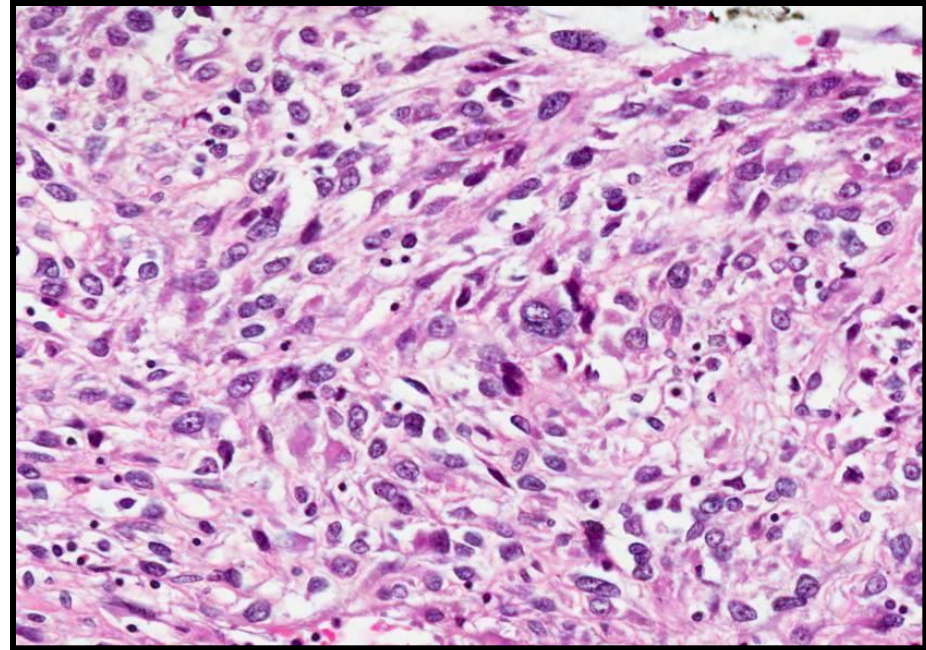
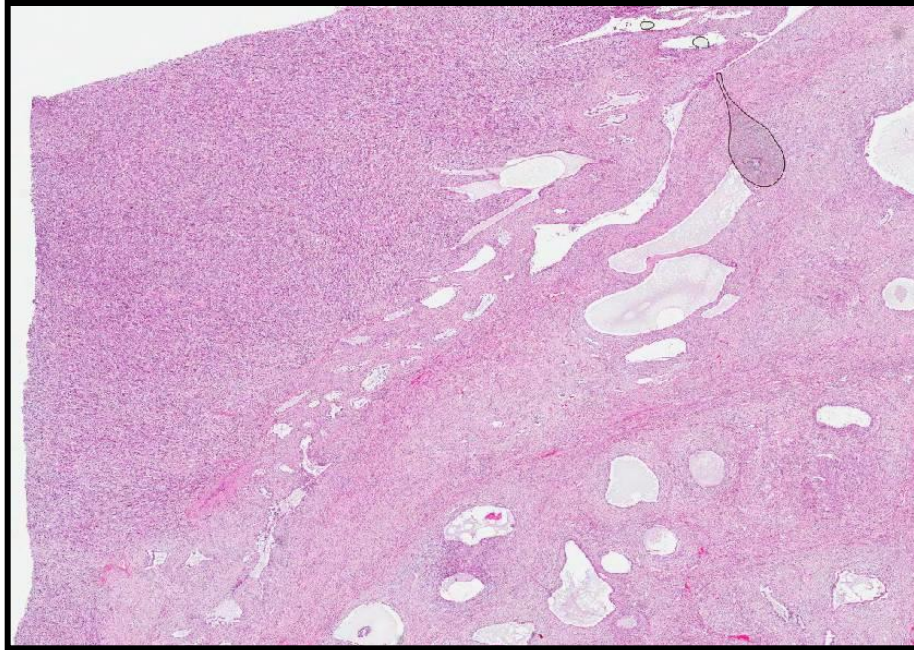


With rhabdomyoblasts-heterologous differentiation

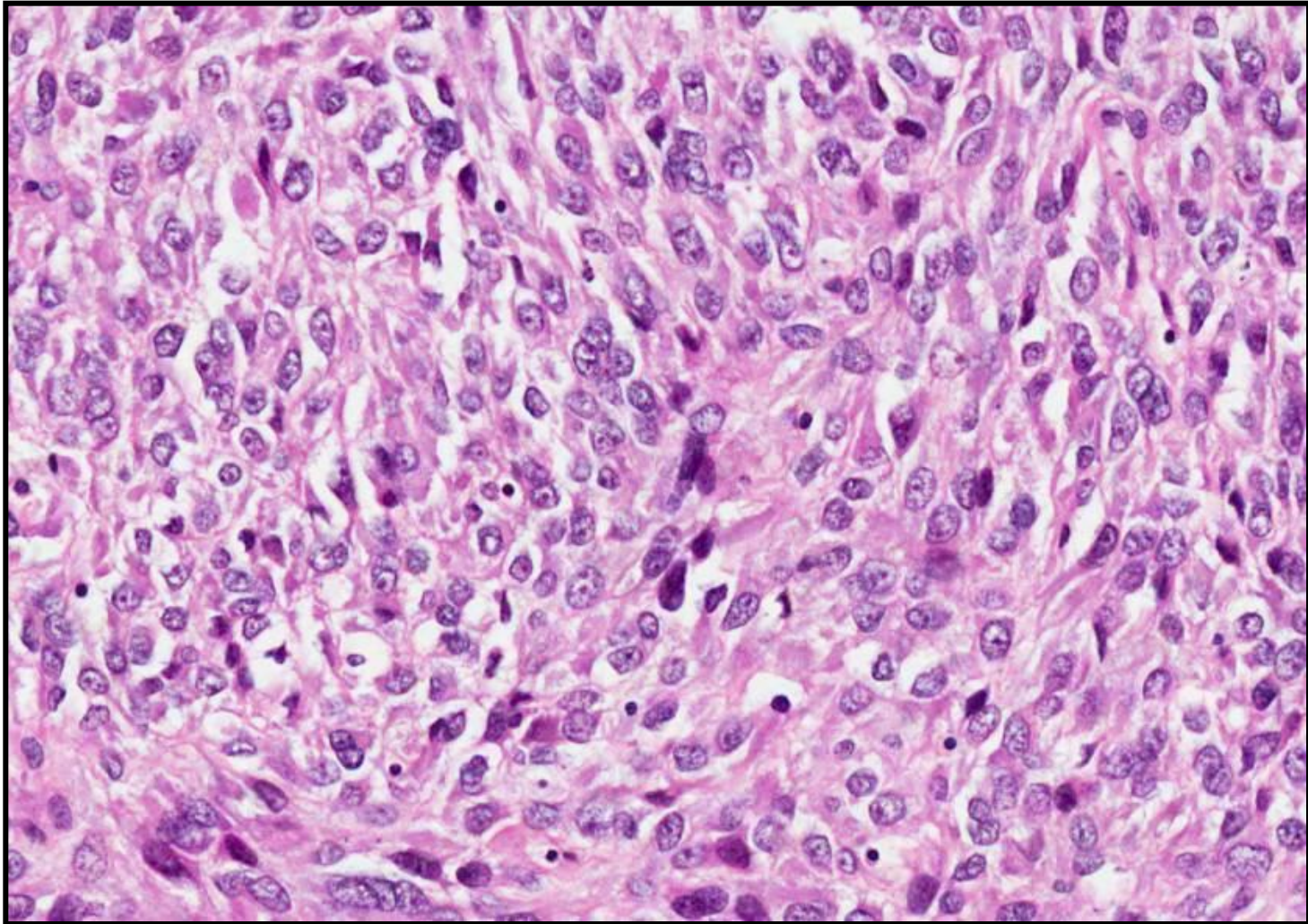
DDx : Adenosarcoma with sarcomatous overgrowth



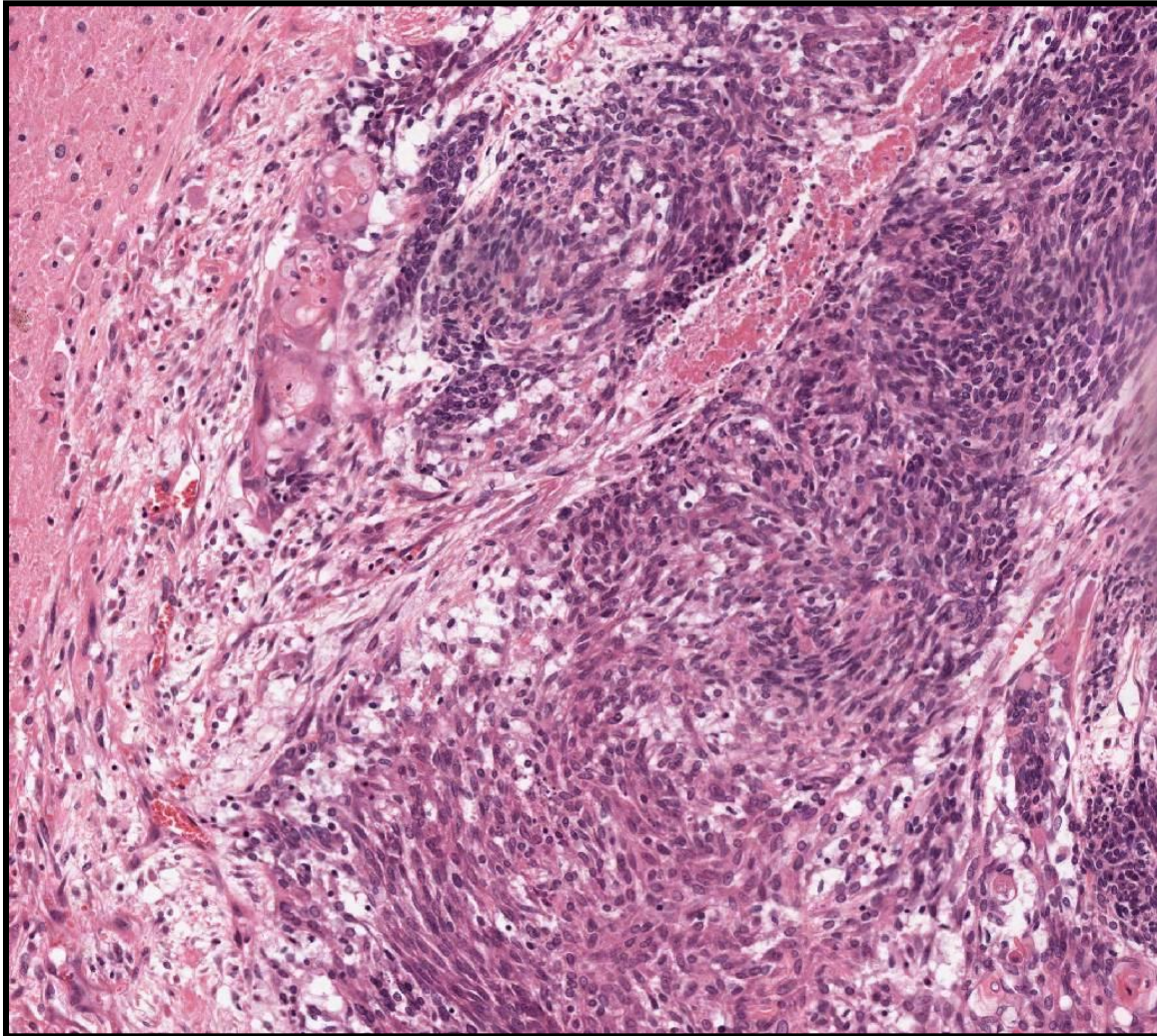
Adenosarcoma with sarcomatous overgrowth



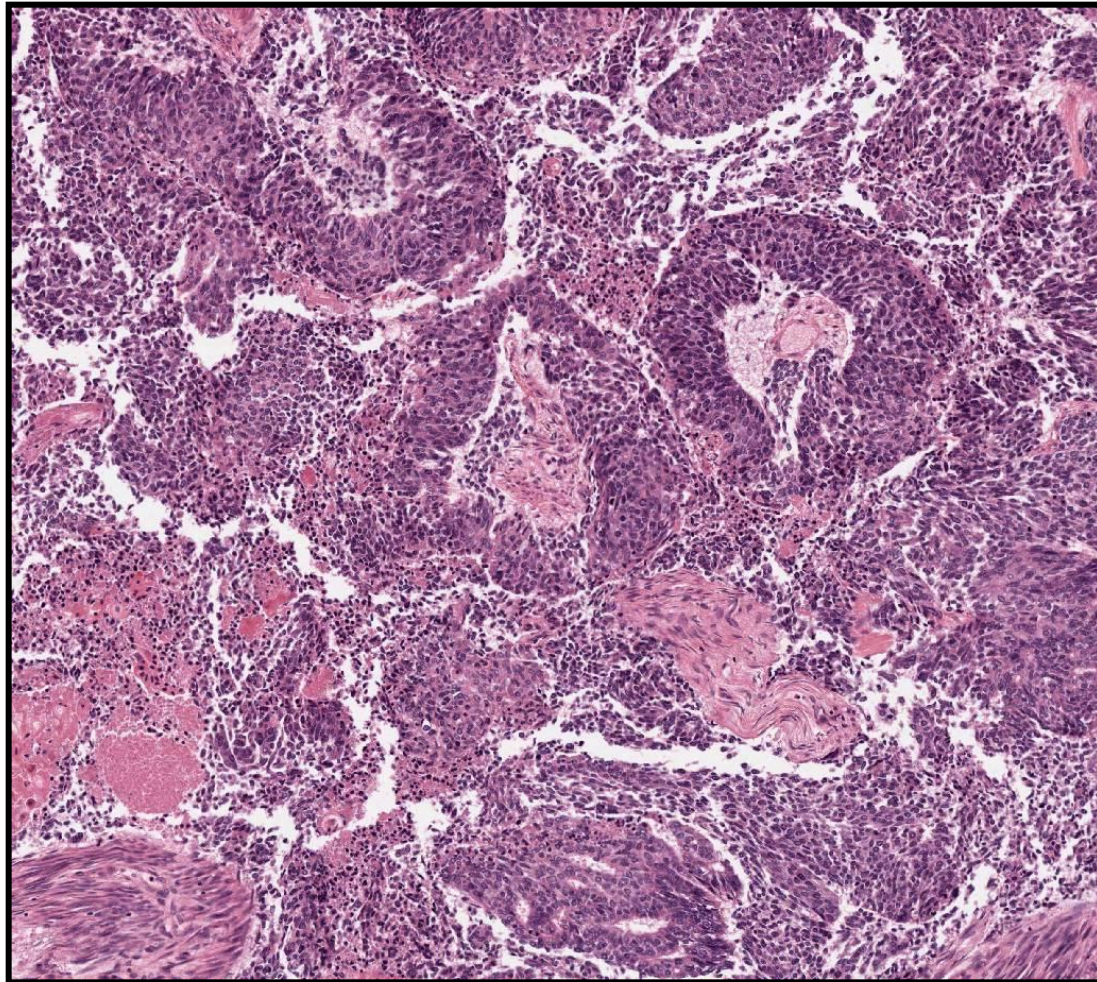
Sarcomatous overgrowth in adenosarcoma



DDx Undifferentiated carcinoma



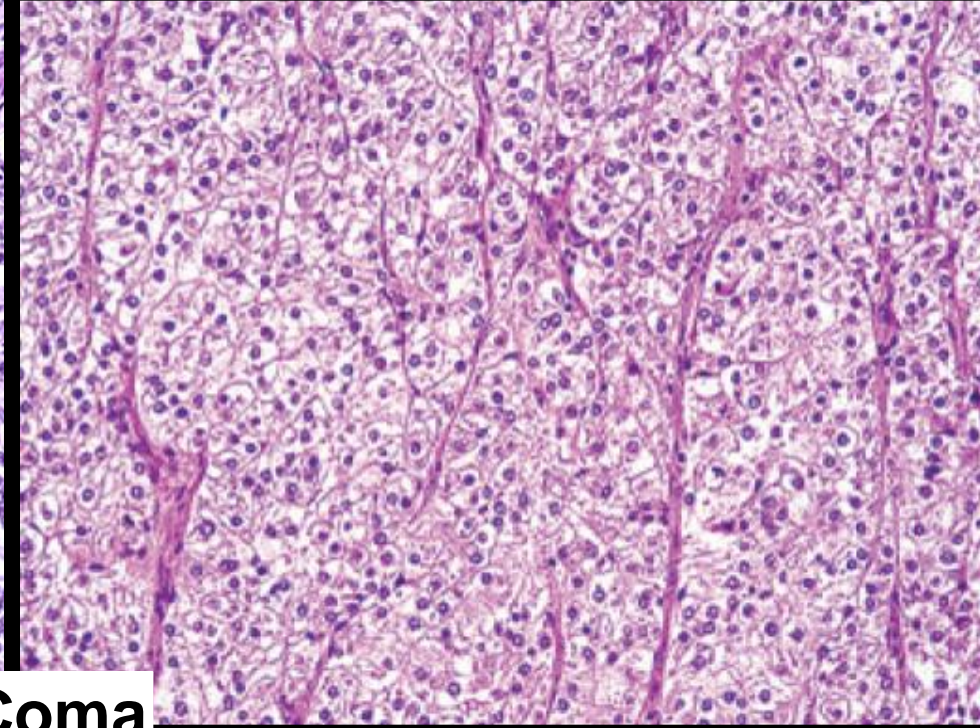
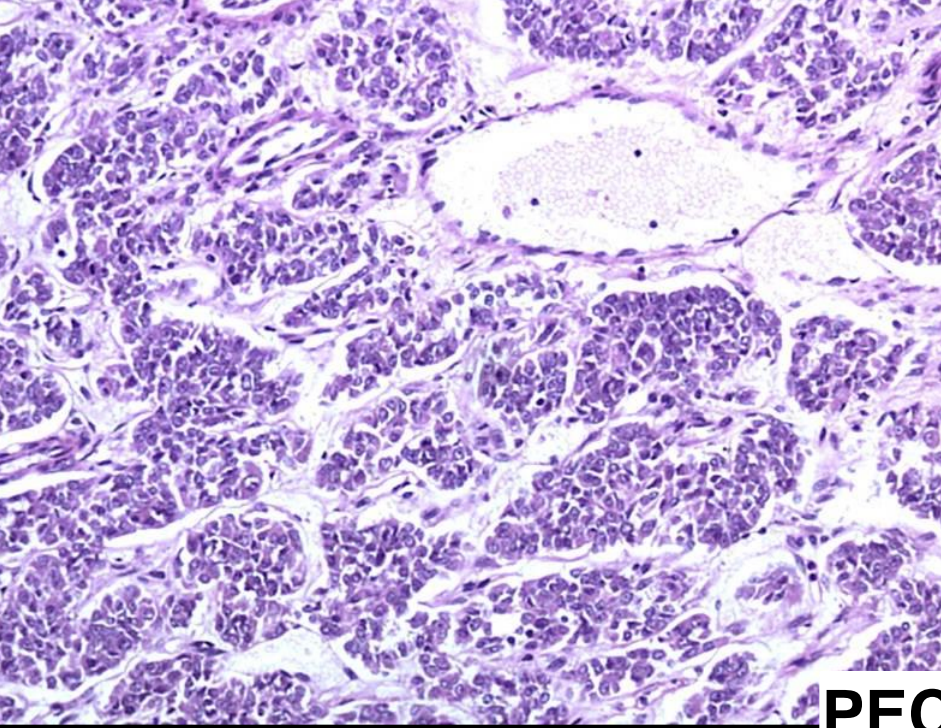
DDx Undifferentiated carcinoma



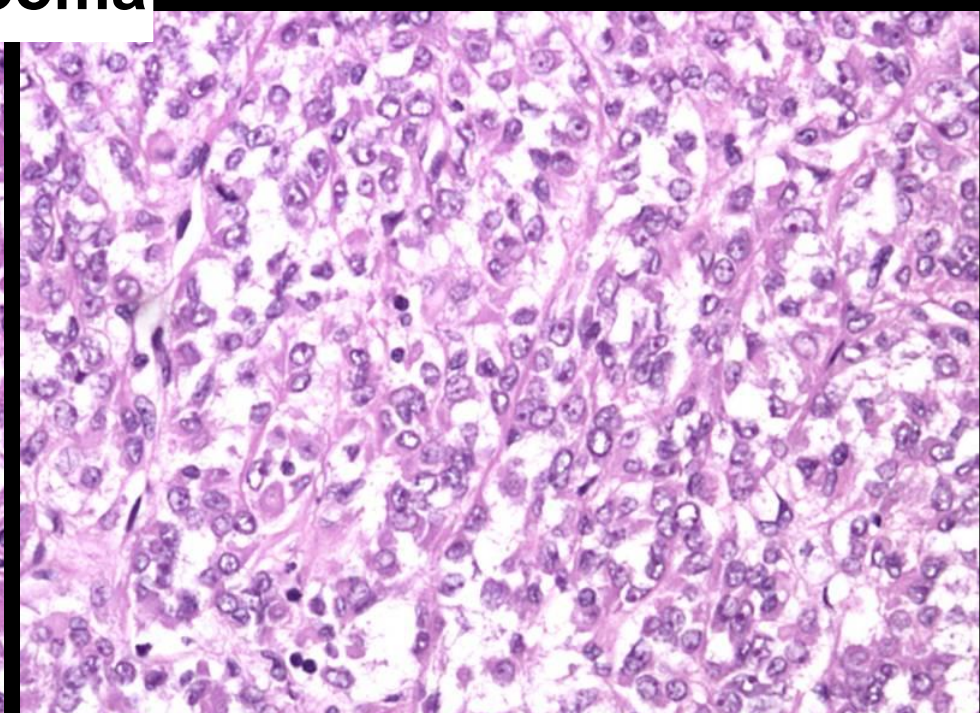
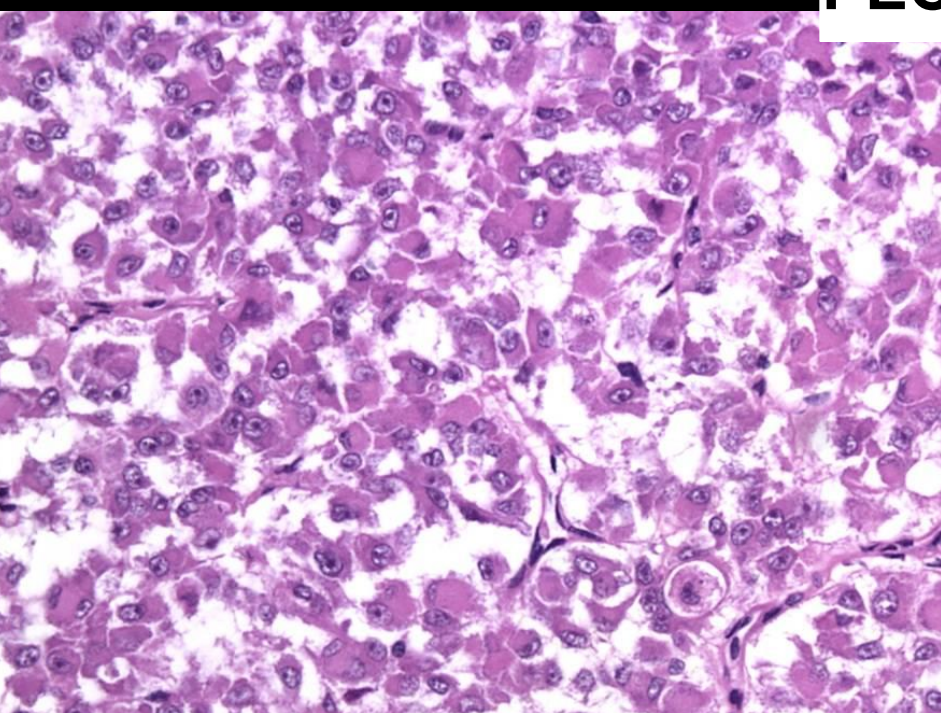
Loss of MMR proteins may be seen

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

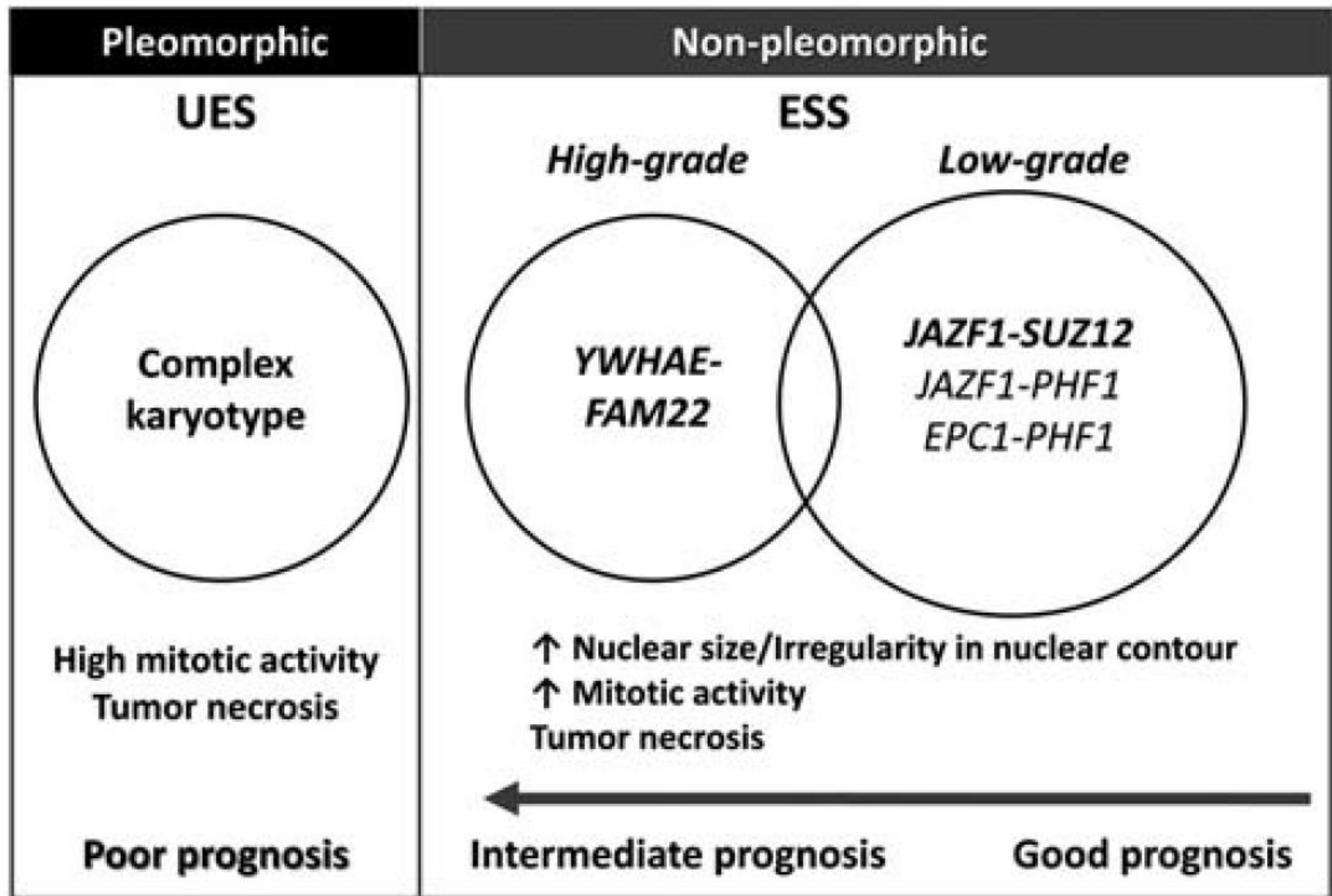


FIGURE 7. Proposed classification for pure uterine sarcomas.

Staging LMS and ESS

FIGO staging for uterine sarcomas (2009).

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

(1) Leiomyosarcomas and endometrial stromal sarcomas^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.

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?

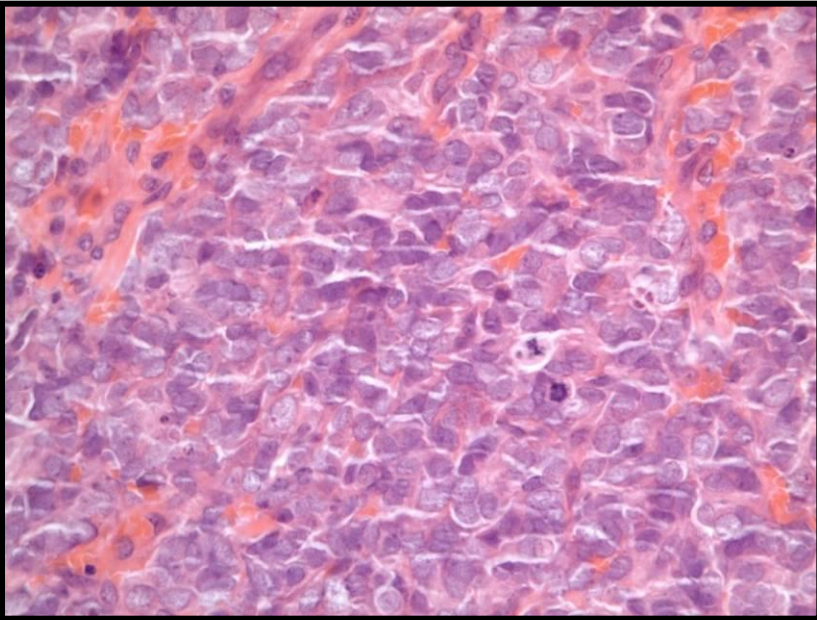
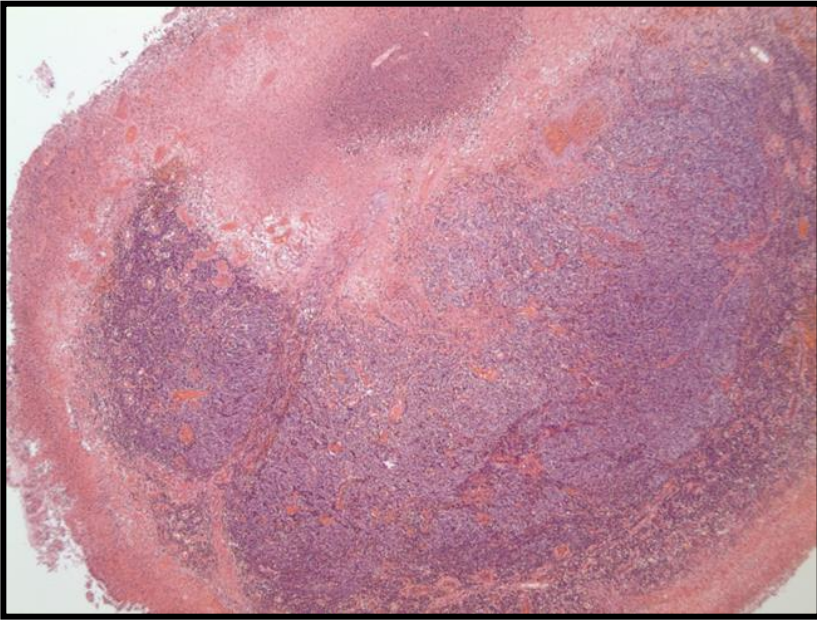
- Low grade ESS (JAZF1 LGESS or ESS without demonstrable genetic arrangement) – FISH or RT-PCR for genetic fusions
- Uterine leiomyoma with intravascular leiomyomatosis
- Note unlikely to be HGESS no documentation of associated smooth muscle differentiation with YWHAE-NUTM2 ESS

De-differentiated ESS

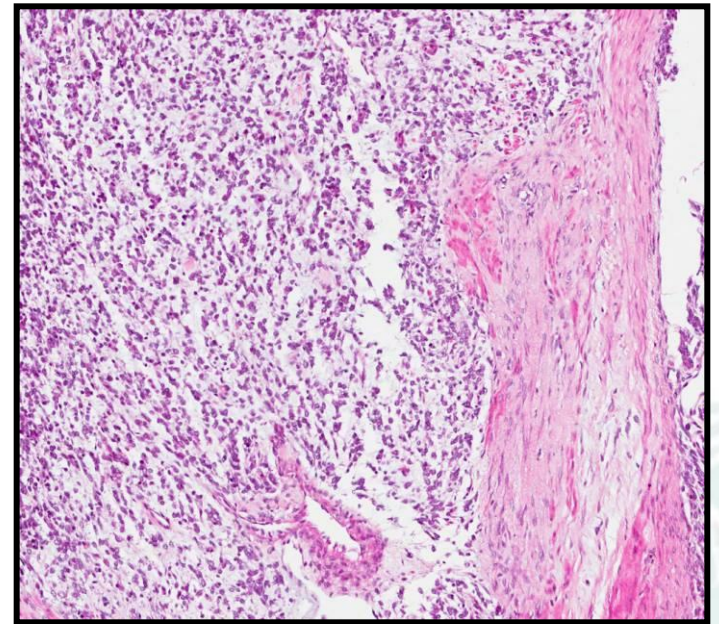
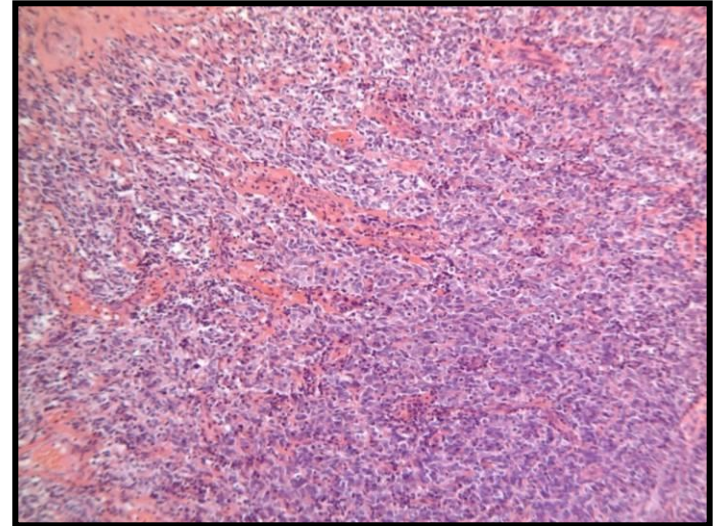
- Biphasic tumour
 - Monomorphic low grade component (ovoid cells)
 - High grade component (round cells)
- De-differentiated ESS (lacks cyclin D1 positivity)
 - Unlike YWHAE- NUTM2 ESS

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

