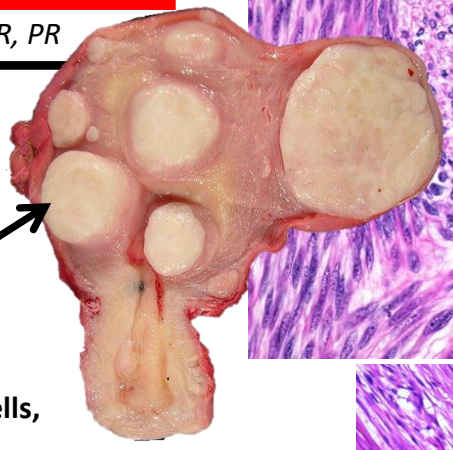
Prepared by Dr. Kurt Schaberg

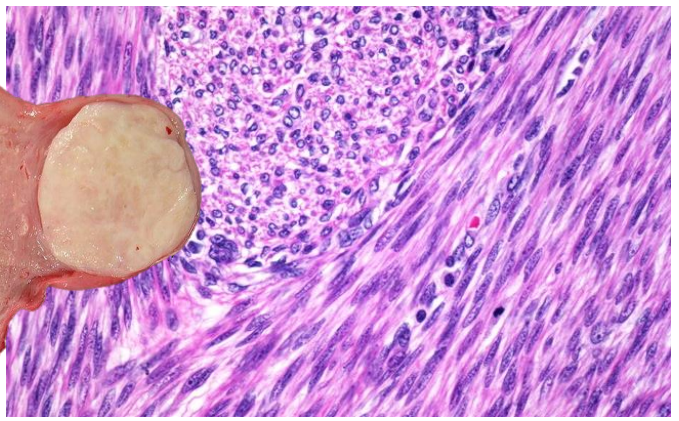
Mesenchymal tumors of the Uterus

Smooth Muscle Tumors

IHC: (+) Desmin, SMA, h-Caldesmon, ER, PR

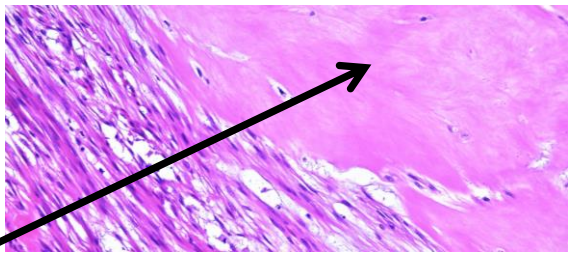
Leiomyoma





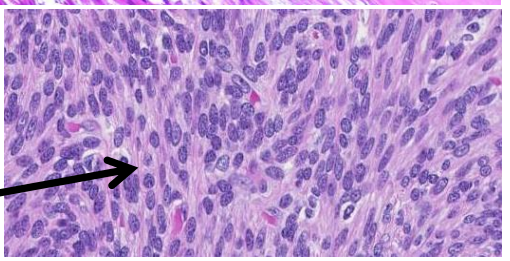
Benign smooth muscle tumor.
Most common uterine tumor.
Can present with pain, bleeding
Grossly, white, firm, whorled
Often **multiple**, **Well-circumscribed**

Usually, Bundles of **bland spindled cells,**
Arranged in intersecting fascicles,
Cigar-like nuclei, Fine chromatin



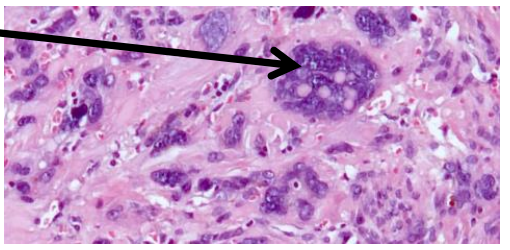
Molecular: MED12 mutations; HMAG1/2 rearrangements

Allowed: **Infarct-type** necrosis—has band of granulation tissue ± hemorrhage and fibrosis between viable and non-viable mummified/hyalinized tumor (different than "Tumor-type" necrosis)



Variants:

Cellular leiomyoma—significantly increased cellularity compared to normal myometrium (but only rare mitoses, no atypia)



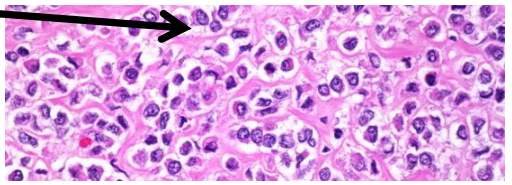
Leiomyoma with bizarre nuclei ("Symplastic")—bizarre nuclei (smudged, hyperchromatic, pleomorphic), but no mits/necrosis

Mitotically active leiomyoma—Mitoses, but no atypia or necrosis

Lipoleiomyoma—contains mature adipocytes

Myxoid leiomyoma—contain hypocellular myxoid stroma

Epitheliod leiomyoma—contain round polygonal cells

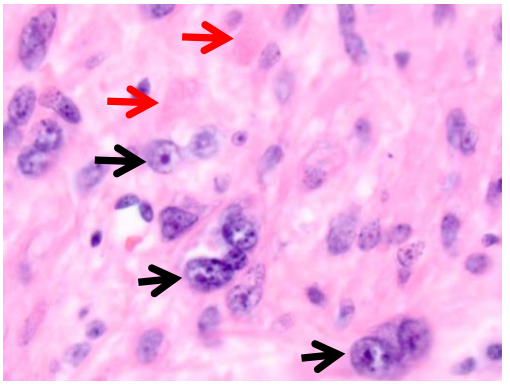


Cotyledonoid/dissecting leiomyoma—irregular nodular dissecting bands of smooth muscle cells within myometrium

Diffuse leiomyomatosis—innumerable, poorly-circumscribed hypercellular tumor nodules

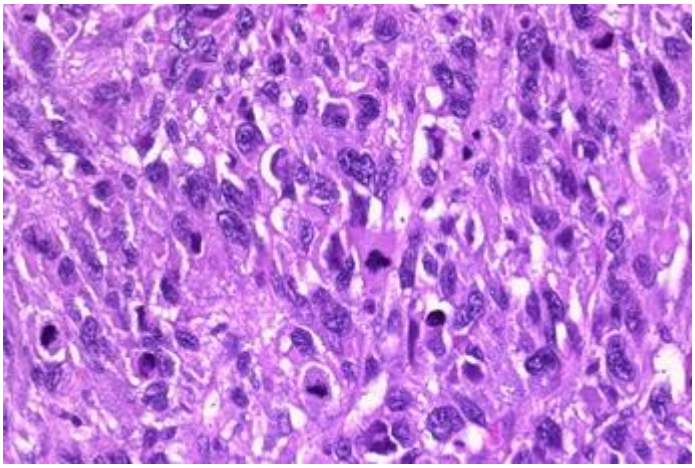
Intravenous leiomyomatosis—intravascular growth outside tumor

"Metastasizing leiomyoma"—a benign-appearing extrauterine leiomyoma in a patient with uterine leiomyoma(s), usually in lung



If tons, particularly at a young age, consider **hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome**. Classically these have staghorn vessels, eosinophilic nucleoli with halos (→), more atypia, edema, and rhabdoid inclusions (→). Show loss of fumarate hydratase (FH), Gain of 2SC

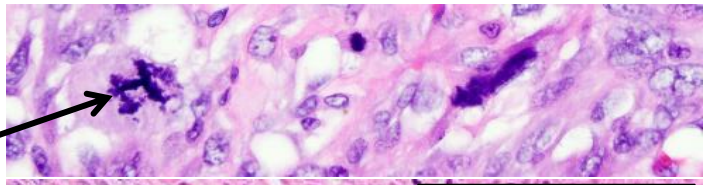
Leiomyosarcoma



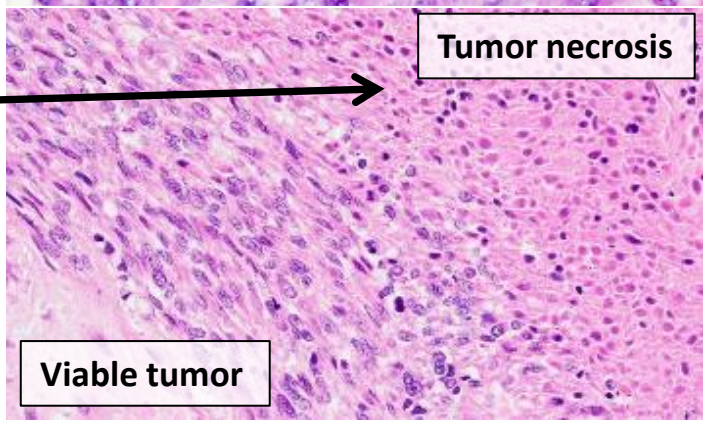
Malignant smooth muscle tumor.
Usually older patients

Typically spindle cell, but can be epithelioid or myxoid
Often abundant mitoses, necrosis, and atypia.
Frequent atypical mitoses.
Genetically complex chromosomal aberrations
Very **poor prognosis**

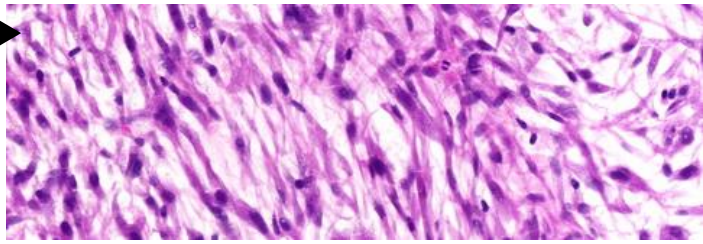
Diagnostic Criteria: *(varies by subtype)*



Conventional: At least two of the following:
1) Marked cytologic **atypia** (2+/3+)
2) Increased **mitoses**, ≥10 mits/10 HPF (≥4 mits/mm^2)
3) **Tumor-type necrosis**—coagulative tumor cell necrosis with a sharp interface between viable tumor (around feeding vessels) and non-viable tumor (with noticeable tumor cell ghosts)



Epithelioid: At least one of the following
1) Moderate to severe cytologic atypia
2) Increased **mitoses**, ≥4 mits/10 HPF (≥1.6 mits/mm^2)
3) **Tumor-type necrosis**



Myxoid: At least one of the following
1) Moderate to severe cytologic atypia
2) Increased **mitoses**, >1 mits/10 HPF (>0.4 mits/mm^2)
3) **Tumor-type necrosis**
4) **Infiltrative** borders/irregular margins

Given the low bar for malignancy, be sure to sample myxoid smooth muscle tumors particularly well!!

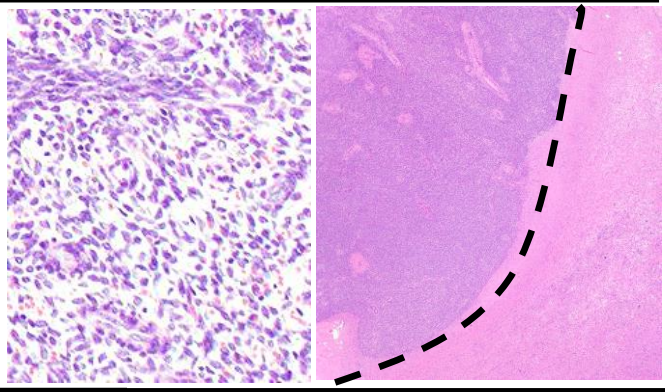
Smooth Muscle Tumor of Uncertain Malignant Potential ("STUMP")

Smooth muscle tumor whose features preclude a definitive diagnosis of leiomyoma vs. leiomyosarcoma
Often equivocal mitoses or necrosis.
Relatively low risk of recurrence
Many IMT's were previously mistakenly Dx'd as this, so consider doing ALK IHC

Endometrial Stromal Tumors

Low-grade/benign tumors stain like normal endometrial stroma with CD10 and ER/PR;
High-grade stains with Cyclin-D1

Endometrial Stromal Nodule

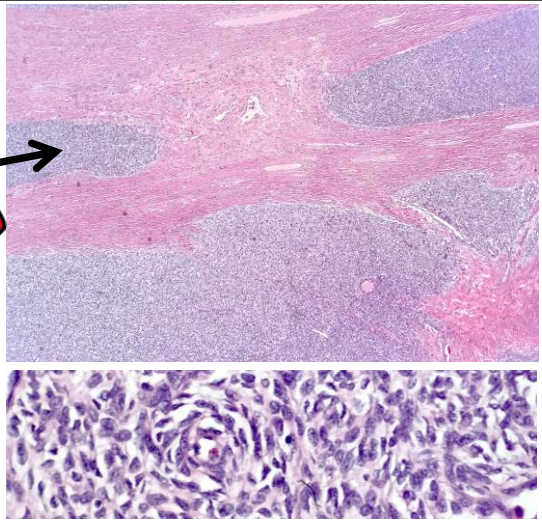


Benign tumor **resembling proliferative endometrial stroma** with a relatively **well-circumscribed** margin and **no LVI.**

Uniform small cells, scant cytoplasm, round/oval nuclei

Molecular: frequent JAZF1-SUZ12 fusions (same as LG-ESS; see below)

Low-grade Endometrial Stromal Sarcoma



Malignant tumor composed of cells resembling **proliferative endometrial stroma** with **infiltrative/permeative growth** into myometrium ± LVI

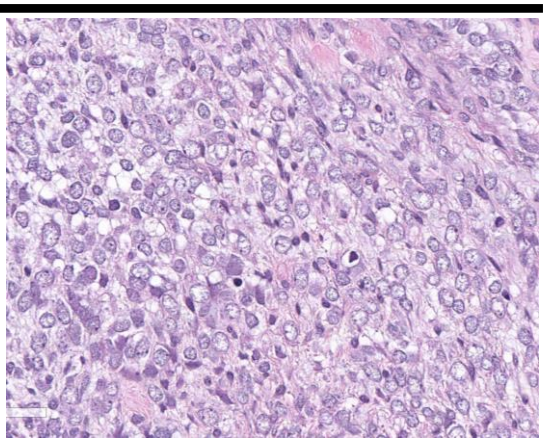
Often have **"tongue-like" growth**

Uniform cells, scant cytoplasm, fusiform nuclei
No atypia. Can have some smooth muscle and/or sex cord differentiation

Molecular: frequent **JAZF1-SUZ12 fusions** *(think "Jazzy Suzie")*

Intermediate prognosis, mostly depending on stage

High-grade Endometrial Stromal Sarcoma



Malignant tumor derived from endometrial stromal cells with **high-grade round cell** and/or spindle cell morphology.
Frequently myxoid.
Typically confluent, permeative, destructive growth.
Usually high mitotic activity, necrosis, and LVI.
Can have a low-grade (LG-ESS-like) areas

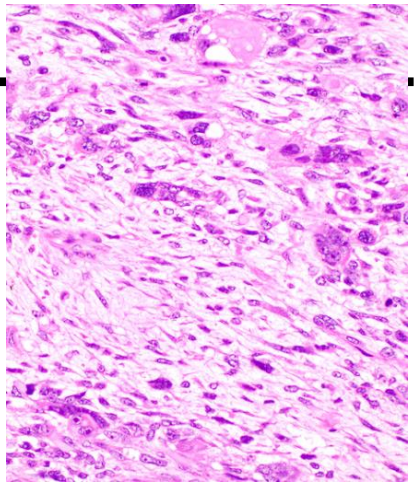
Molecular: **YWHAE-NUTM2A/B fusions or BCOR alterations**

More aggressive

	CD10	ER/PR	Cyclin-D1	BCOR	Desmin/Caldesmon	SMA
ESN/LG-ESS	+	+	-	-	-/+	+/-
YWHAE HG-ESS	-	-	+	-	-	-
ZC3H7B-BCOR HG-ESS	+	-	+	-/+	-	-
BCOR ITD HG-ESS	+/-	-	+	+/-	-	-

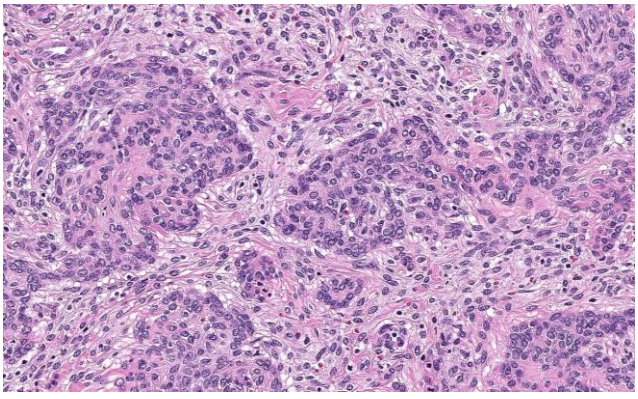
Other Mesenchymal

Undifferentiated Uterine Sarcoma



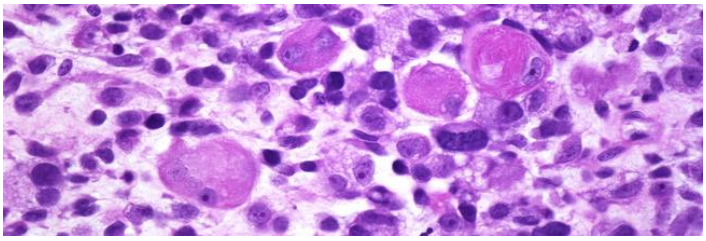
Malignant tumor arising in the endomyometrium with high-grade cytologic atypia and **no specific line of differentiation**.
Destructive invasion. Marked cytologic atypia and brisk mitotic activity.
Diagnosis of exclusion (must rule out carcinosarcoma, LMS, ESS, etc..)
IHC: Variable, negative for most specific markers
Complex genetically
Most patients present at high stage. **Poor prognosis.**

Uterine Tumor Resembling Ovarian Sex Cord Tumor ("UTROSCT")



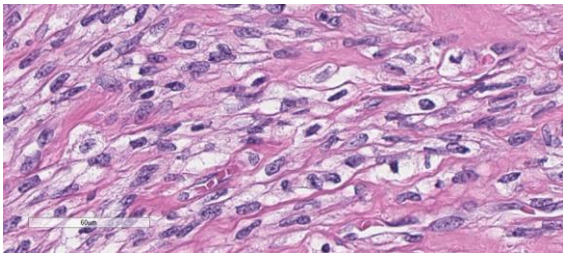
Neoplasms **resembling ovarian sex cord tumors** *without* a recognizable endometrial stromal component
Usually well-circumscribed. Minimal atypia/mitoses
Sheets, cords, trabeculae, and/or tubules
Scant to abundant eosinophilic cytoplasm.
IHC: Frequently WT-1 positive, variable expression of sex cord markers **Inhibin, calretinin, and Melan-A**
Recurrent NCOA translocations
Benign course typically.

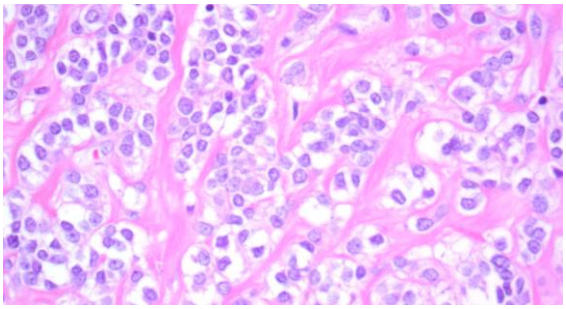
Rhabdomyosarcoma



Malignant tumor showing skeletal muscle differentiation (like rhabdomyosarcomas elsewhere)
IHC: **(+) Myogenin, MyoD1**, desmin,

Perivascular Epithelioid Cell Tumor (PEComa)





Mesenchymal tumor containing epithelioid to spindled cells with clear to eosinophilic, granular cytoplasm demonstrating **melanocytic and smooth muscle differentiation**, thought to be derived from so-called "Perivascular Epithelioid Cells."

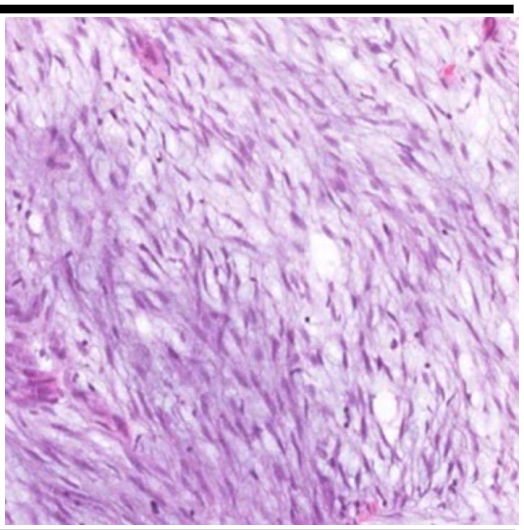
IHC: **(+) HMB45**, Melan-A, and/or Cathepsin K;
Variable smooth muscle markers (SMA, Desmin, Caldesmon)

Molecular: TSC mutations or TFE3 fusions

Features to evaluate for malignancy: 1)≥5cm, 2)High-grade atypia, 3)>1 mitoses/50HPF, 4)Necrosis, 5)LVI, 6)Infiltrative,

If <3 Benign/Uncertain malignant potential; ≥3 Malignant

Inflammatory Myofibroblastic Tumor (IMT)

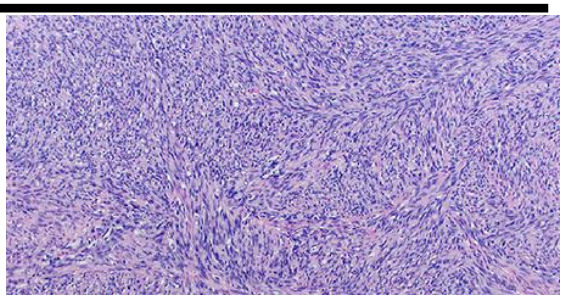


Bland spindled myofibroblastic cells growing in fascicles.
Prominent **inflammation** (usu. Lymphoplasmacytic).
Often have **myxoid stroma**.
IHC: **ALK positive** (>95%); variable smooth muscle markers
Molecular: ALK rearrangements.

Consider ALK IHC in any myxoid uterine tumor, if there is much inflammation, and any STUMP

Usually benign. Features that predict aggressive behavior: Size >7cm, Necrosis, Severe cytologic atypia, Mitoses, LVI.

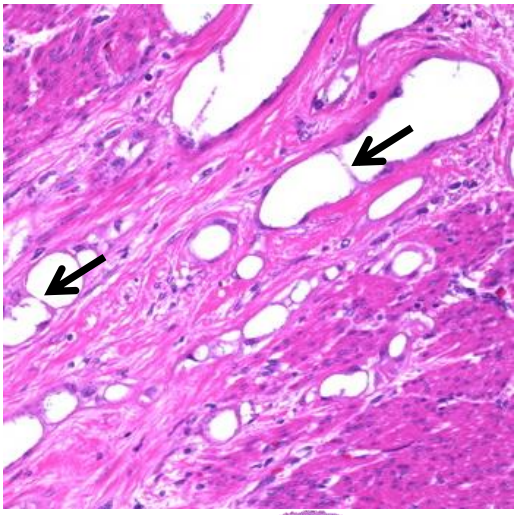
NTRK-Rearranged Spindle Cell Neoplasm



Usually in the **cervical stroma** of younger women.
Uniform spindled cells with variable architecture.
Often, mitotic activity, and sometimes lymphocytic infiltrate.
IHC: **(+)CD34, S100,** TRK, Cyclin-D1
Molecular: **NTRK rearrangements**

Tumors with an Epithelial/Mesothelial component

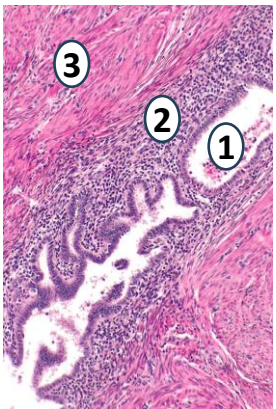
Adenomatoid tumor

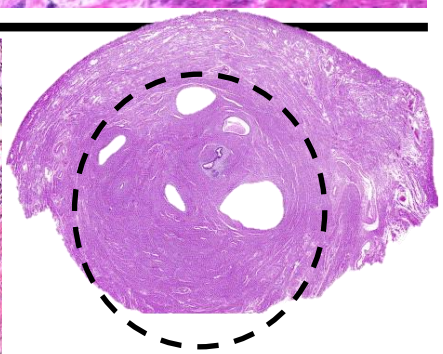


Benign tumor of ***mesothelial*** origin.
Inter-anastomosing pseudo-glands with variably sized tubules (sometimes with a signet ring appearance) and slit-like spaces with associated smooth muscle hypertrophy (so can be mistaken for a mesenchymal tumor!)
Helpful feature: "thread-like bridging strands" (→)

IHC: Tumor cells express CK AE1/AE3 and Mesothelial markers (D2-40, WT-1, Calretinin); Intact BAP1.
Molecular: TRAF7 missense mutations

Adenomyoma

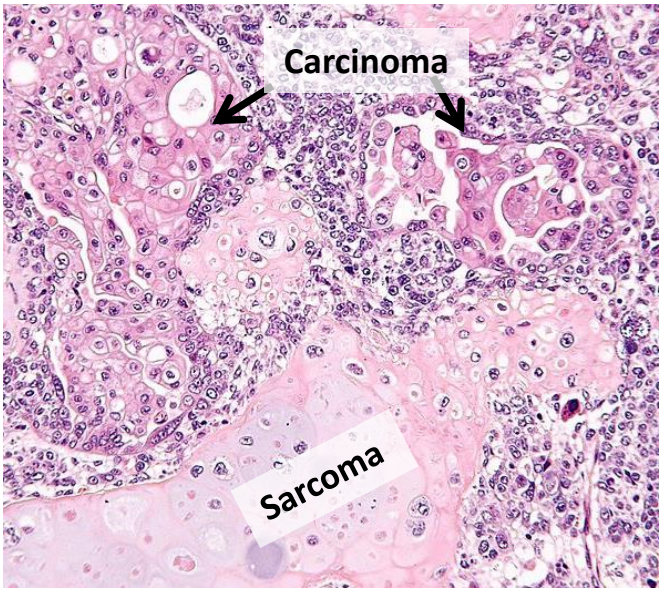




Benign nodule/polyp composed of:
1)Endometrioid glands
2)Endometrial stroma
3)Smooth muscle

(Essentially, Adenomyosis + Leiomyoma)

Carcinosarcoma



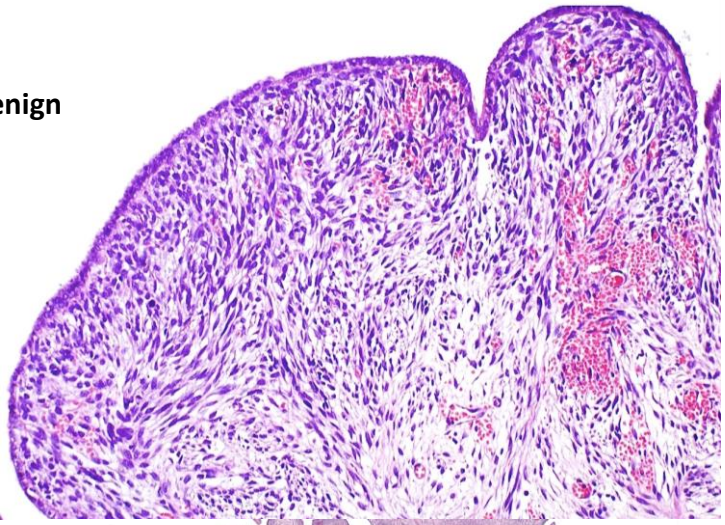
Biphasic tumor with malignant **carcinomatous *and*** **sarcomatous** elements.

Usually old women with a mass prolapsing out of the cervix. Often **advanced stage and poor prognosis**

Carcinoma: Often serous, sometimes endometrioid
Sarcoma: Often high-grade non-specific sarcoma, but can make heterologous elements (osteosarcoma, chondrosarcoma, rhabdosarcoma, etc…)

Example of ***"Epithelial → Mesenchymal transition"*** (transdifferentiation of carcinoma to sarcoma)
Molecular: often **TP53 mutations**

Adenosarcoma



Mixed epithelial and mesenchymal tumor with a **benign epithelial component *and*** **malignant stroma**.
Often protrude out cervical os.

Think: Phyllodes tumor

Broad, leaf-like polypoid projections of stroma
Stroma condensation, "cuffing" around glands

Can show heterologous elements and sarcomatous overgrowth.

IHC: Stroma stains with CD10, ER, PR

Low-grade malignant, with often favorable outcomes