

# Skříčkový seminář Případ č. 733

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pod záštitou Slovenskej spoločnosti patológov SLS  
a Slovenskej divízie IAP usporiadajú

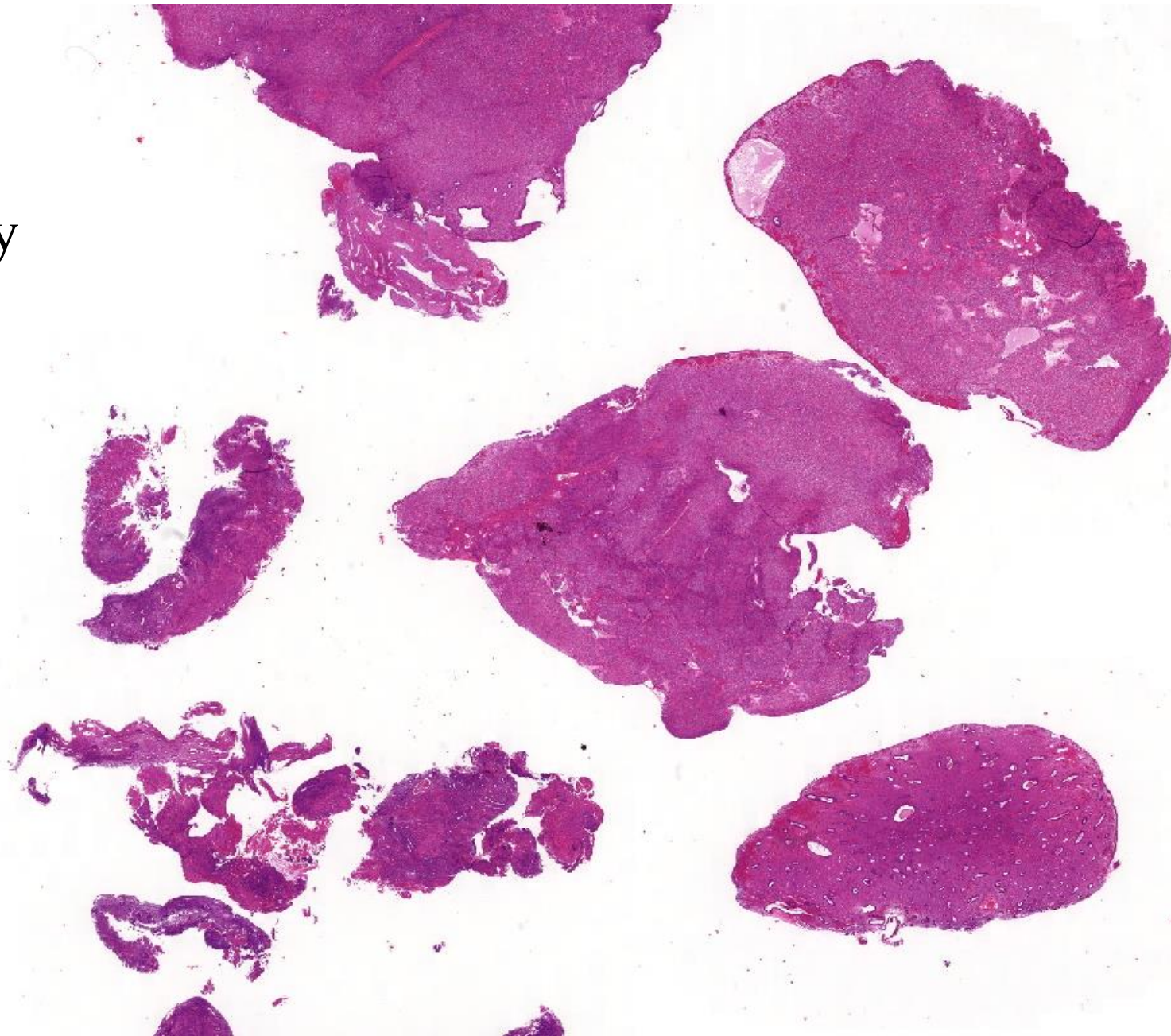
## LETNÝ BIOPTICKÝ SEMINÁR SD IAP

Piatok, 28. jún 2019

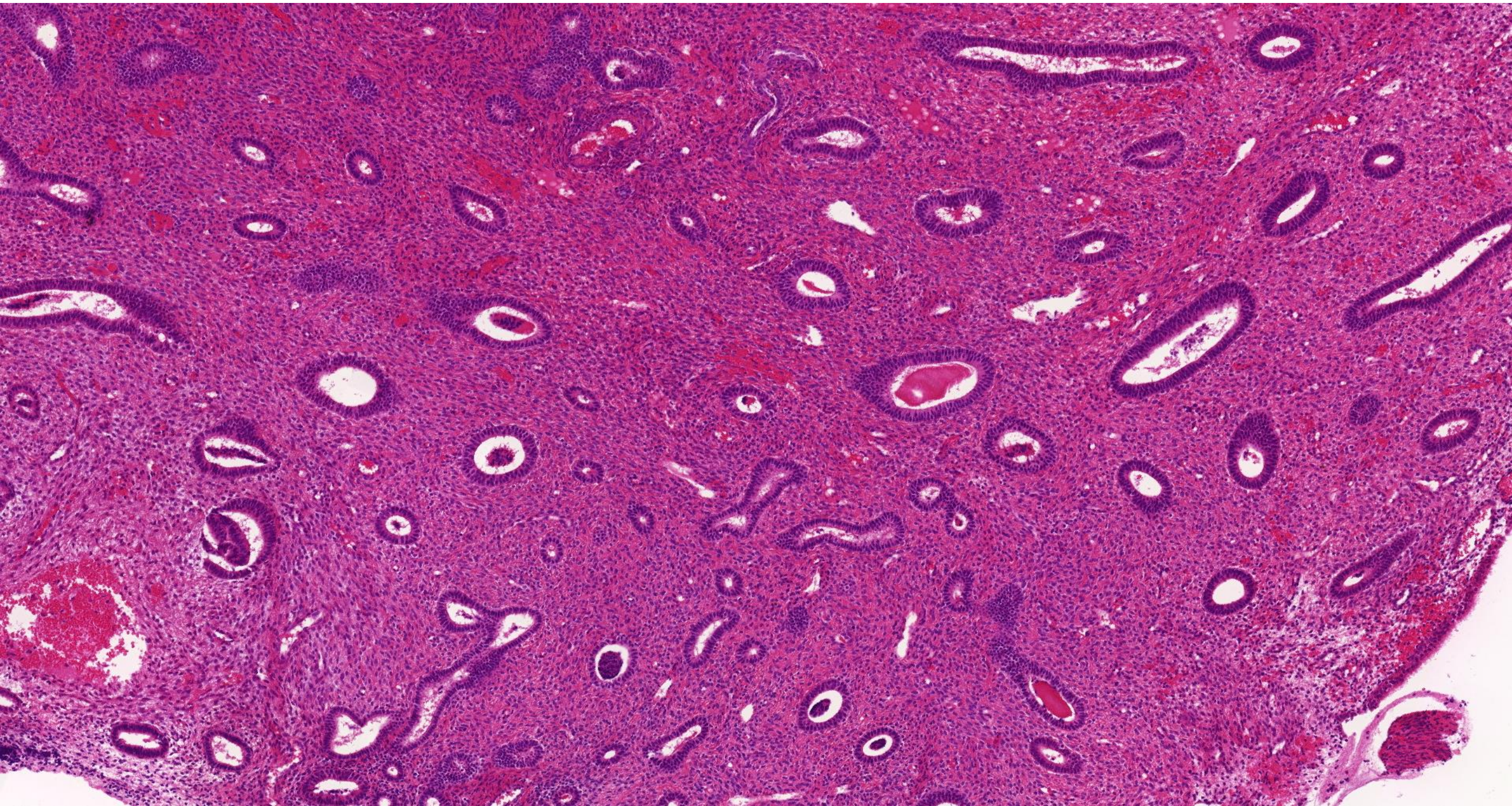
HOTEL SENEC, Slnéčné jazerá

MUDr. Peter Vereš, prezident SSP SLS  
MUDr. Peter Szépe, CSc., prezident SD-IAP  
MUDr. Marián Švajdler, Ph.D., odborný garant podujatia

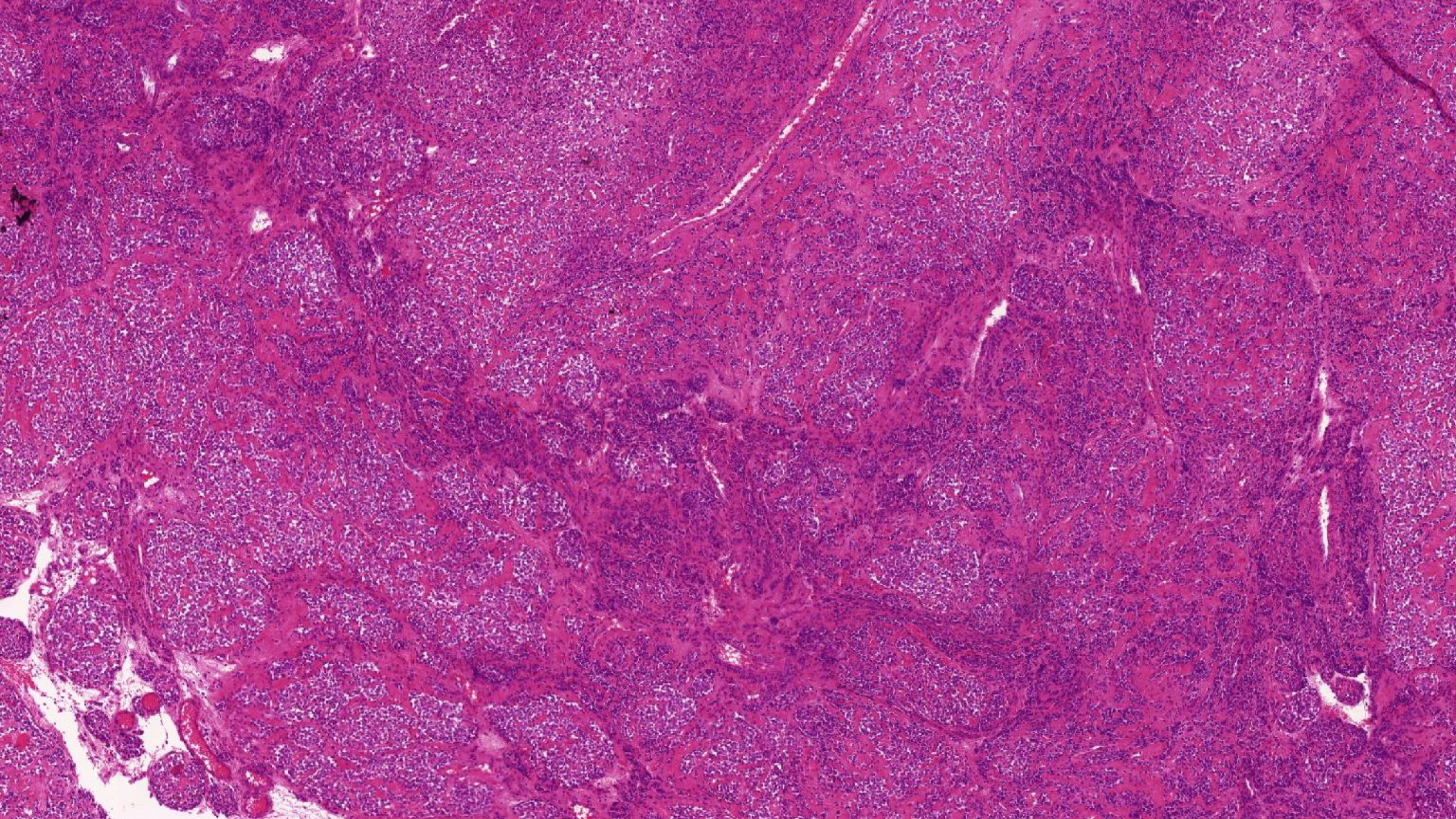
- 56 let
- tumor dělohy



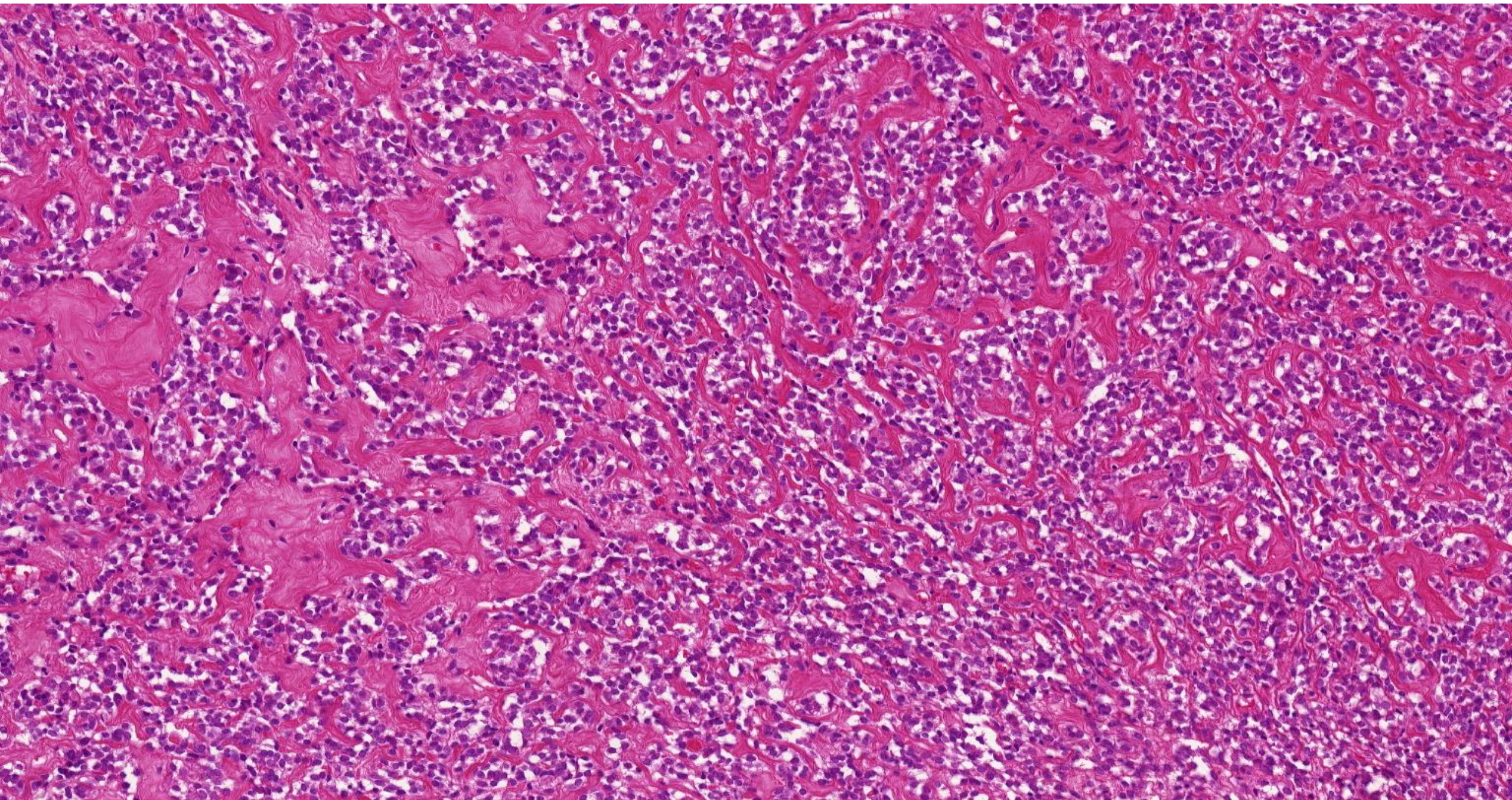




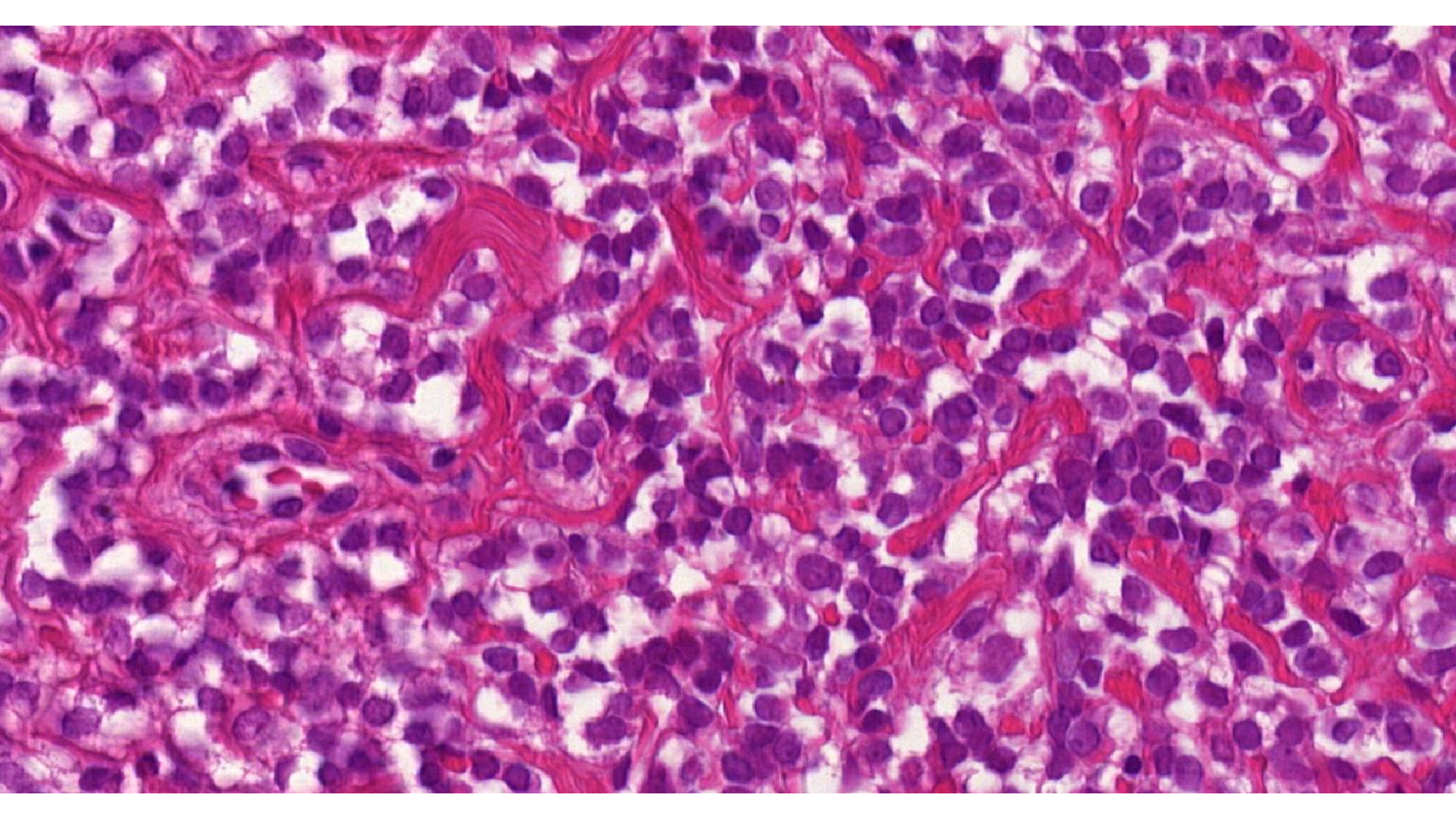




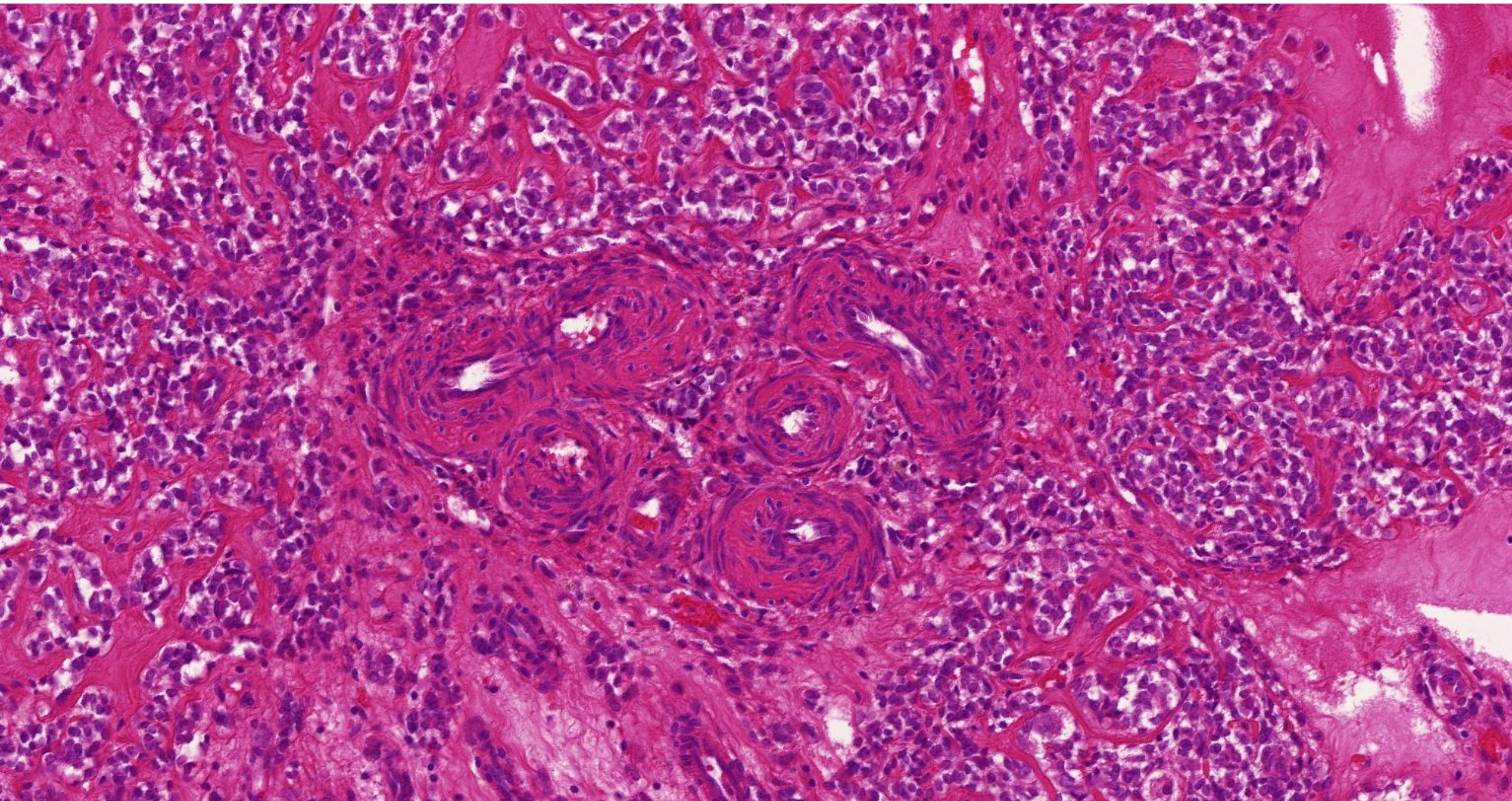




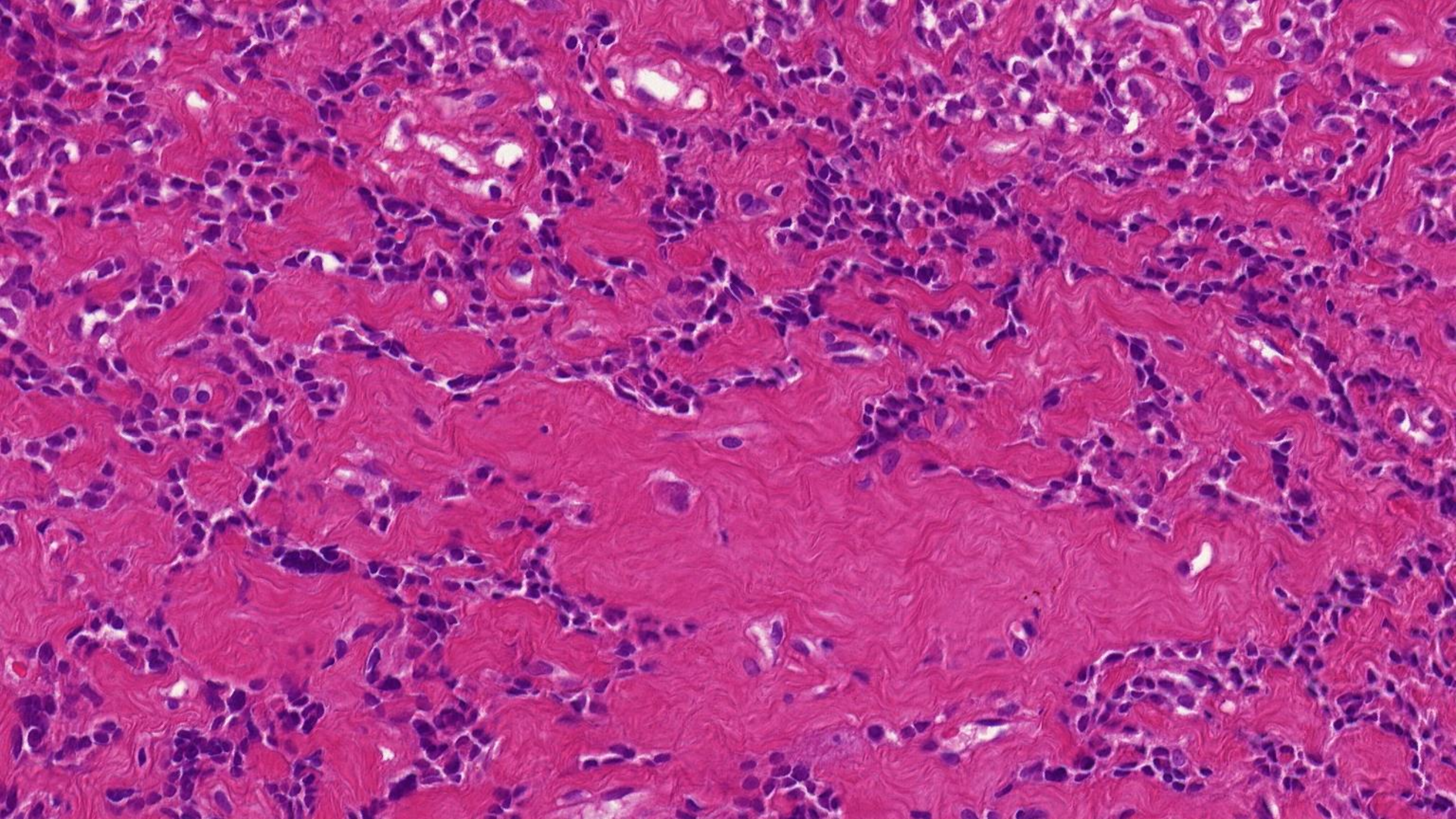






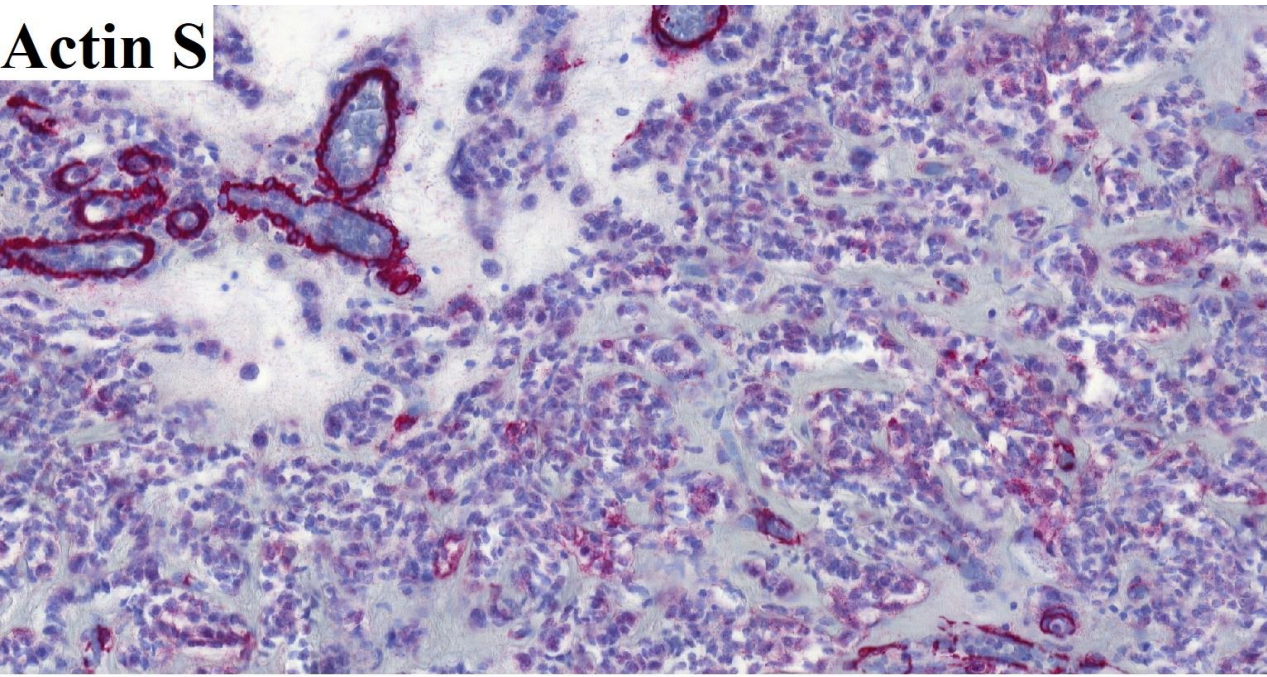




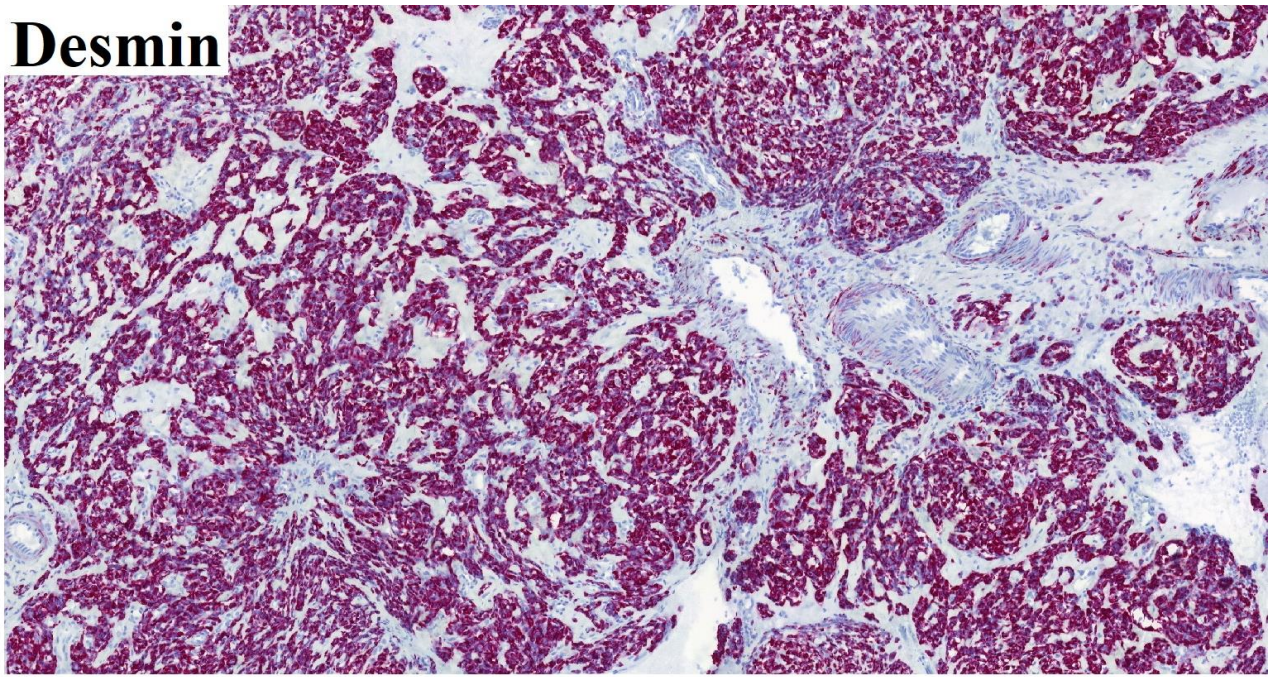




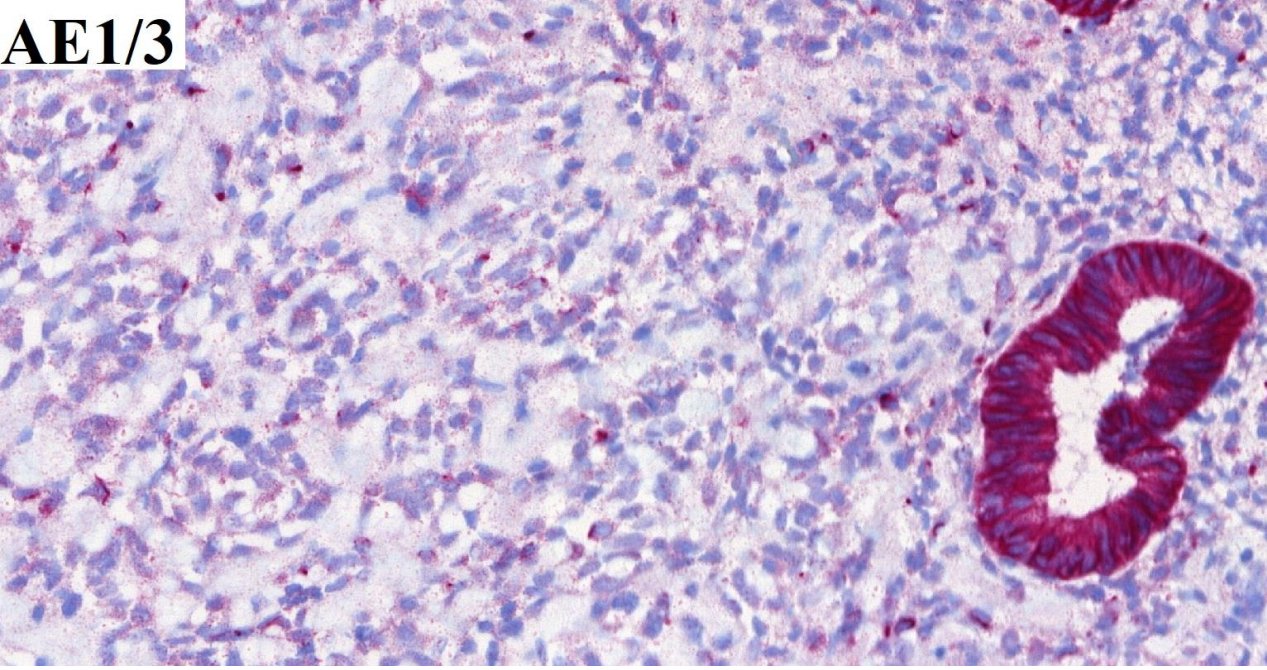
**Actin S**



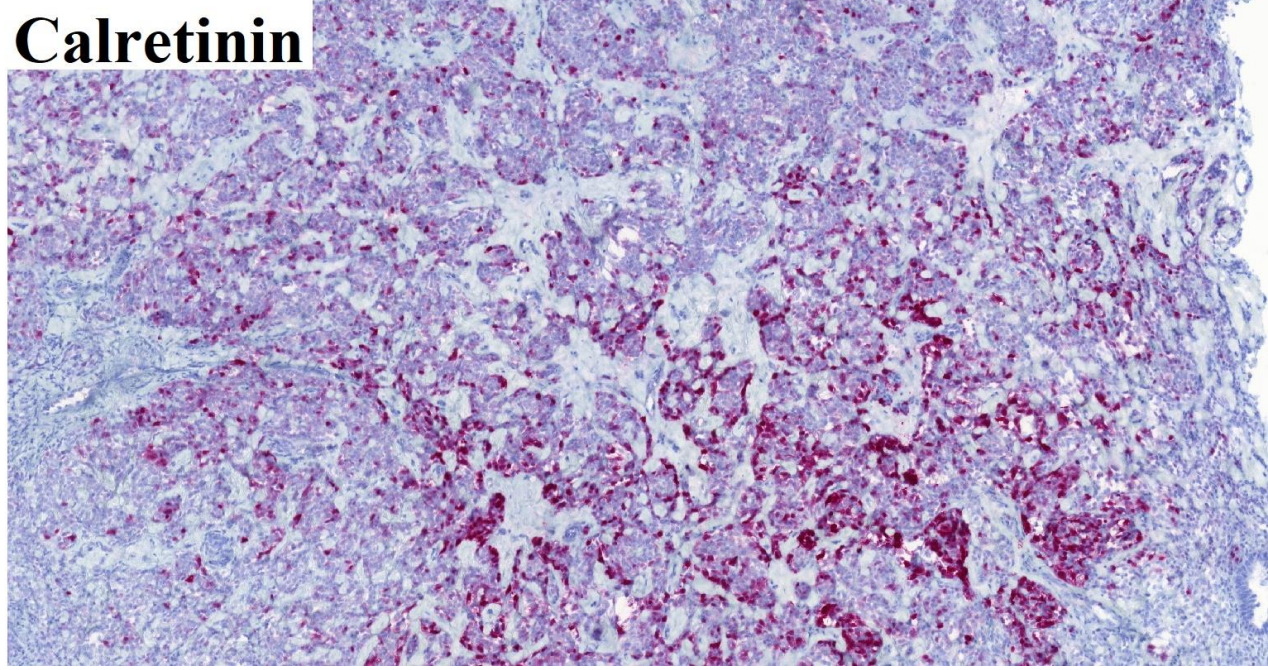
**Desmin**



**AE1/3**

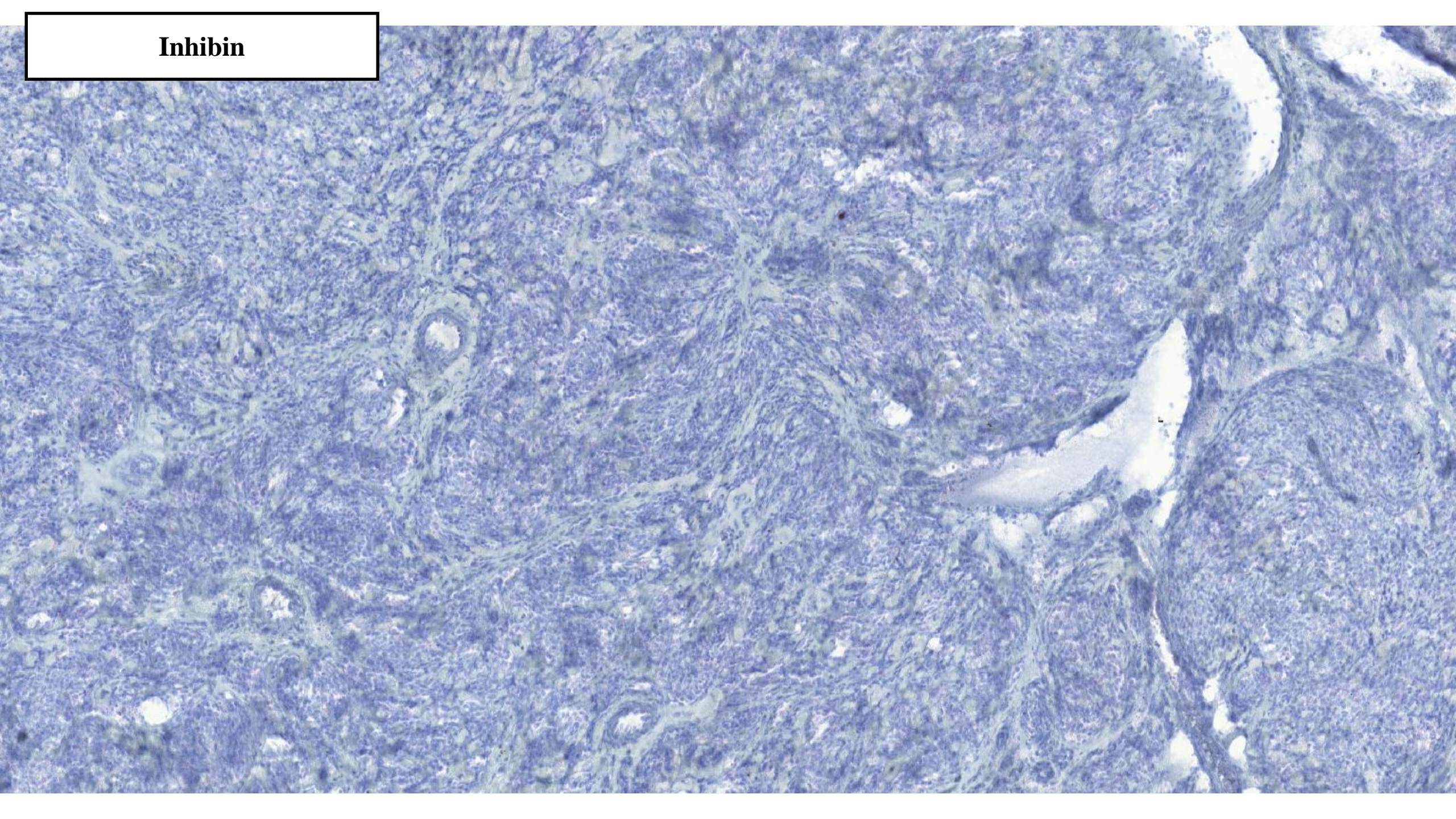


**Calretinin**



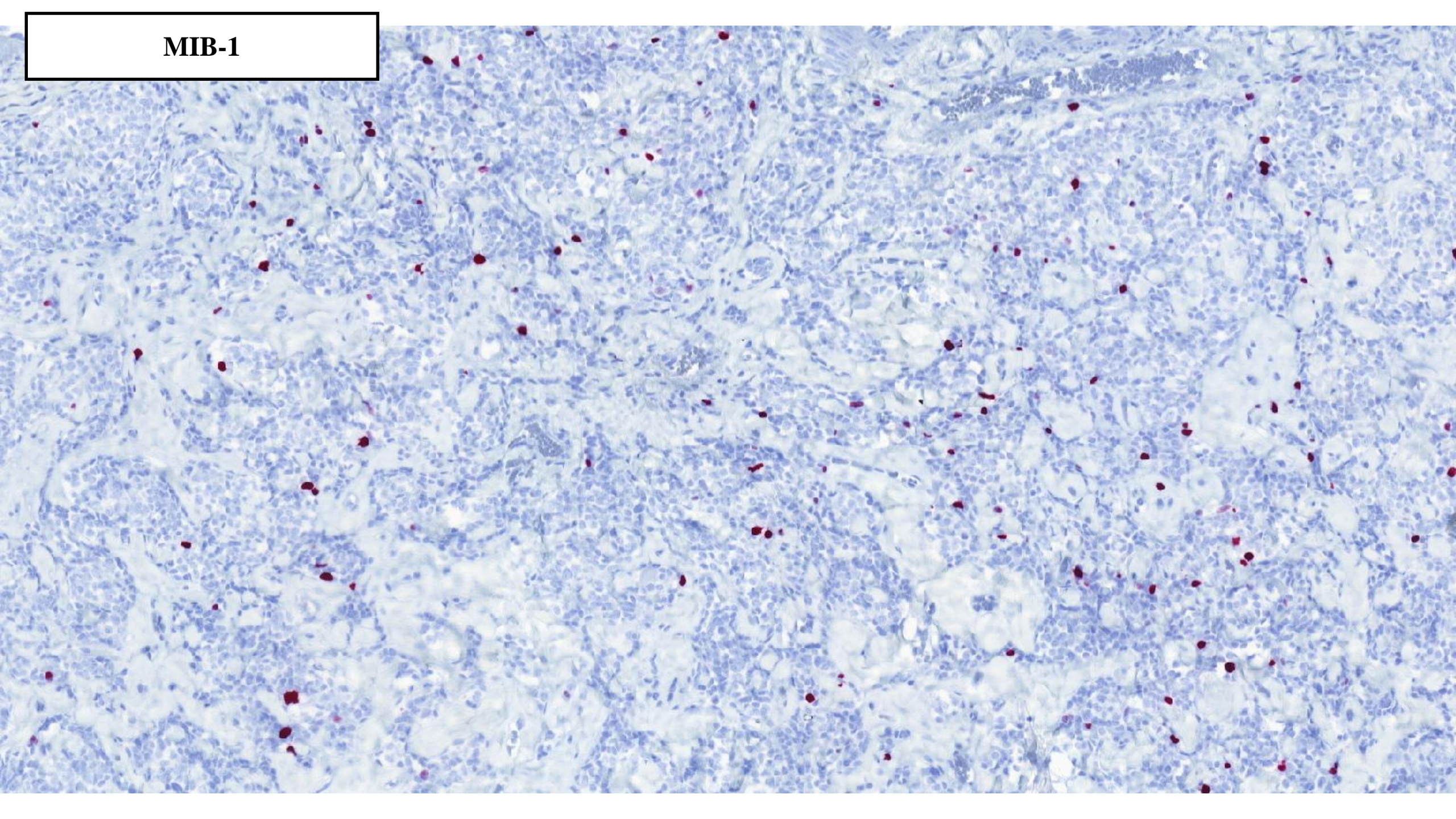


**Inhibin**





MIB-1







**DIAGNÓZA:**

**LOW-GRADE ENDOMETRIÁLNÍ STROMÁLNÍ SARKOM SE SEX-CORD –  
LIKE DIFERENCIACÍ**



# ENDOMETRIÁLNÍ STROMÁLNÍ SARKOMY

## LOW-GRADE ENDOMETRIÁLNÍ STROMÁLNÍ SARKOM

## HIGH-GRADE ENDOMETRIÁLNÍ STROMÁLNÍ SARKOM

## NEDIFERENCOVANÝ ENDOMETRIÁLNÍ STROMÁLNÍ SARKOM

*JAZF1-SUZ12*

*PHF1*

*YWHAE-NUTM2*

*ZC3H7B-BCOR*  
(*BCOR* ITD)

Nepopsáno  
(*TP53* missence mutace)

- podobný stromatu v proliferačním endometriu

- sex-cord – like diferenciace

- kulaté uniformní bb se zvýšeným N/C poměrem a >10mit/10HPF, nekrózy
- 50% má komponentu LG-ESS

- vřetenité bb v myxoidním stromatu, výrazná mitotická aktivita-

- diagnóza per exclusionem

CD10+, ER+, PR+, WT1+

**HG:** cyclin D1+,  
BCOR+, CD117+, ER-,  
PR- a CD10-  
**LG:** CD10+, ER+, PR+

CD10+, cyclin D1+,  
BCOR+, ER, PR+/-  
SMA+/-, desmin+/-

p53+, ER-, PR-,  
CD10+/-



# ENDOMETRIÁLNÍ STROMÁLNÍ SARKOMY

## LOW-GRADE ENDOMETRIÁLNÍ STROMÁLNÍ SARKOM

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- vřetenité bb v myxoidním stromatu, výrazná mitotická aktivita-

- diagnóza per exclusionem
- pleomorfní, rhabdoidní bb, nekrózy, atypické mitózy...

CD10+, ER+, PR+, WT1+

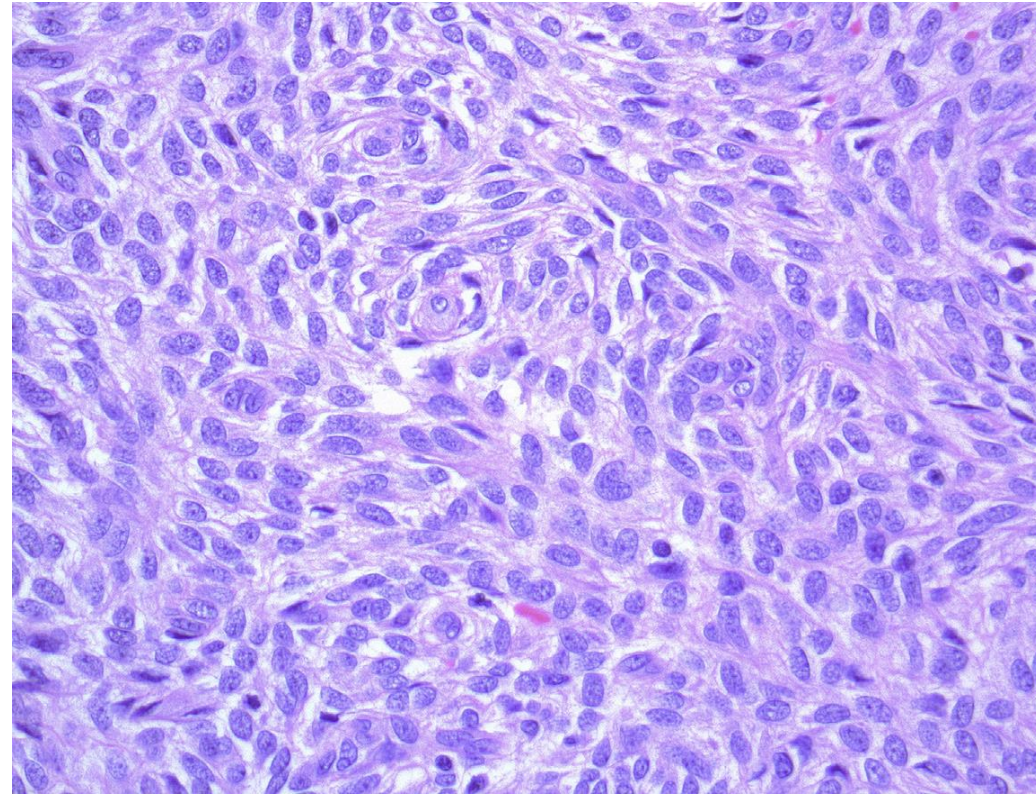
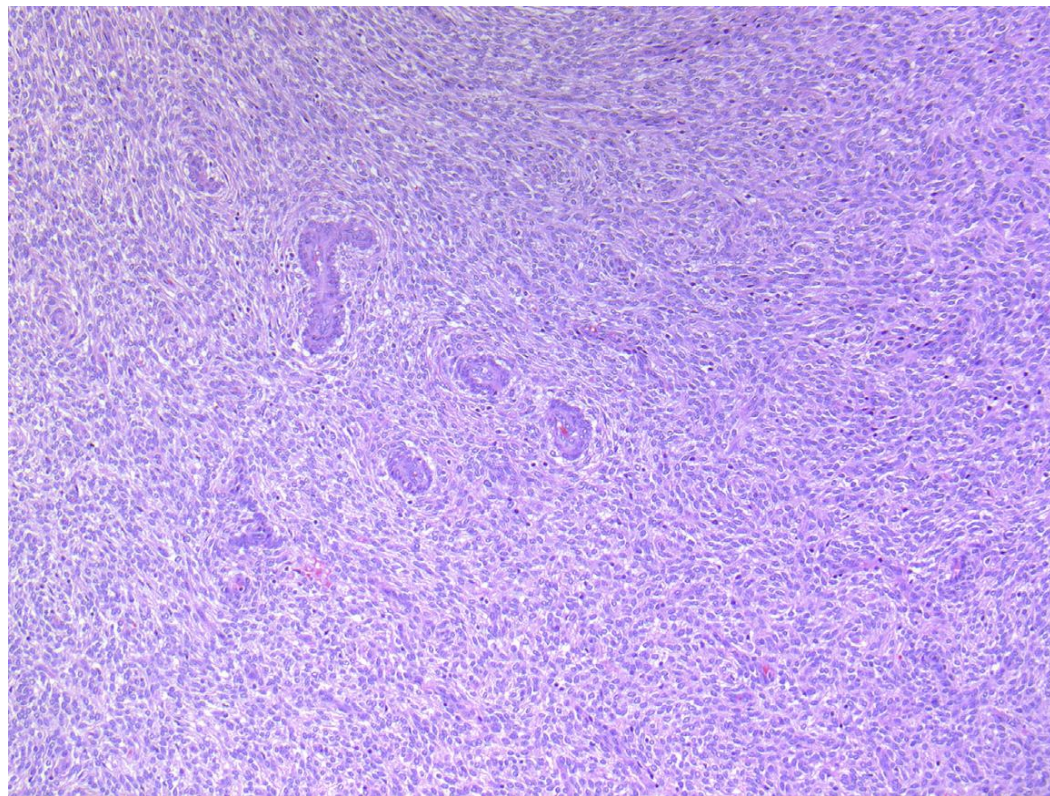
HG: cyclin D1+,  
BCOR+, CD117+, ER, PR  
a CD10-  
LG: CD10+, ER+, PR+

CD10+, cyclin D1+,  
BCOR+, ER, PR+/-  
SMA+/-, desmin+/-

p53+, ER-, PR-,  
CD10+/-



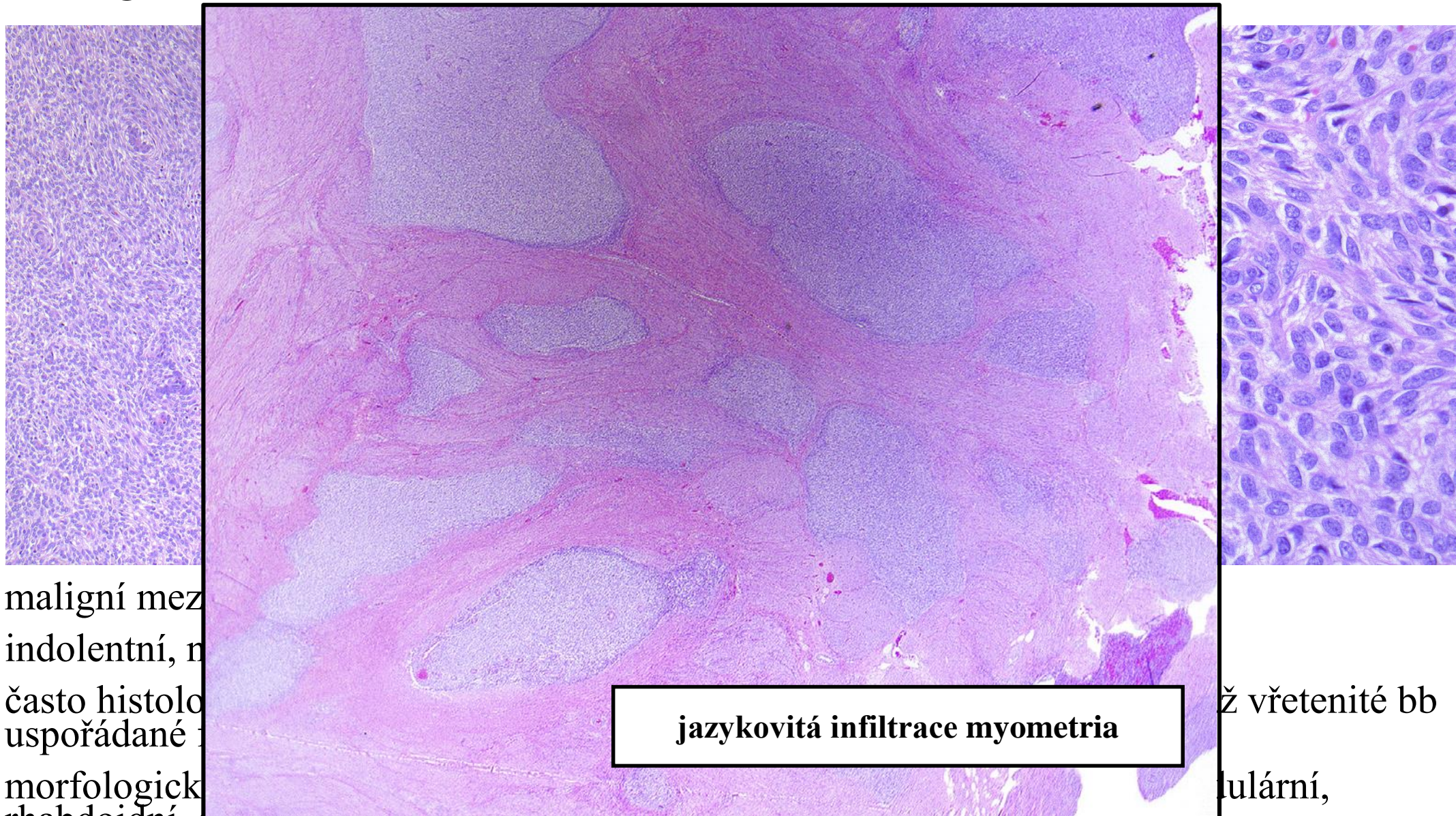
# Low-grade endometriální stromální sarkom (LG-ESS)



- maligní mezenchymální tumor dělohy
- indolentní, nejdůležitější stage
- často histologicky napodobují endometriální stroma – monomorfní oválné až vřetenité bb uspořádané fascikulárně či do hnízd, nízká mitotická aktivita
- morfologicky heterogenní -hladkosvalová, fibromyxoidní, epiteloidní, glandulární, rhabdoidní, sex-cord – like diferenciacie



# Low-grade endometriální stromální sarkom (LG-ESS)



- maligní mez
- indolentní, n
- často histolo  
uspořádané t
- morfologick  
rhabdoidní, sex-cord = nke diferenciace

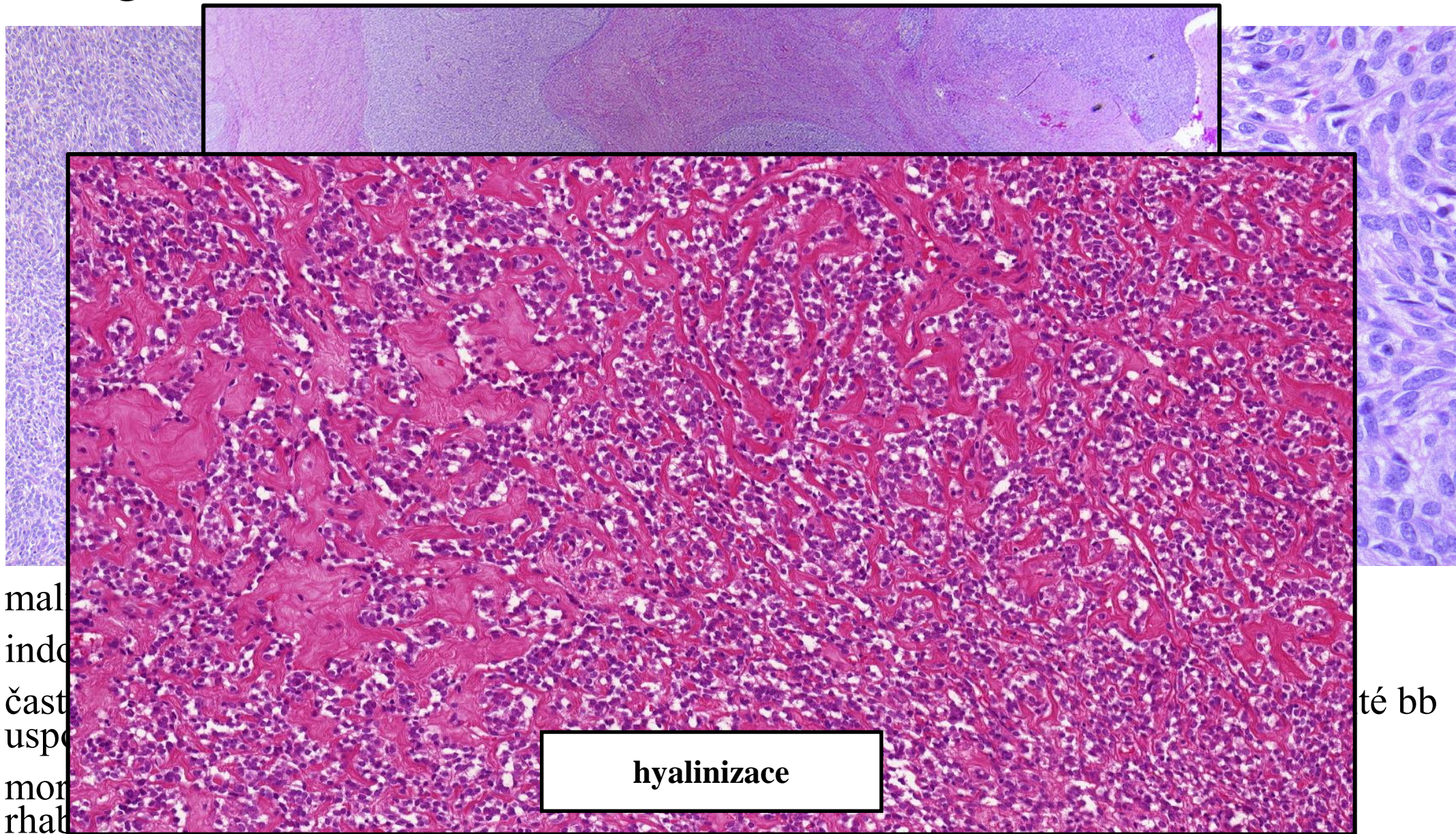
**jazykovitá infiltrace myometria**

ž vřetenité bb

ulární,



# Low-grade endometriální stromální sarkom (LG-ESS)



- mal
- indo
- čast
- uspo
- mor
- rhab

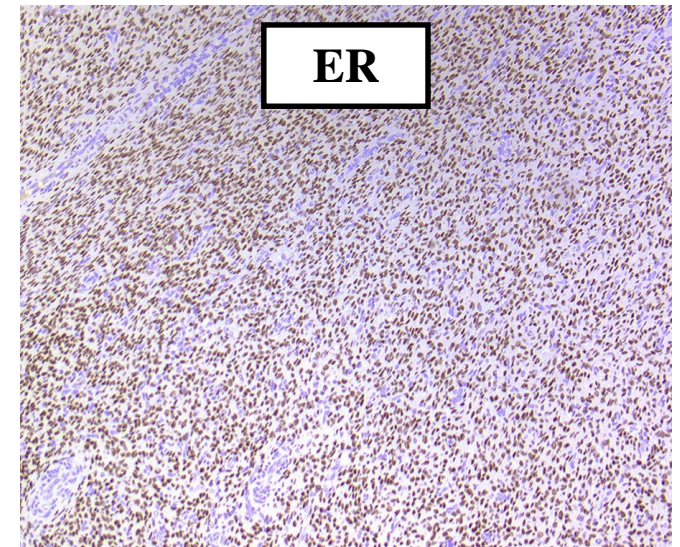
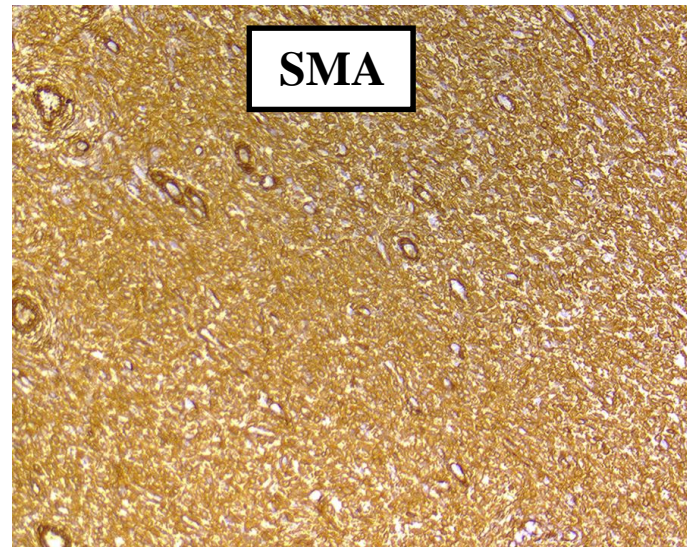
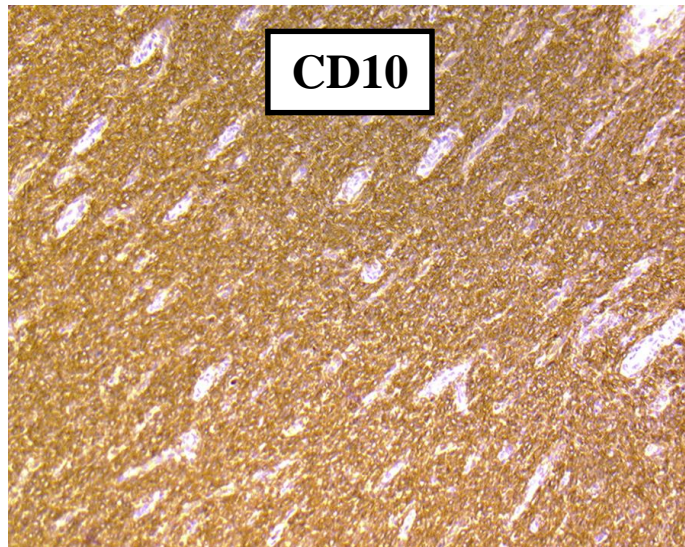
té bb

hyalinizace



# IHC LG-ESS

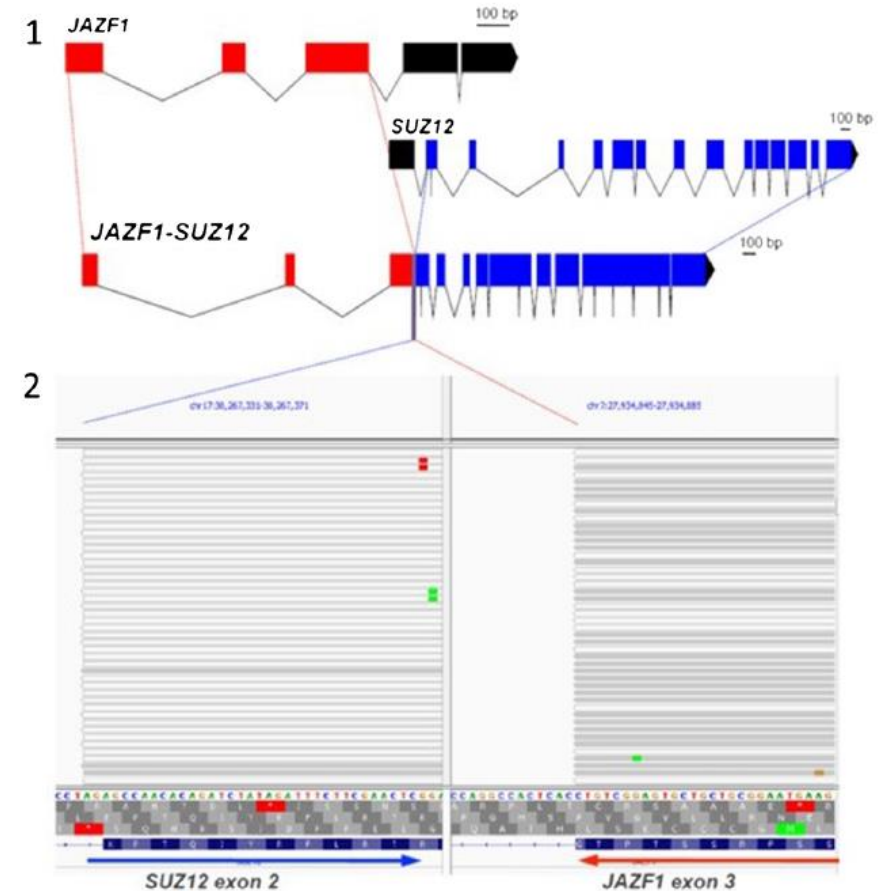
- CD10+, ER+, PR+, WT1+
- SMA, desmin +/- , h-caldesmon většinou -
- CK+ v epiteloidních bb nebo v oblastech se sex-cord – like diferenciací
- BCOR-, cyclin D1-, CD117 -





# Molekulární znaky LG-ESS

- **JAZF1-SUZ12** – asi polovina případů
- fúze s **PHF1** - *BRD8-PHF1*, *EPC1-PHF1*, *EPC2-PHF1*, *JAZF1-PHF1*, *MEAF6-PHF1*
- *EPC1-SUZ12*
- *MBTD1-CXorf67*





# Endometrial Stromal Sarcomas With Sex Cord Differentiation Are Associated With *PHF1* Rearrangement

Emanuela D'Angelo, MD,\* Rola H. Ali, MD,† Inigo Espinosa, MD,\*  
Cheng-Han Lee, MD,† David G. Huntsman, MD,‡ Blake Gilks, MD,†  
and Jaime Prat, MD, PhD, FRCPath\*

*Am J Surg Pathol* • Volume 37, Number 4, April 2013

Endometrial Stromal Tumors

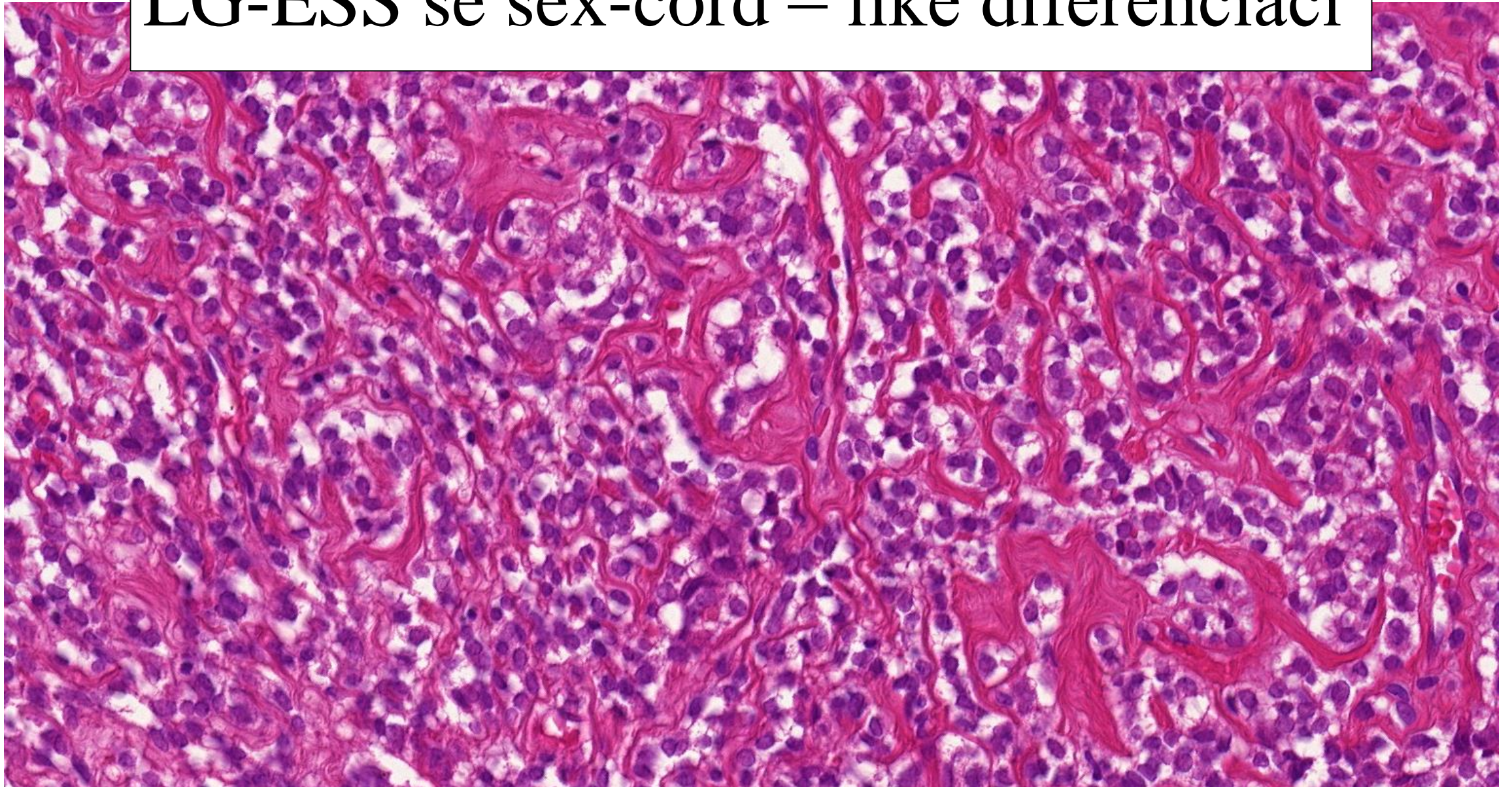
**TABLE 1.** Clinicopathologic Features and Gene Rearrangement Status of 23 ESTs

Case	Histologic Diagnosis	Age	Size	Mitosis	Stage	Distant Metastases	Patient Status	FISH
1	ESN	35	8	0	IB	No	NED at 4 y	<i>JAZF1; SUZ12</i>
2	ESN	41	10	0	IB	No	NED at 12 y	<i>JAZF1-SUZ12</i>
3	ESN smooth muscle + skeletal muscle + sex cord	29	8	2	IB	No	NED at 20 y	Negative
4	ESS classic	47	7	1	IB	Yes	NED at 11 y	Nonconclusive
5	ESS classic	42	8	2	IB	Yes	NED at 12 y	<i>JAZF1</i>
6	ESS classic	19	3.5	5	IA	Yes	AWT at 4 y	Negative
7	ESS classic	41	11	3	IIIB	No	AWT at 6 y	Negative
8	ESS classic	40	12	5	IIB	No	AWT at 5.5 y	Negative
9	ESS classic + epithelioid	39	15	8	IIB	Yes	DOC at 11 y	Negative
10	ESS sex cord	49	9	5	IIB	Yes	AWT at 6.2 y	<i>PHF1</i>
11	ESS sex cord	53	50	3	IB	No	NED at 6 y	<i>PHF1; EPC1</i>
12	ESS sex cord	56	25	4	IB	No	NED at 4.5 y	<i>PHF1</i>
13	ESS sex cord	48	7	5	IIIC	Yes	AWT at 6 y	<i>PHF1</i>
14	ESS sex cord + fibromyxoid	65	8.2	4	IB	No	NED at 5 y	<i>PHF1</i>
15	ESS sex cord + smooth muscle	34	8	2	IB	No	NED at 12 y	<i>JAZF1; PHF1; JAZF1-PHF1</i>
16	ESS smooth muscle	44	15	3	IB	No	NED at 12 y	<i>PHF1</i>
17	UES uniform	55	14	15	IIB	Yes	AWT at 4 y	Negative
18	UES uniform	54	22	22	IB	No	NED at 3 y	Negative
19	UES uniform	46	29	13	IIB	Yes	AWT at 9 y	Negative
20	UES pleomorphic	84	11	19	IB	Yes	DOT at 0.9 y	Negative
21	UES pleomorphic	65	8	20	IB	Yes	DOT at 0.1 y	Negative
22	UES pleomorphic	48	20	15	IIIC	Yes	DOT at 0.2 y	Negative
23	UES pleomorphic + skeletal muscle	53	9	7	IB	Yes	DOT at 0.6 y	Negative

AWT indicates alive with tumor; DOC, died of other causes; DOT, died of tumor; NED, no evidence of disease.



# LG-ESS se sex-cord – like diferenciáci





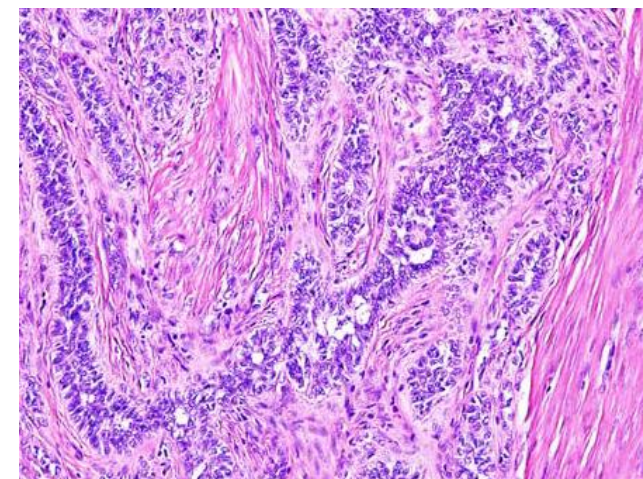
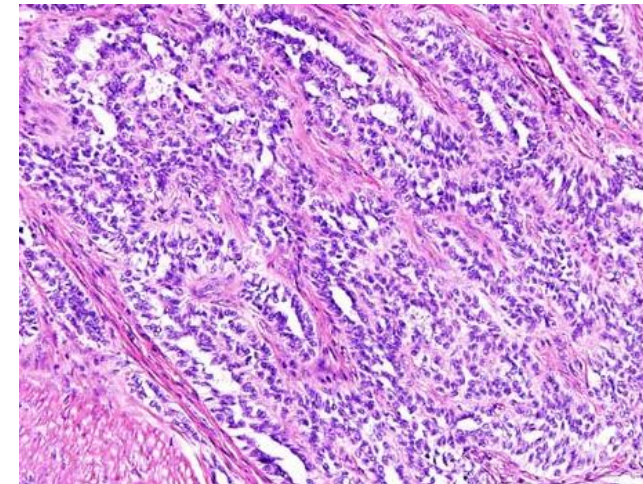
# Sex-cord – like diferenciace v tumorech dělohy

- v mnoha primárních tumorech dělohy – hladkosvalové tumory, mulleriánský adenosarkom, ESS, tumor dělohy napodobující ovariální sex-cord tumor (UTROSCT: uterine tumor resembling ovarian sex cord tumor)
- napodobuje ovariální nádor z bb granulózy či Sertoli cell tumor
  - hnízda, pruhy, trámce či tubuly epiteloidních bb s variabilním množstvím cytoplazmy, kulatým jádrem (jaderné zářezy), malým jadérkem a minimální mitotickou aktivitou
- IHC průkaz sex-cord markerů variabilní



# Tumor dělohy napodobující ovariální sex-cord tumor (UTROSCT: uterine tumor resembling ovarian sex cord tumor)

- sex-cord diferenciace je predominantní komponenta tumoru
- typické sex-cord elementy – Sertoli-like bb a granulóza-like bb tvořící tubulární, retiformní nebo stlačené pruhovité struktury
- bez stromální složky napodobující proliferativní endometrium
- AE1/3+, calretinin+, WT-1+, ER+, PR+
- CD10 +/- , EMA +/- , inhibin +/-, FOXL2 +/-, SF-1 +/- desmin +/-, SMA +/-, calponin +/-, h-caldesmon +/-
- nemají rearanže *PHF1* a *JAZF1-SUZ12*
- nemají mutace *FOXL2* a *DICER1*
- fúze genů *NCOA2* a *NCOA3*: *ESR1-NCOA3*, *ESR1-NCOA2*, *GREB1-NCOA2* a *GREB1-CTNNB1*





# GREB1 rearanžované sarkomy dělohy

- 4 případy:
  - GREB1-NCOA2
  - GREB1-NR4A3
  - GREB1-SS18
  - GREB1-NCOA1

## Clinicopathologic Characterization of GREB1-rearranged Uterine Sarcomas With Variable Sex-Cord Differentiation

Cheng-Han Lee, MD, PhD, FRCPC,\* Yu-Chien Kao, MD,† Wan-Ru Lee, BS,‡  
 Yi-Wen Hsiao, MS,§ Tzu-Pin Lu, PhD,§ Chia-Ying Chu, MD,|| Yi-Jia Lin, MD,¶  
 Hsuan-Ying Huang, MD,# Tsung-Han Hsieh, PhD,\*\* Yun-Ru Liu, PhD,\*\*  
 Cher-Wei Liang, MD,†† Tom Wei-Wu Chen, MD,‡‡ Stephen Yip, MD, PhD, FRCPC,§§  
 Amy Lum, BS,§§ Kuan-Ting Kuo, MD,‡ Yung-Ming Jeng, MD, PhD,‡ Shih-Chen Yu, MS,#  
 Yung-Chuan Chung MS,‡ and Jen-Chieh Lee, MD, PhD‡

**Abstract:** Uterine mesenchymal tumors are genetically heterogeneous; those with uniform cytomorphology, best exemplified by endometrial stromal tumors, often contain various fusion genes. Novel fusions involving *ESR1* and *GREB1*, key factors in sex hormone pathways, have been implicated in rare uterine mesenchymal tumors. Particularly, the fusions between 5'-*ESR1*/*GREB1* and 3'-*NCOA2*/*NCOA3* were recently identified in 4 uterine tumors resembling ovarian sex-cord tumor (UTROSCT). By RNA

sequencing, pathology review, and FISH screening, we identified 4 uterine sarcomas harboring rearranged *GREB1*, including *GREB1-NCOA2* and the novel *GREB1-NR4A3*, *GREB1-SS18*, and *GREB1-NCOA1*, validated by RT-PCR and/or FISH. They occurred in the myometrium of postmenopausal women and were pathologically similar despite minor differences. Tumor cells were generally uniform and epithelioid, with vesicular nuclei and distinct to prominent nucleoli. Growth patterns included solid sheets, trabeculae/cords, nests, and fascicles. Only 1 tumor showed small foci of definitive sex-cord components featuring well-formed tubules, retiform structures, Leydig-like cells, and lipid-laden cells and exhibiting convincing immunoreactivity to sex-cord markers (calretinin,  $\alpha$ -inhibin, and Melan-A). In contrast, all the 4 classic UTROSCT we collected occurred in premenopausal patients, consisted predominantly of unequivocal sex-cord elements, prominently expressed multiple sex-cord markers, and harbored *ESR1-NCOA3* fusion. Combined with previously reported cases, *GREB1*-rearranged tumors involved significantly older women ( $P=0.001$ ), tended to be larger and more mitotically active, showed more variable and often inconspicuous sex-cord differentiation, and appeared to behave more aggressively than *ESR1*-rearranged UTROSCT. Therefore, these 2 groups of tumors might deserve separate consideration, despite some overlapping features and the possibility of belonging to the same disease spectrum.

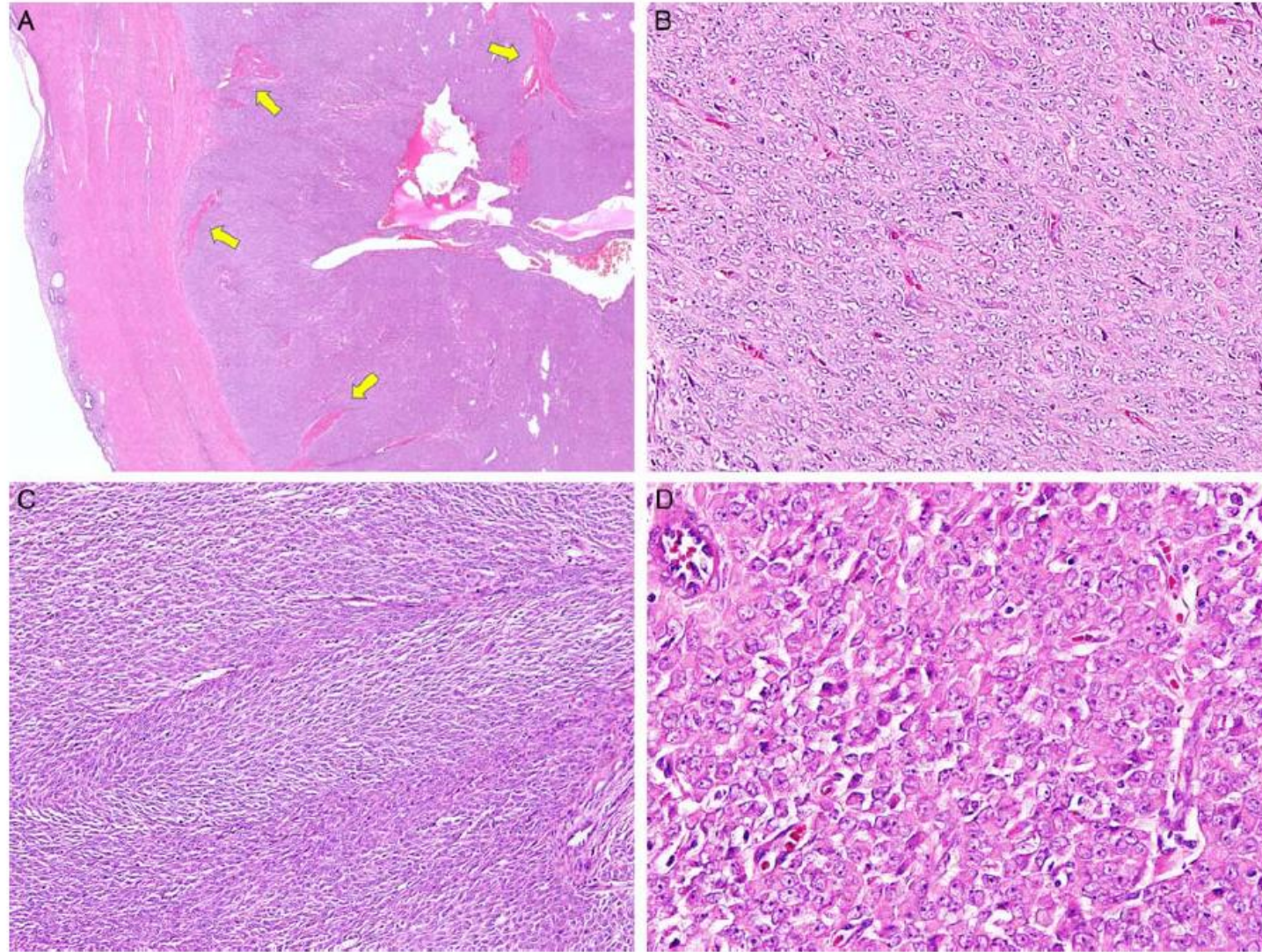
**Key Words:** uterine sarcoma, sex cord tumor, *GREB1*, *ESR1*

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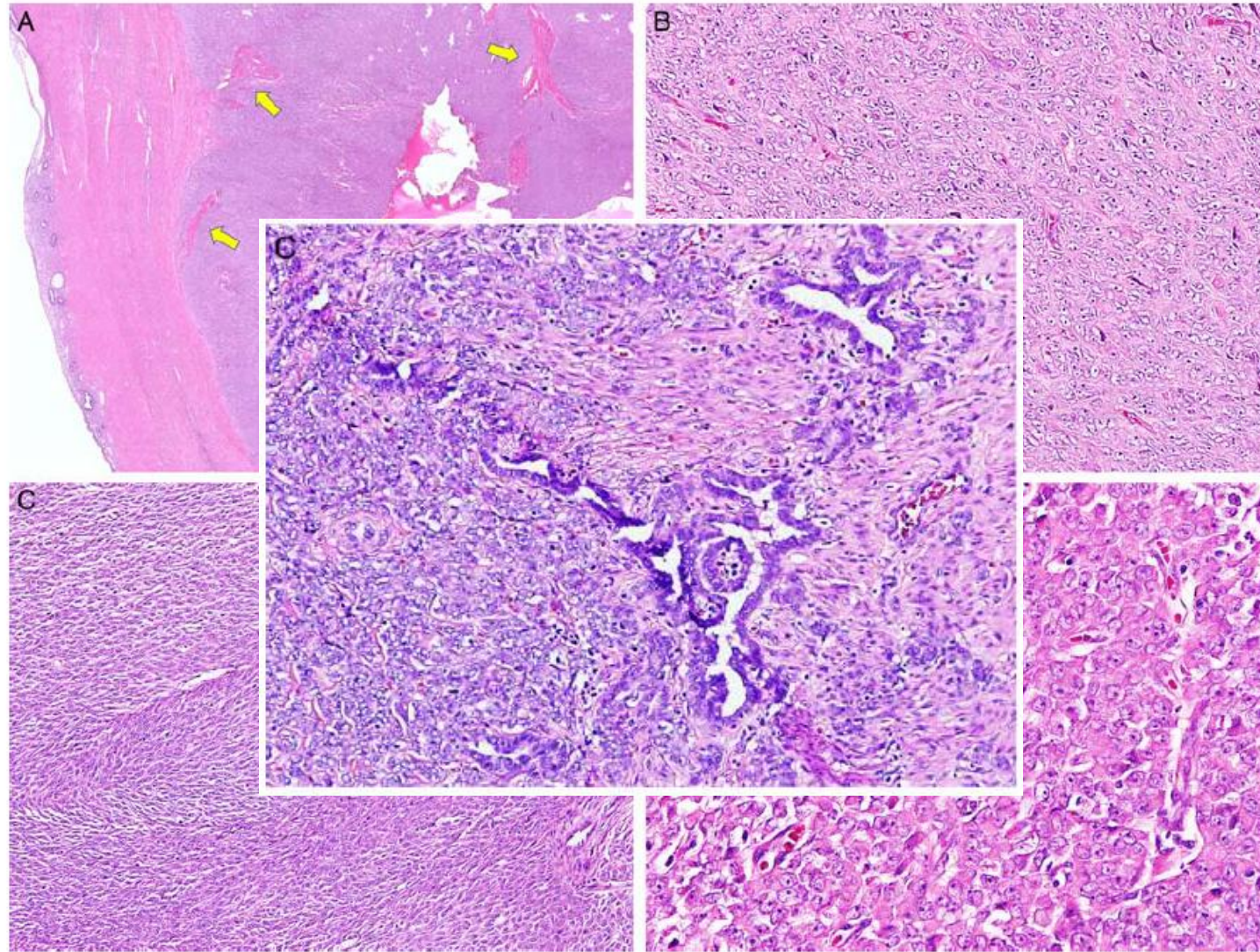
C.H.L. and Y.C.K. contributed equally.





**FIGURE 1.** Histology of case G1. A, At the scanning view, the tumor appears to be well demarcated, although multifocal myometrial entrapment can be observed (arrows). Cystic change is also occasionally seen. B, Predominantly diffuse sheet-like growth pattern; epithelioid to ovoid cells with vesicular nuclei and small distinct nucleoli, intervened by a rich but inconspicuous capillary network. C, Focal fascicular growth pattern, reminiscent of fibrosarcoma or synovial sarcoma. D, Occasional rhabdoid features with more prominent nucleoli.





**FIGURE 1.** Histology of case G1. A, At the scanning view, the tumor appears to be well demarcated, although multifocal myometrial entrapment can be observed (arrows). Cystic change is also occasionally seen. B, Predominantly diffuse sheet-like growth pattern; epithelioid to ovoid cells with vesicular nuclei and small distinct nucleoli, intervened by a rich but inconspicuous capillary network. C, Focal fascicular growth pattern, reminiscent of fibrosarcoma or synovial sarcoma. D, Occasional rhabdoid features with more prominent nucleoli.



## ***GREB1* rearanžované ESS**

- Postmenopauzálně
- Agresivnější biologické chování (metastázy do plic)
- Sex-cord diferenciace buď chybí nebo je přítomna v malé části tumoru
- Uniformní, epiteloidní, s vezikulárním jádrem a prominentním jadérkem

## **UTROSC**

- Premenopauzálně
- Indolentní
- Sex-cord diferenciace je predominantní komponenta tumoru
- Typické sex-cord elementy – Sertoli-like bb a granulóza-like bb tvořící tubulární, retiformní nebo stlačené pruhovité struktury



# Závěr

- endometriální stromální tumory jsou na základě molekulárních alterací členěny na low-grade, high-grade a nediferencovaný endometriální stromální sarkom
- LG-ESS se vyznačují fúzemi *JAZF1-SUZ12* (50%) a *PHF1*
- *PHF1* rearanžované tumory mají často sex-cord – like diferenciaci
- další tumory dělohy se sex-cord - like diferenciací:
  - hladkosvalové tumory
  - mulleriánský adenosarkom
  - UTROSCT
  - (*GREB1* rearanžované ESS)





*Děkuji za pozornost*

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