

右大腿内側に腫瘍を自覚

4ヶ月目

体動時に疼痛が出現

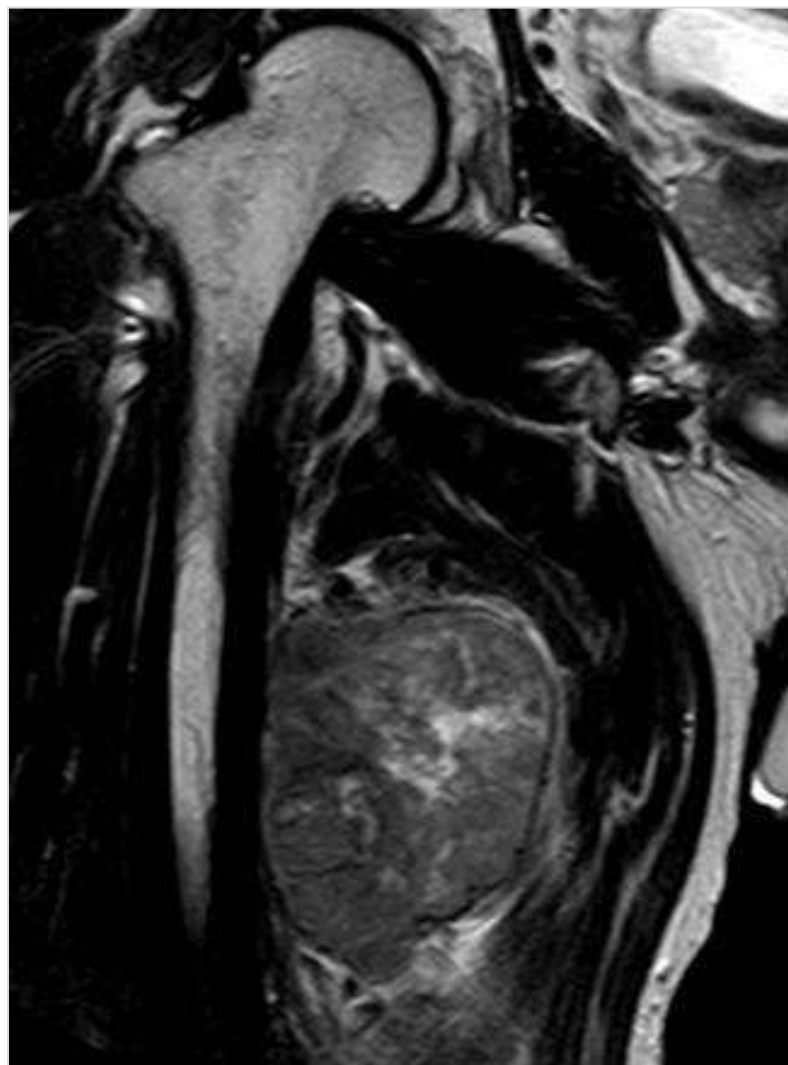
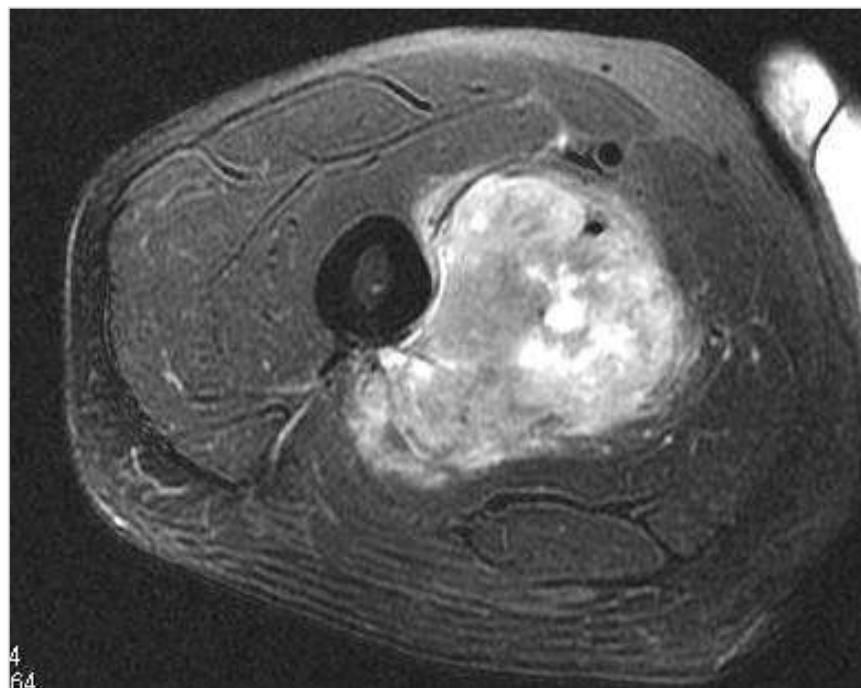
11ヶ月目

疼痛が増悪するために近医を受診

MRIで筋肉内に腫瘍あり

鼠径部にもリンパ節転移と考えられる腫瘍あり

PET-CTで肺と膵臓にも転移が疑われた。



12ヶ月目

当院に紹介となり、生検

15ヶ月目

疼痛管理目的に、鼠径部と大腿部の腫瘍切除

術後化学療法を希望せず

22ヶ月目

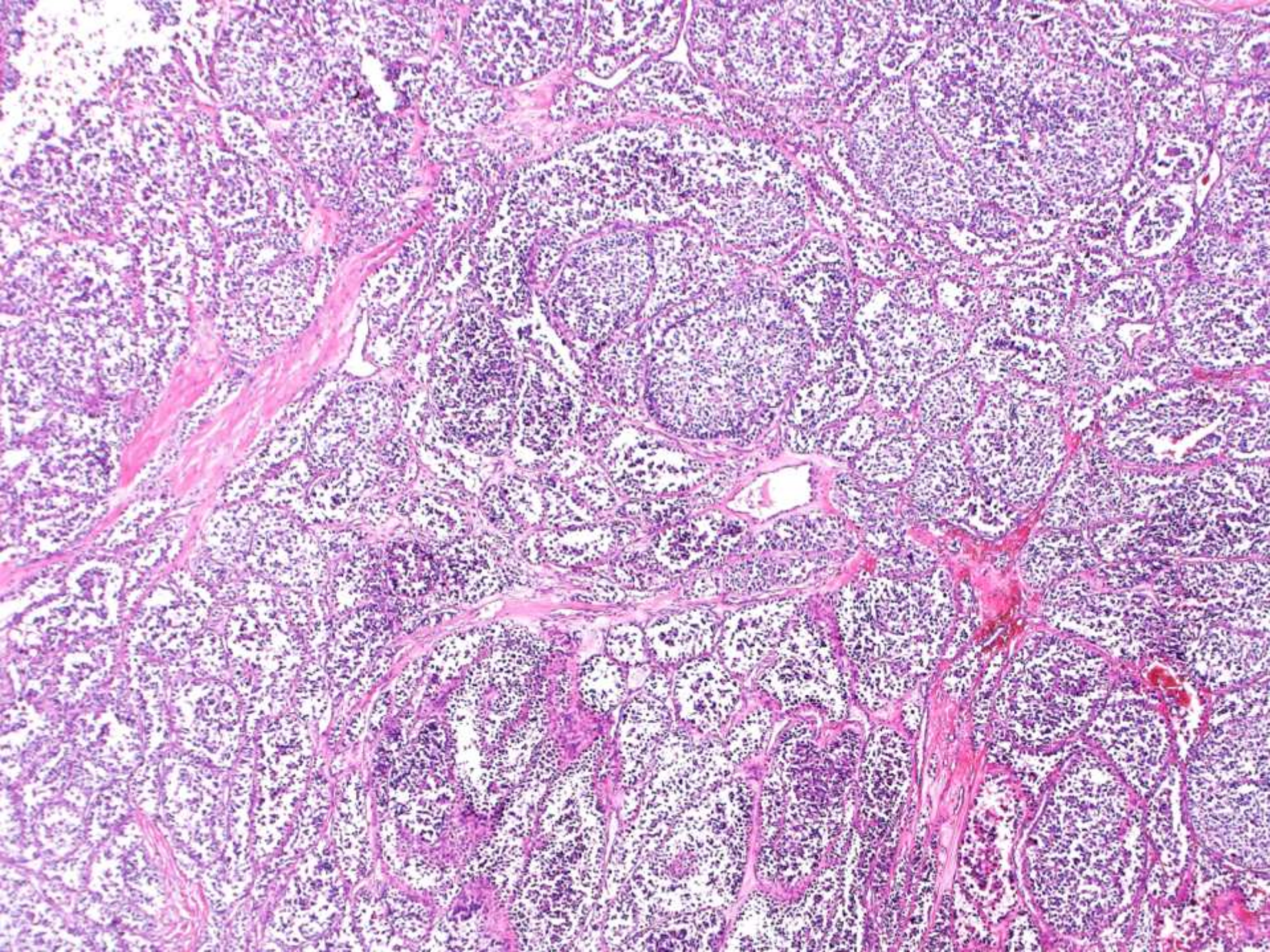
全身転移のため死亡全経過22ヶ月。

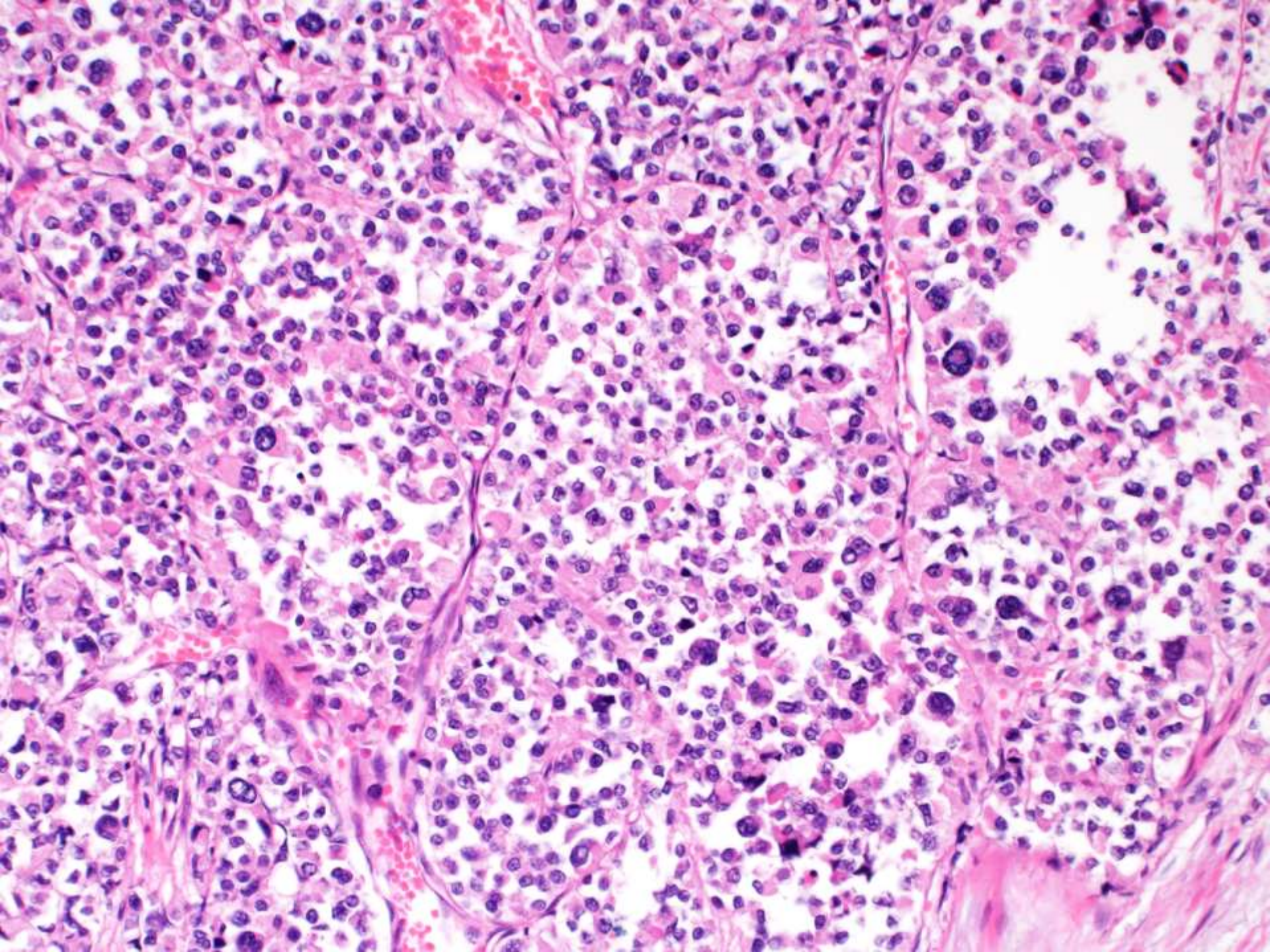


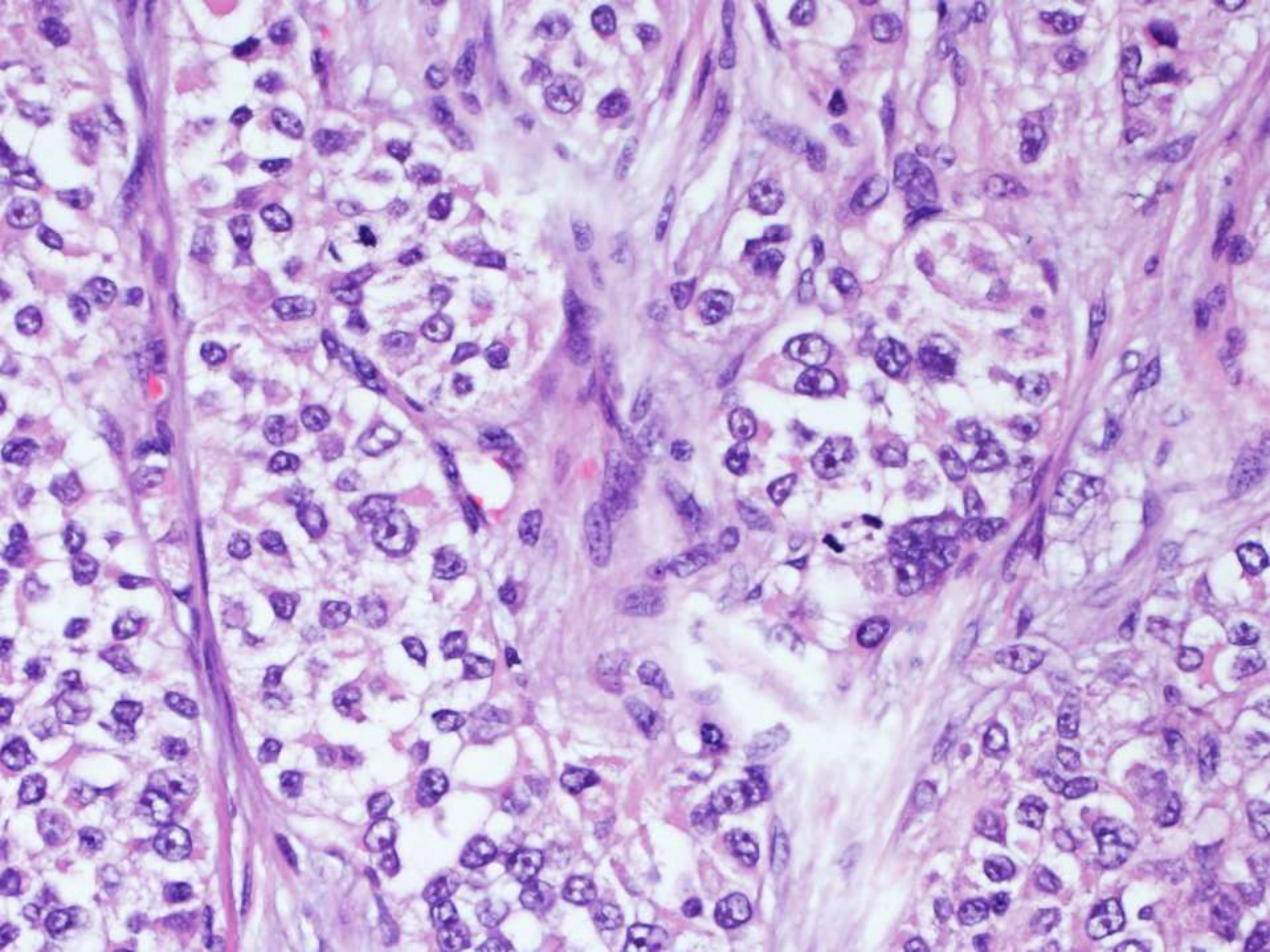
120×70 mm

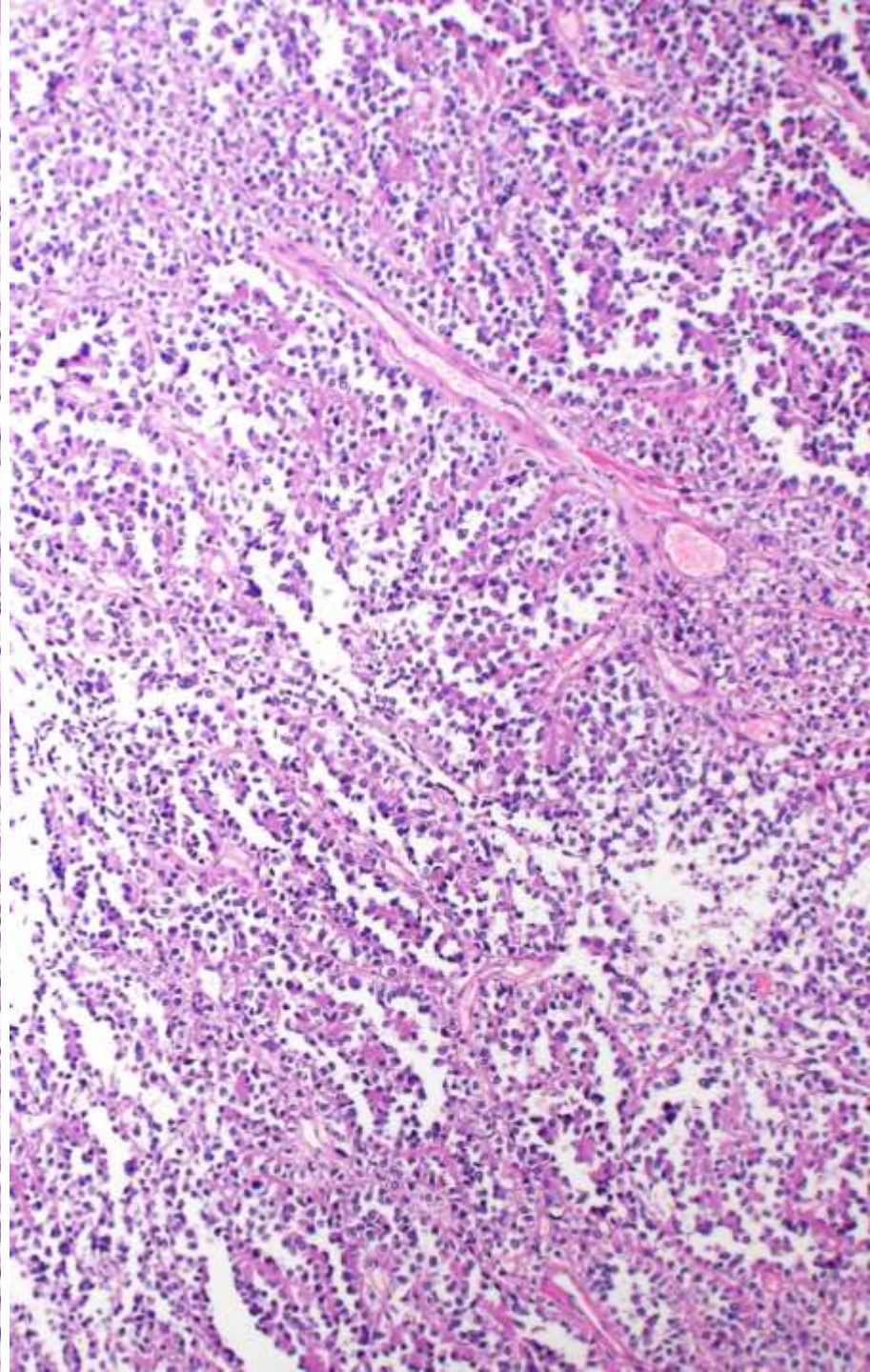
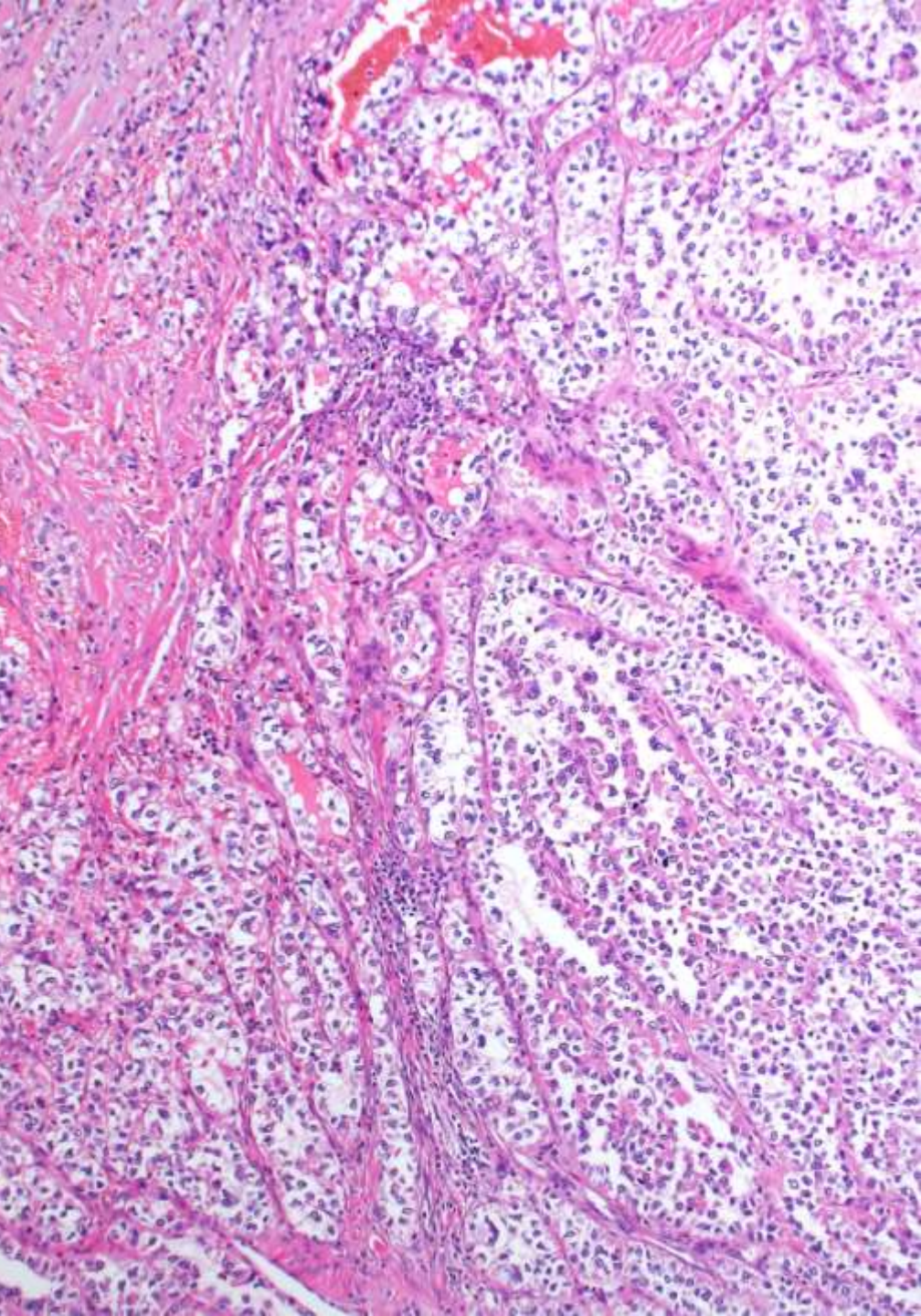


黄白色充实性

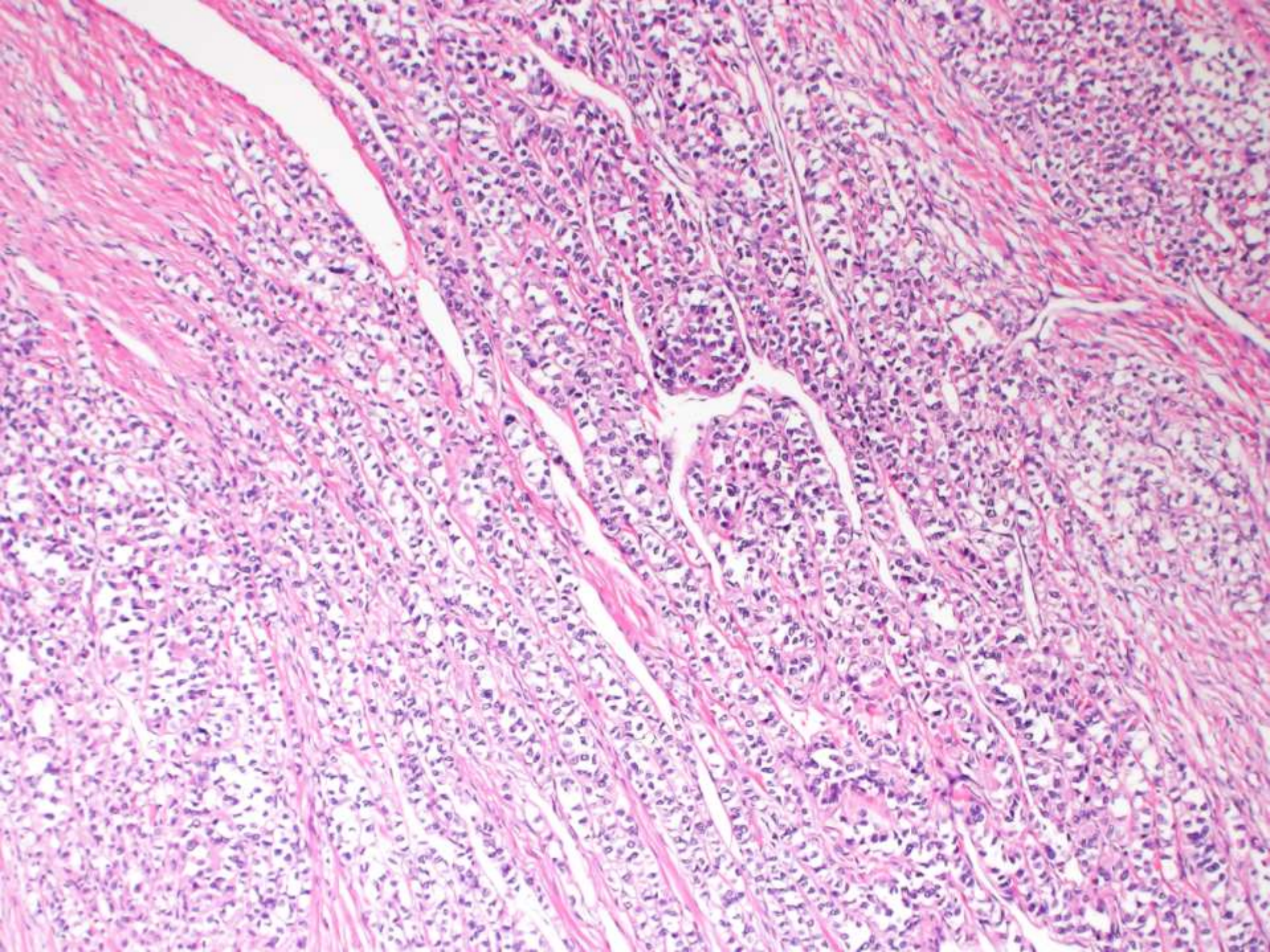


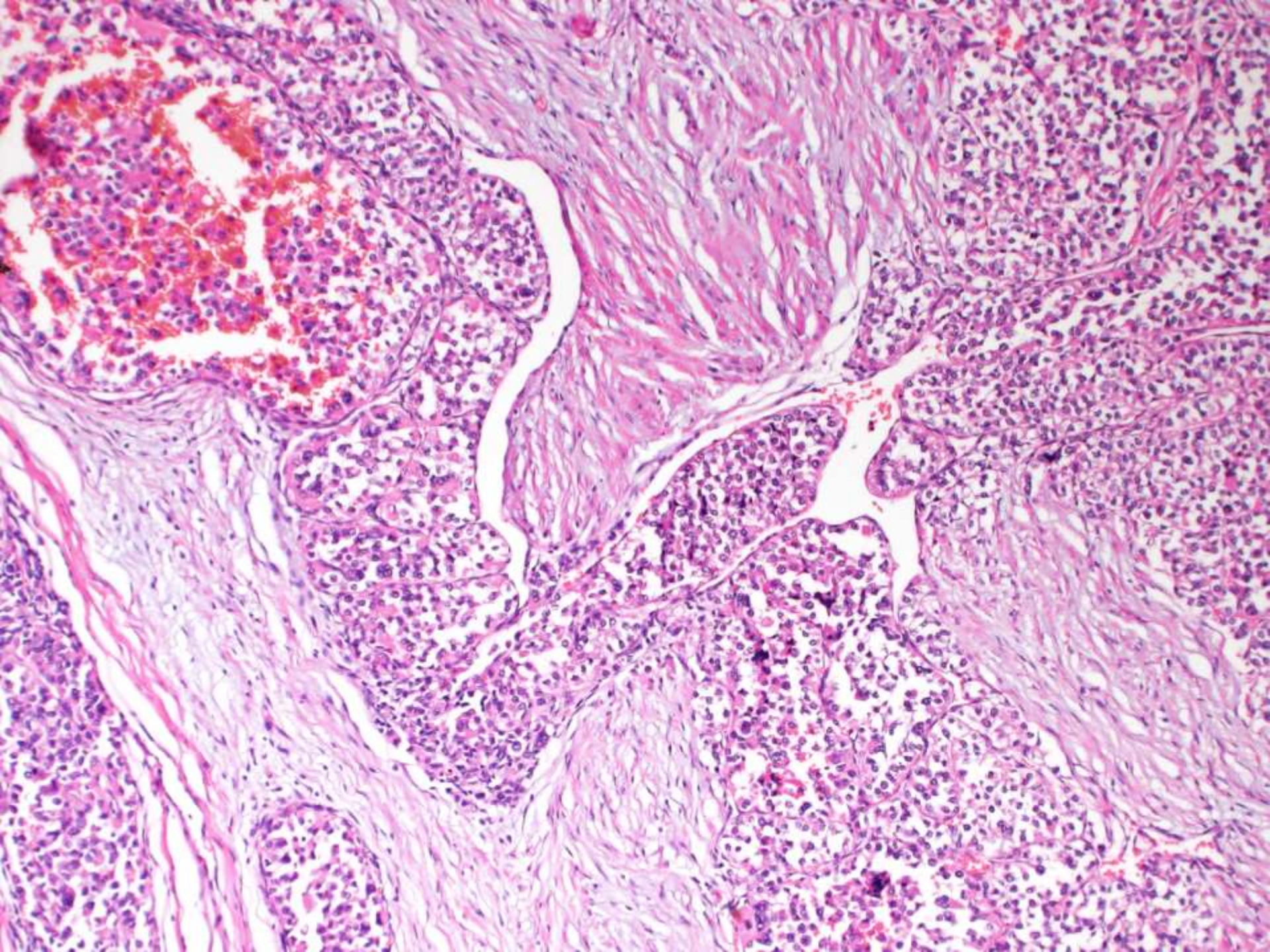


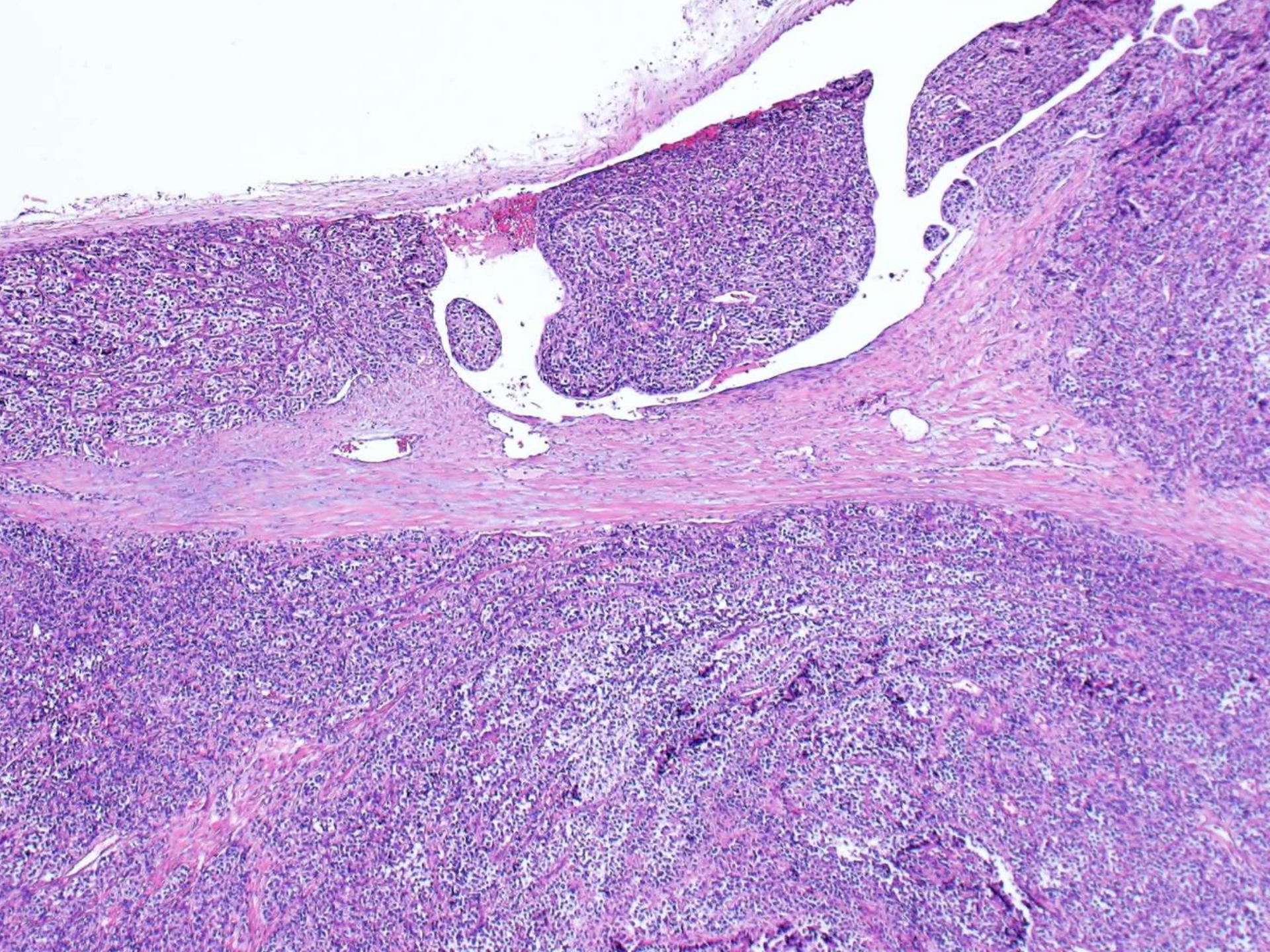




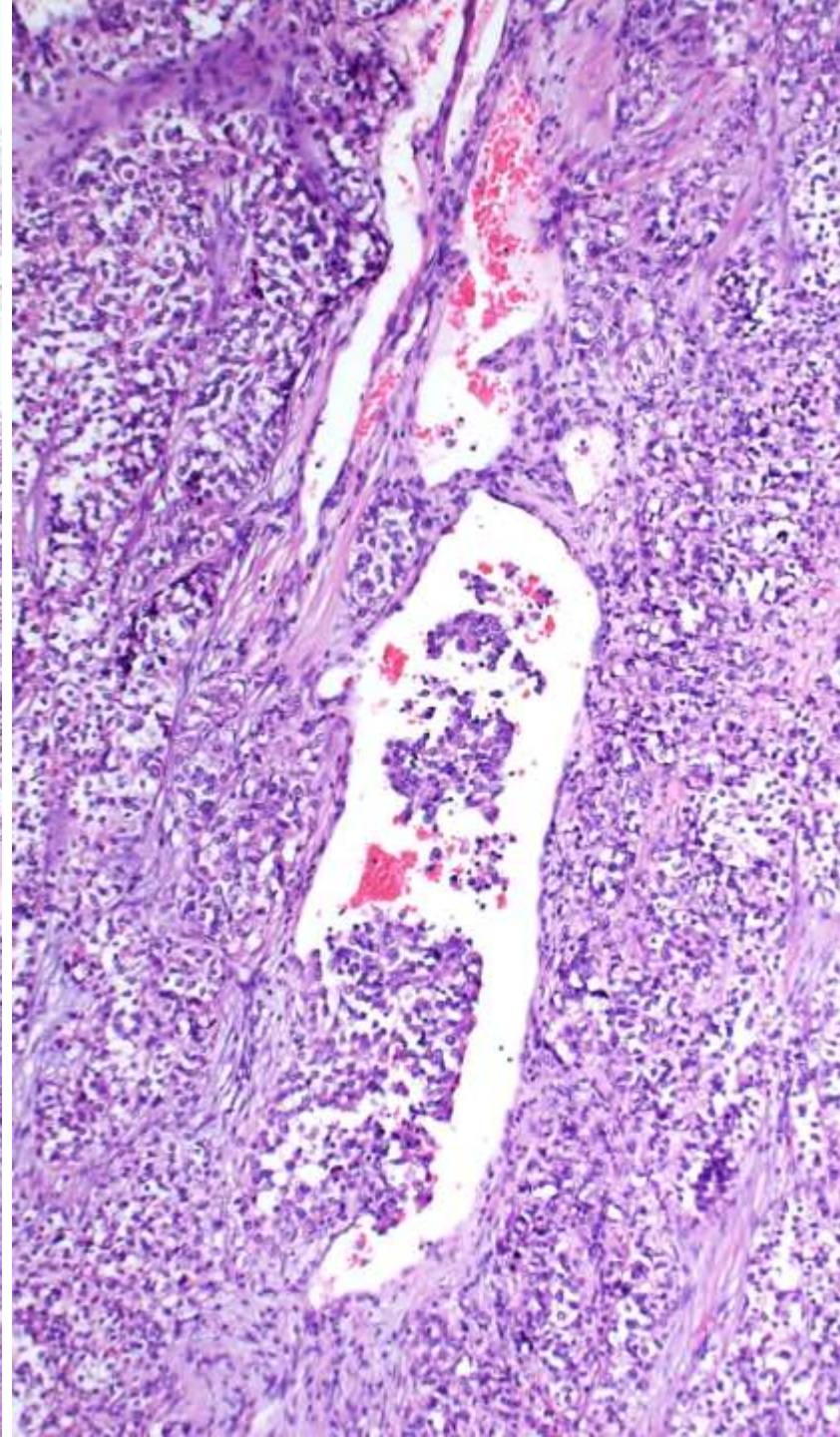
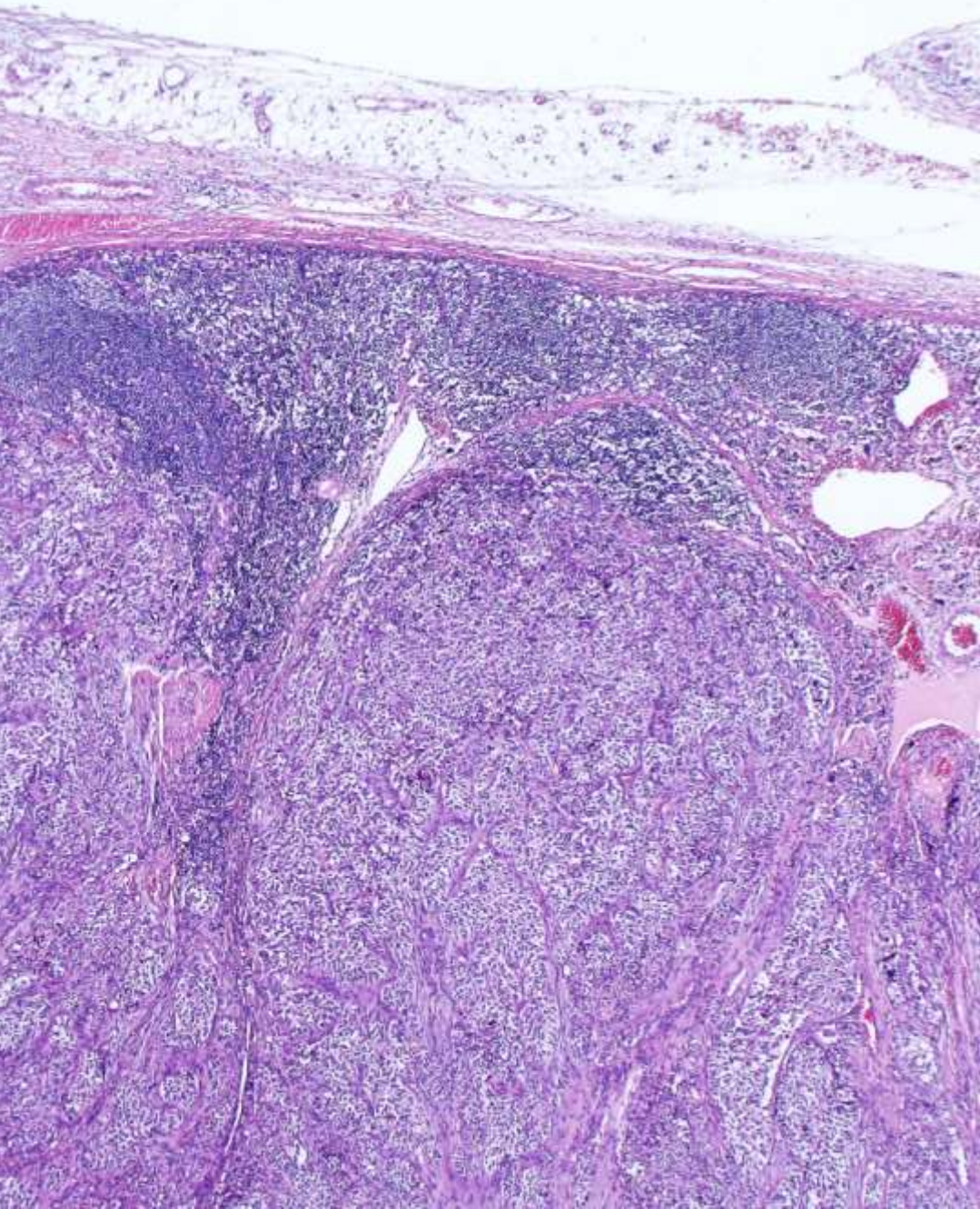








# 鼠径部リンパ節転移



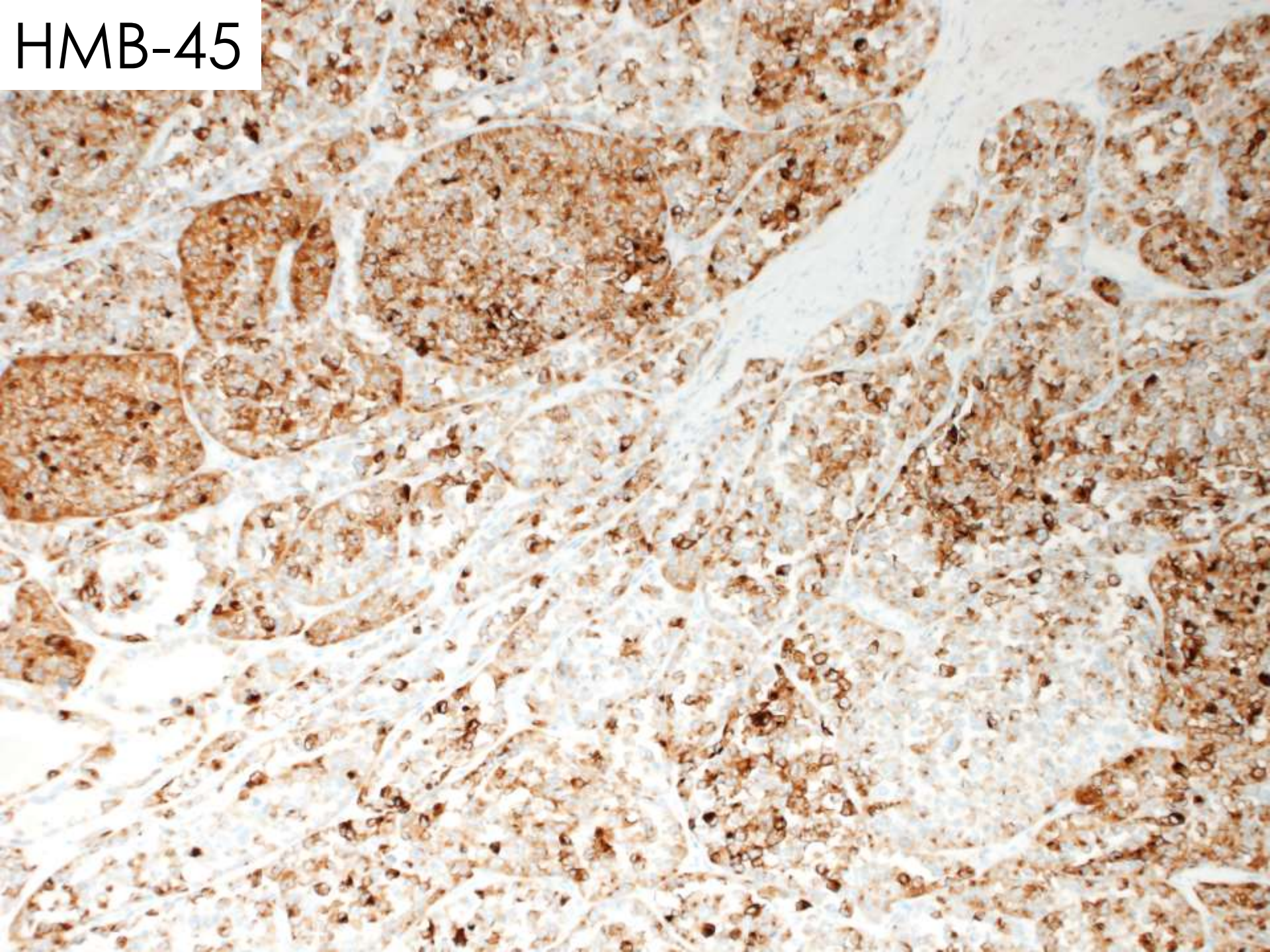
# 組織所見

- 胞巣状、偽乳頭状、充実性
- 類上皮細胞  
ラブドイド、多形性、核分裂像
- スリット状構造、脈管侵襲
- リンパ節転移

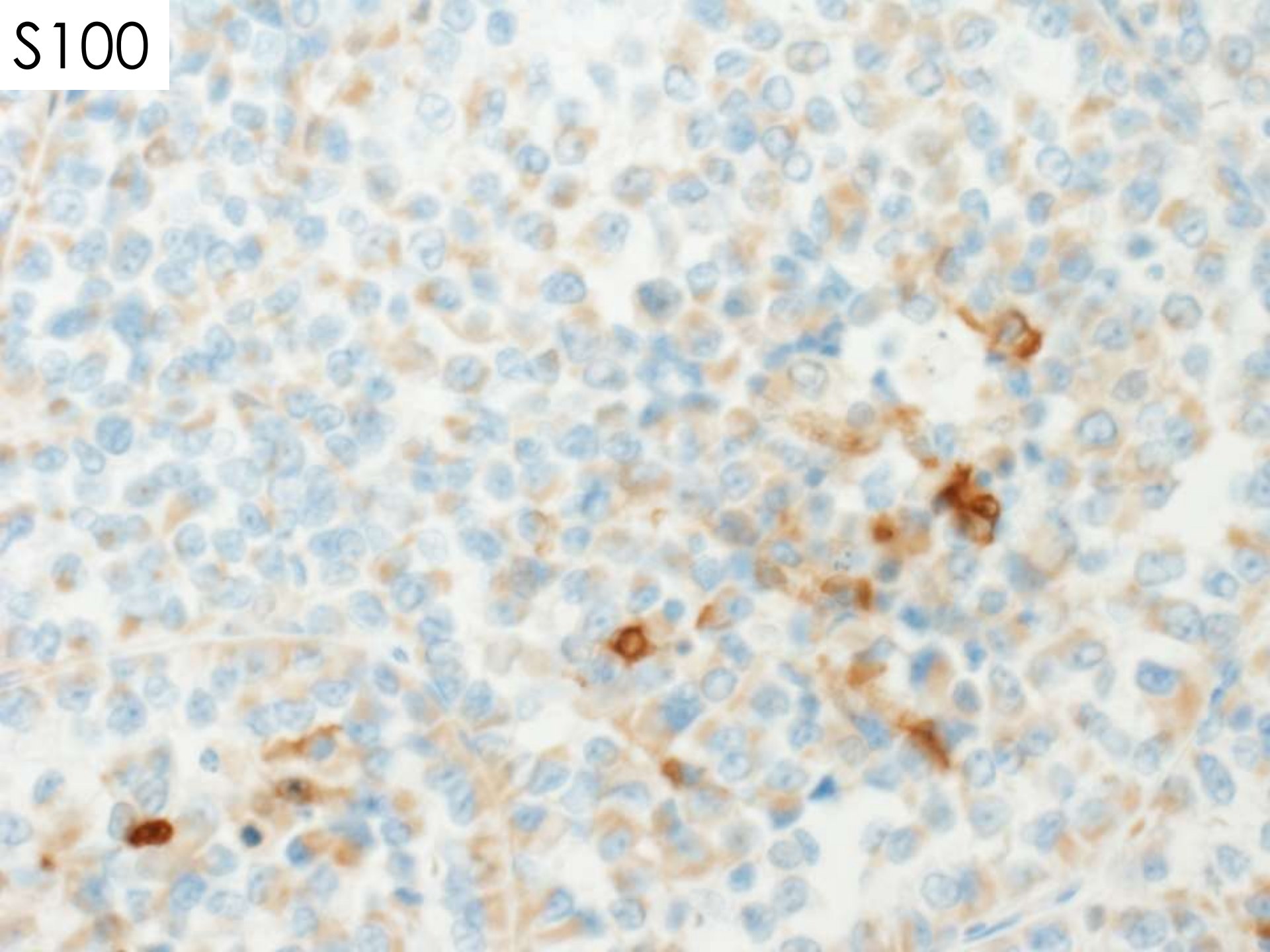
# 鑑別診斷

- Alveolar rhabdomyosarcoma
- Clear cell sarcoma
- Alveolar soft part sarcoma
- PEComa  
(perivascular epithelioid cell tumor)
- Metastatic carcinoma  
(*esp.* renal cell carcinoma)

HMB-45

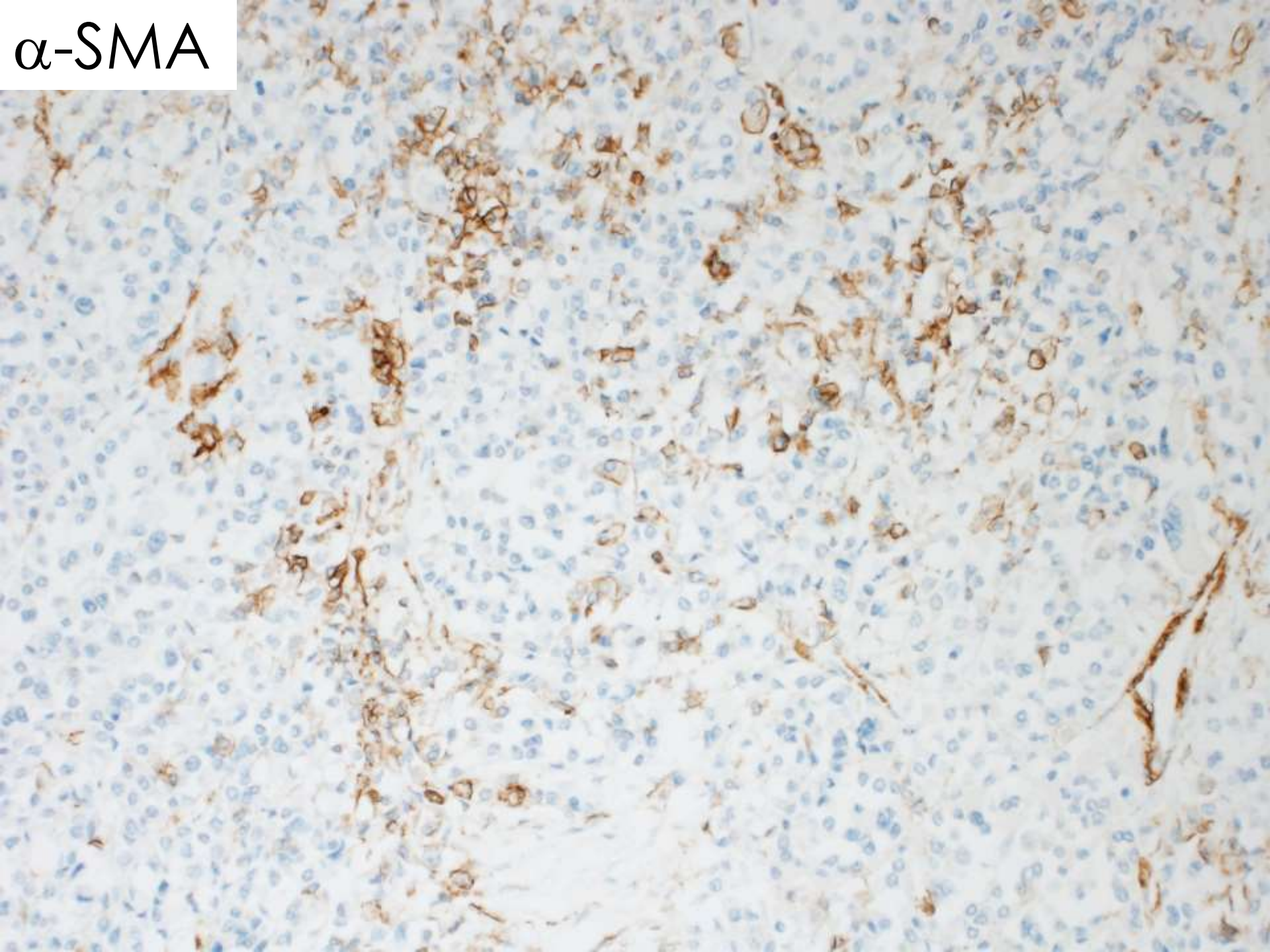


S100

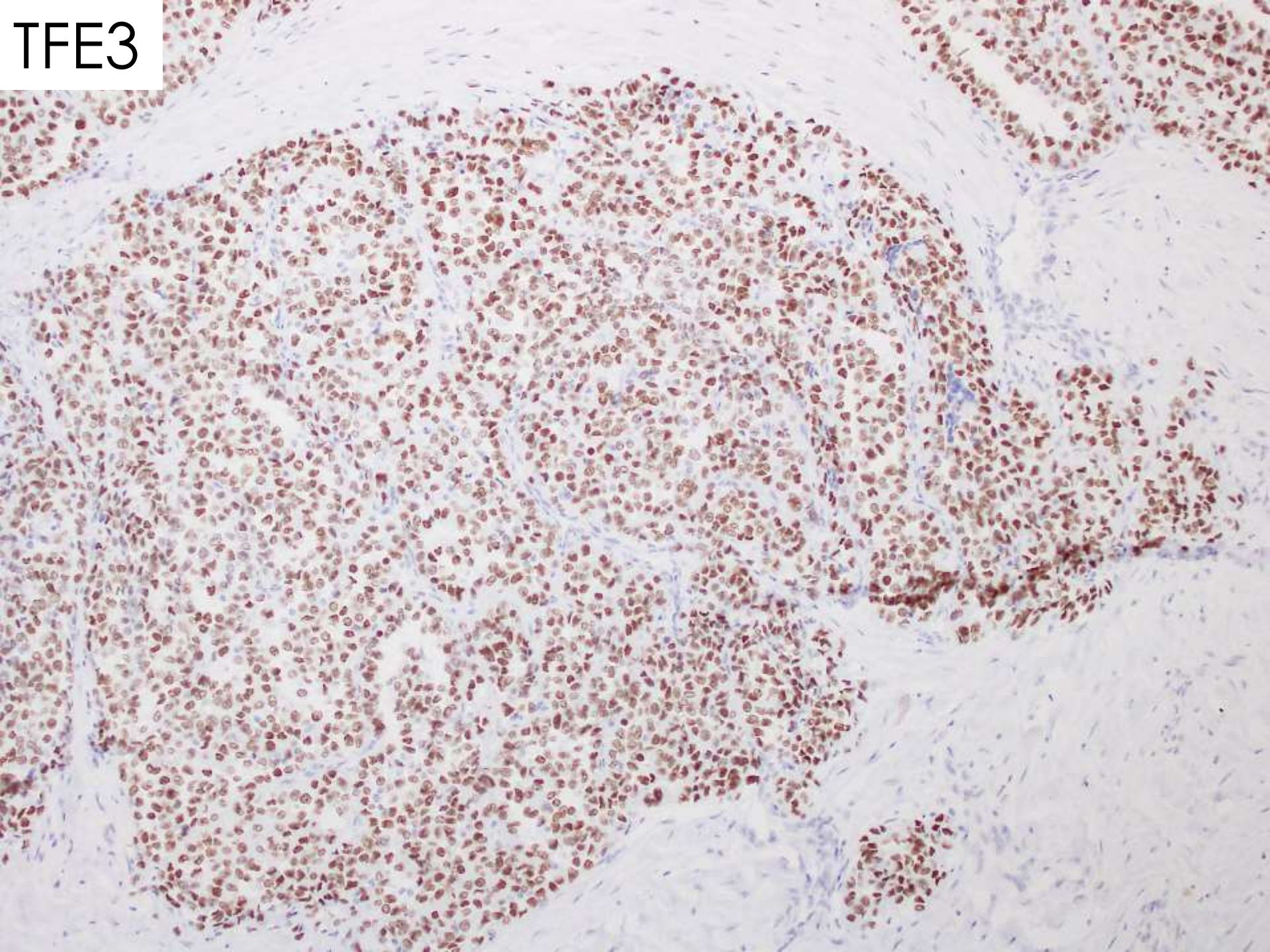




$\alpha$ -SMA



TFE3



# 免疫染色

## 陽性

- TFE3 (diffuse)
  - HMB-45
- 

## 陽性？

- S100
- $\alpha$ -SMA
- p63

## 陰性

- CKs (AE1/AE3, 34bE12, CK5/6, 7, 19, 20)
- EMA
- desmin, caldesmon, myoglobin, MyoD1
- Bcl-2, CD99, CD56, CD10
- $\beta$ -catenin, Melan A
- vimentin, PAX8

# TFE3とは

[www.ncbi.nlm.nih.gov/gene/7030](http://www.ncbi.nlm.nih.gov/gene/7030)

(transcription factor binding to IGHM enhancer 3)

MiTF family 遺伝子 (MiTF, TFE3, TFEB)

遺伝子座: Xp11.22

TGF- $\beta$  シグナル伝達の下流にある転写因子

細胞増殖や代謝に関連

栄養応答転写因子？

# TFE3とは

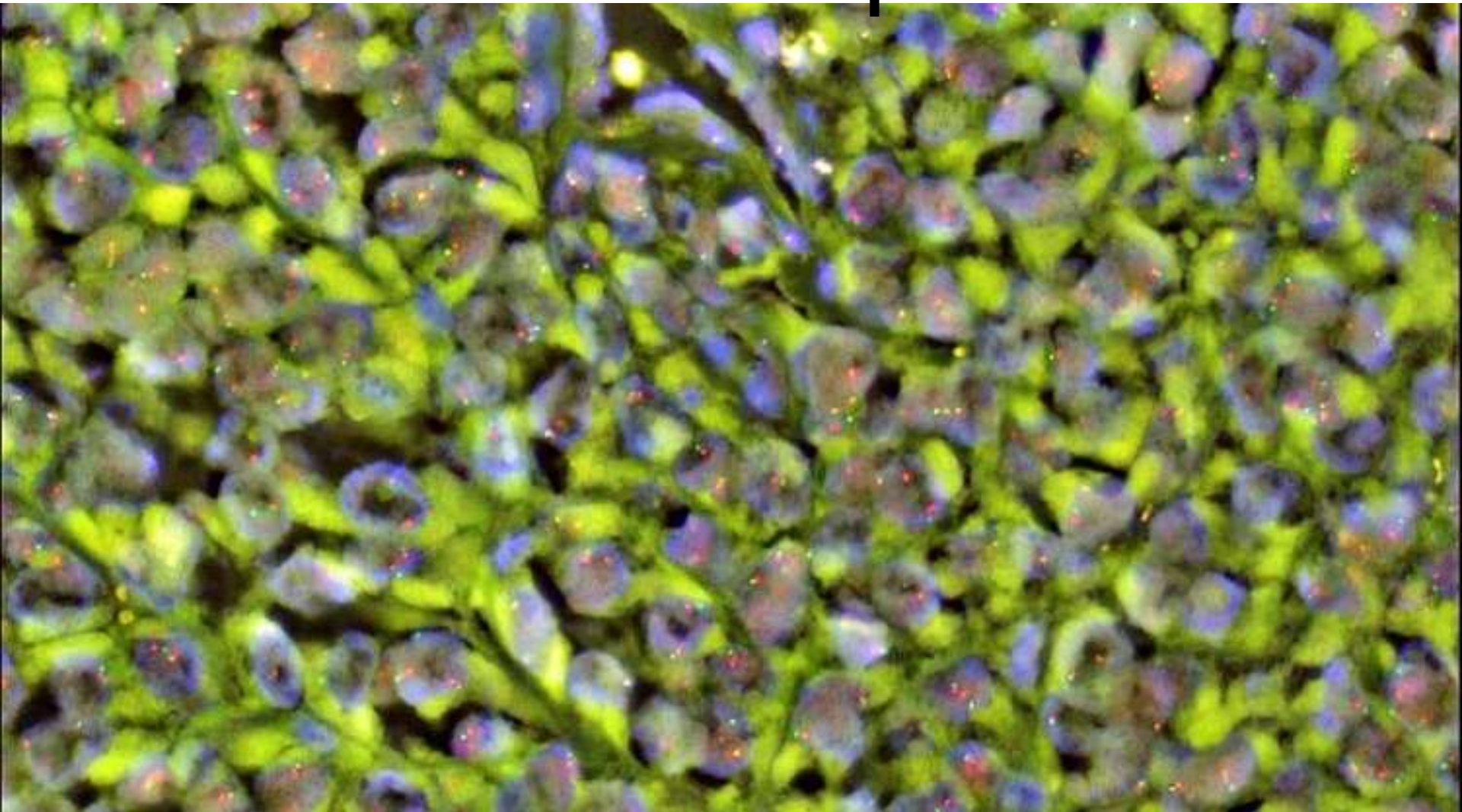
[www.ncbi.nlm.nih.gov/gene/7030](http://www.ncbi.nlm.nih.gov/gene/7030)

(transcription factor binding to IGHM enhancer 3)

転座による融合遺伝子が種々の腫瘍発生に関連

- Alveolar soft part sarcoma (ASPSCR1-TFE3)
- Renal cell carcinoma (ASPSCR1-TFE3, PRCC-TFE3, SFPQ-TFE3, NONO-TFE3, CLTC-TFE3 , NONO-TFE3, DVL2-TFE3)
- Epithelioid hemangioendothelioma (YAP1-TFE3)
- PEComa (SFPQ-TFE3, DVL2-TFE3 , NONO-TFE3)

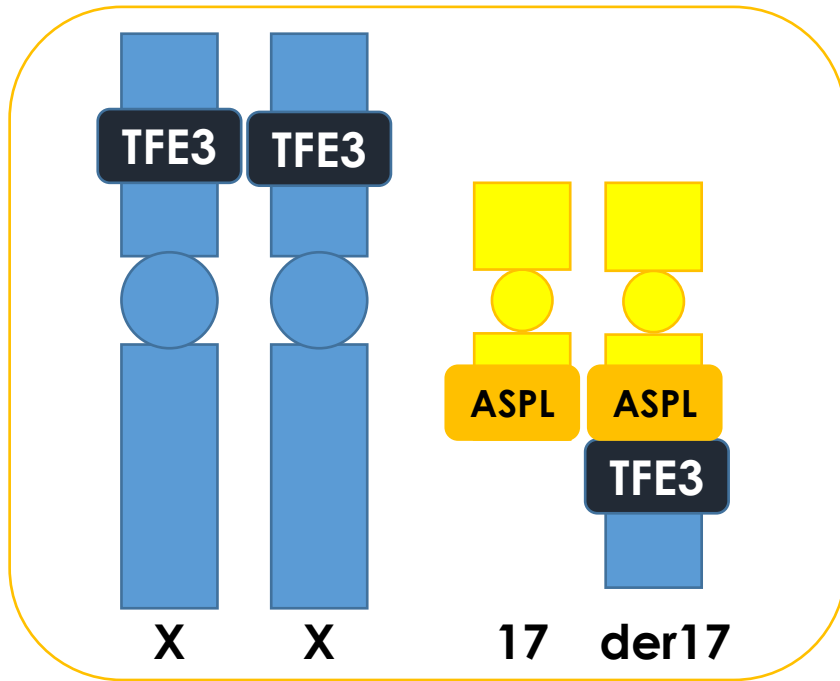
# TFE3 break-apart FISH



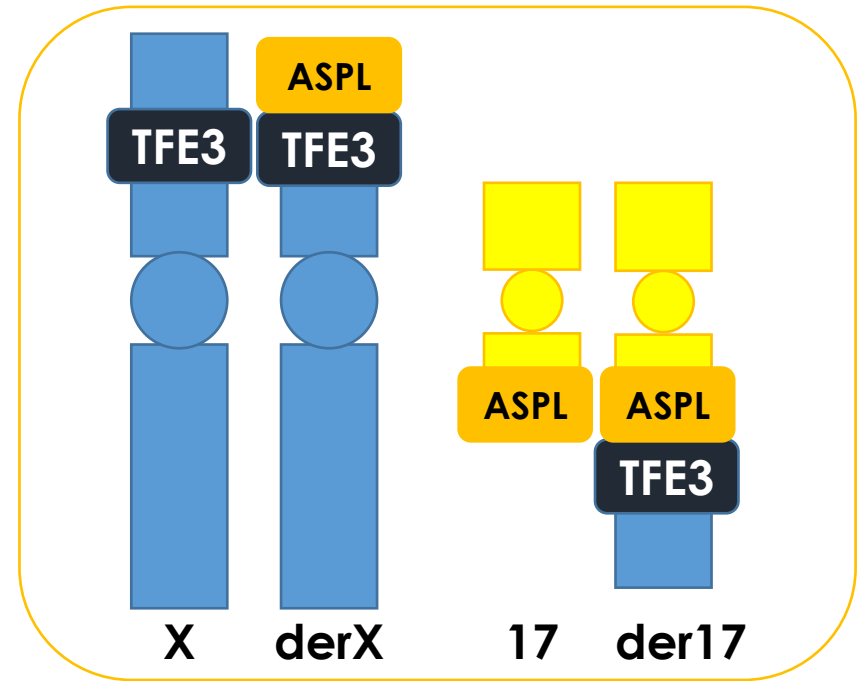
56.68%の細胞にbreak-apart

高知赤十字病院

# Translocation in ASPS

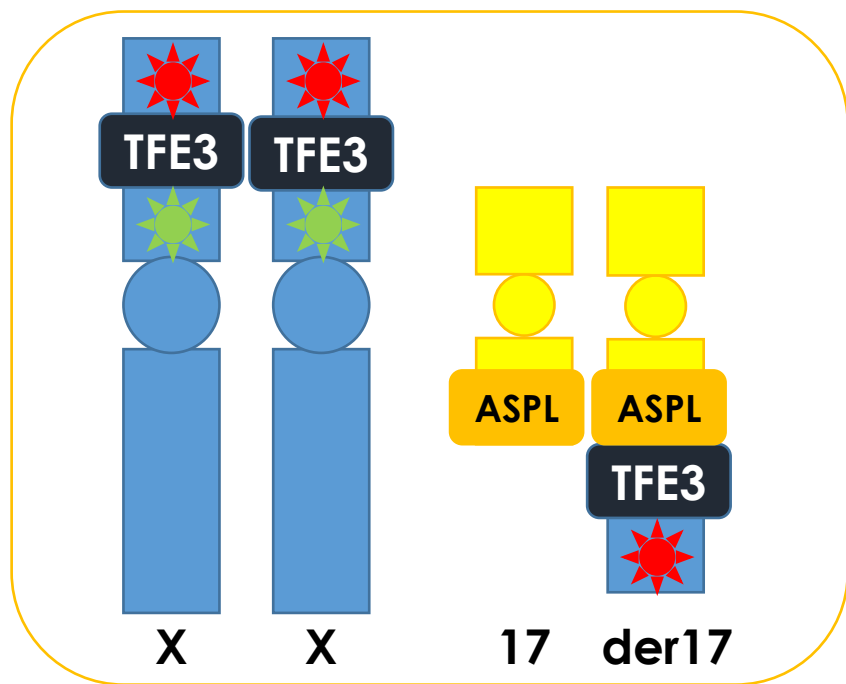


**ASPS: Unbalanced**

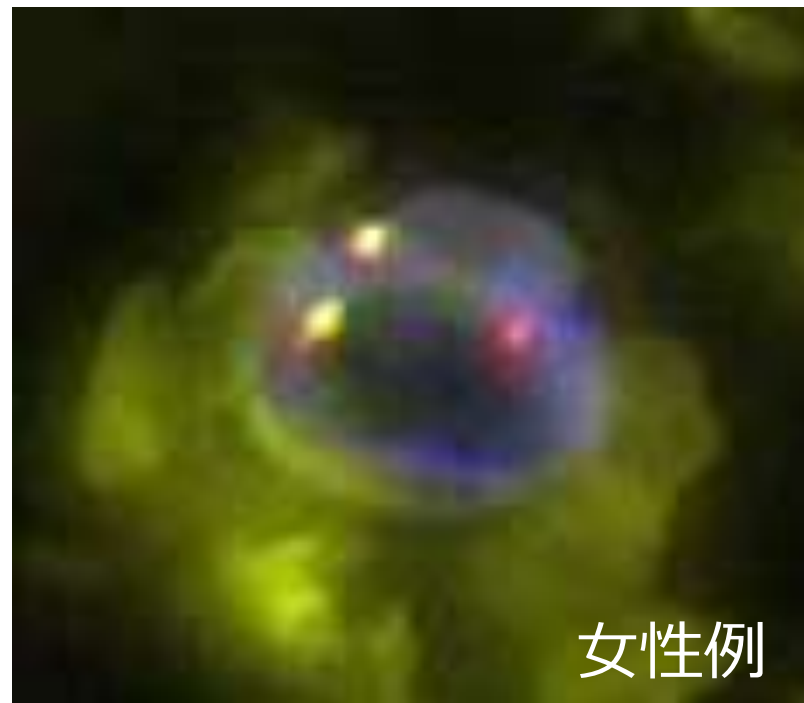


**Xp11.2 RCC: Balanced**

# Translocation in ASPS



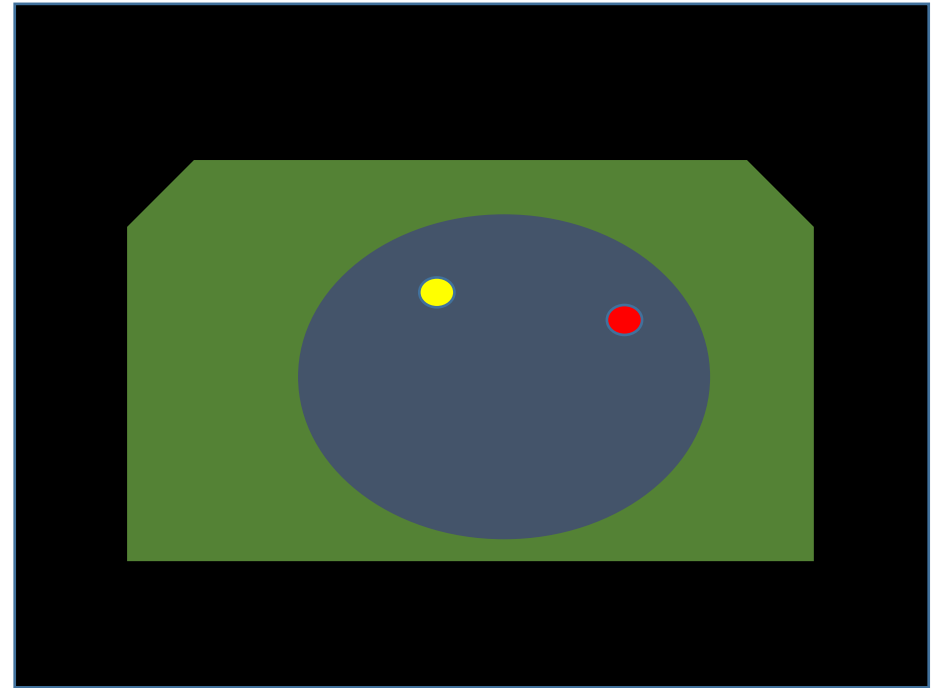
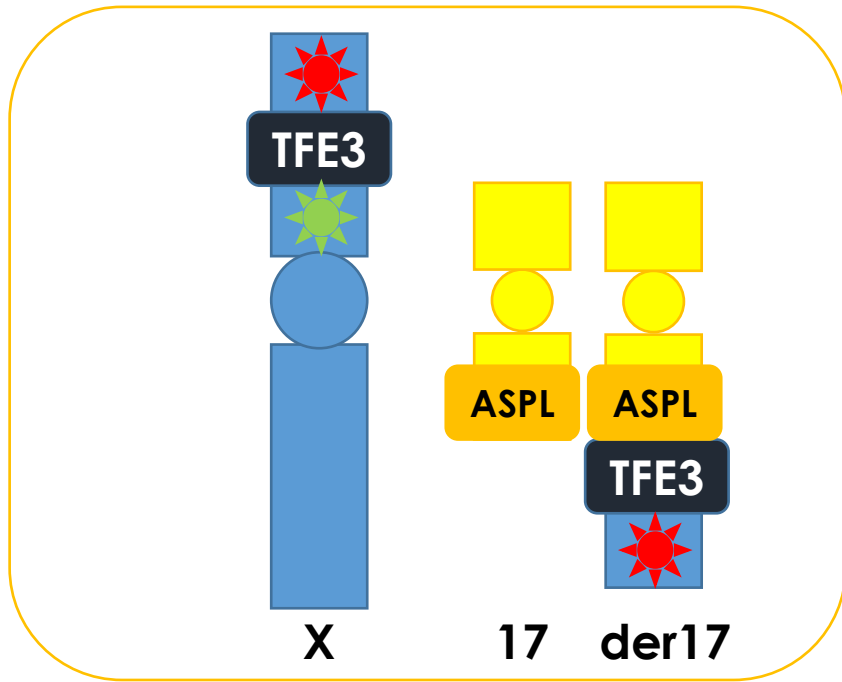
女性例 ASPS



女性例

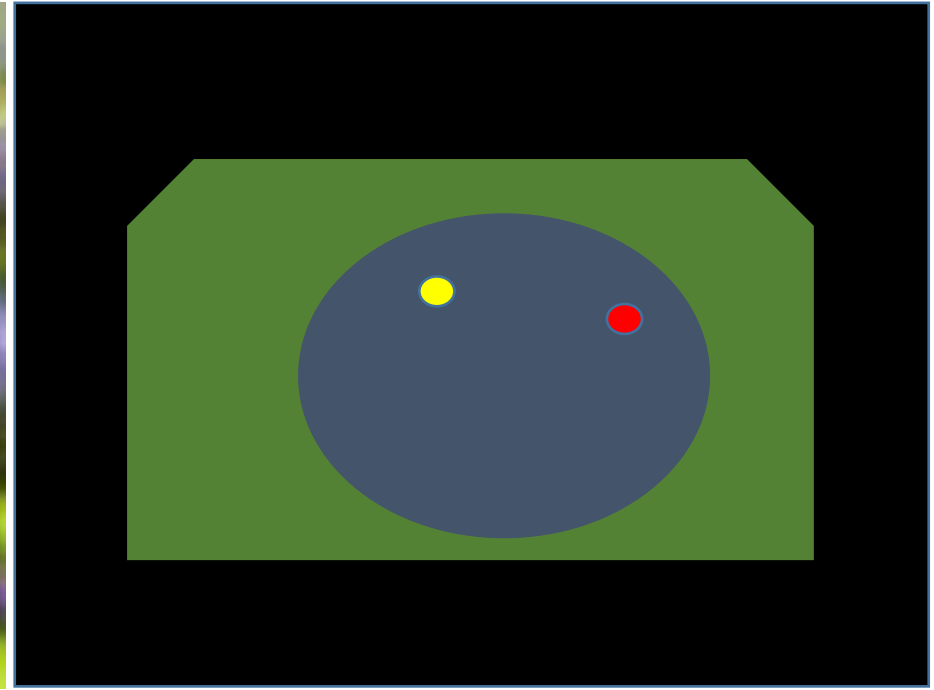
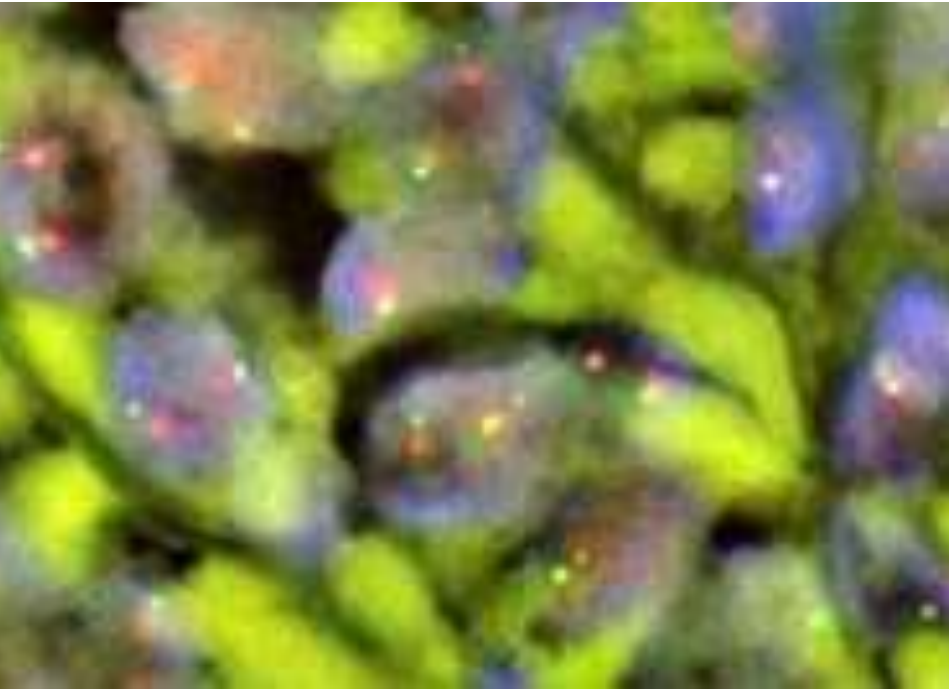


# TFE3 break-apart FISH



男性例 ASPS

# TFE3 break-apart FISH



本例(男性例) ≠ ASPS(男性例)

# 鑑別診斷

- Alveolar rhabdomyosarcoma
- Clear cell sarcoma
- Alveolar soft part sarcoma
- PEComa  
(perivascular epithelioid cell tumor)
- Metastatic carcinoma  
(esp. renal cell carcinoma)

# PEComa with TFE3

2005年、軟部・婦人科臓器の PEComa の一部で TFE3 陽性を報告(5例/17例)

*Folpe et al. AJSP 2005;29:1558*

2009年、TFE3陽性 PEComa の一部で TFE3 遺伝子の転座を報告(SFPQ-TFE3)

*Tanaka et al. AJSP 2009;33:1416*

## **PEComa with *TFE3* gene rearrangement**

現在まで、種々の臓器で報告

# PEComa with *TFE3* gene rearrangement

Argani et al

Am J Surg Pathol • Volume 34, Number 10, October 2010

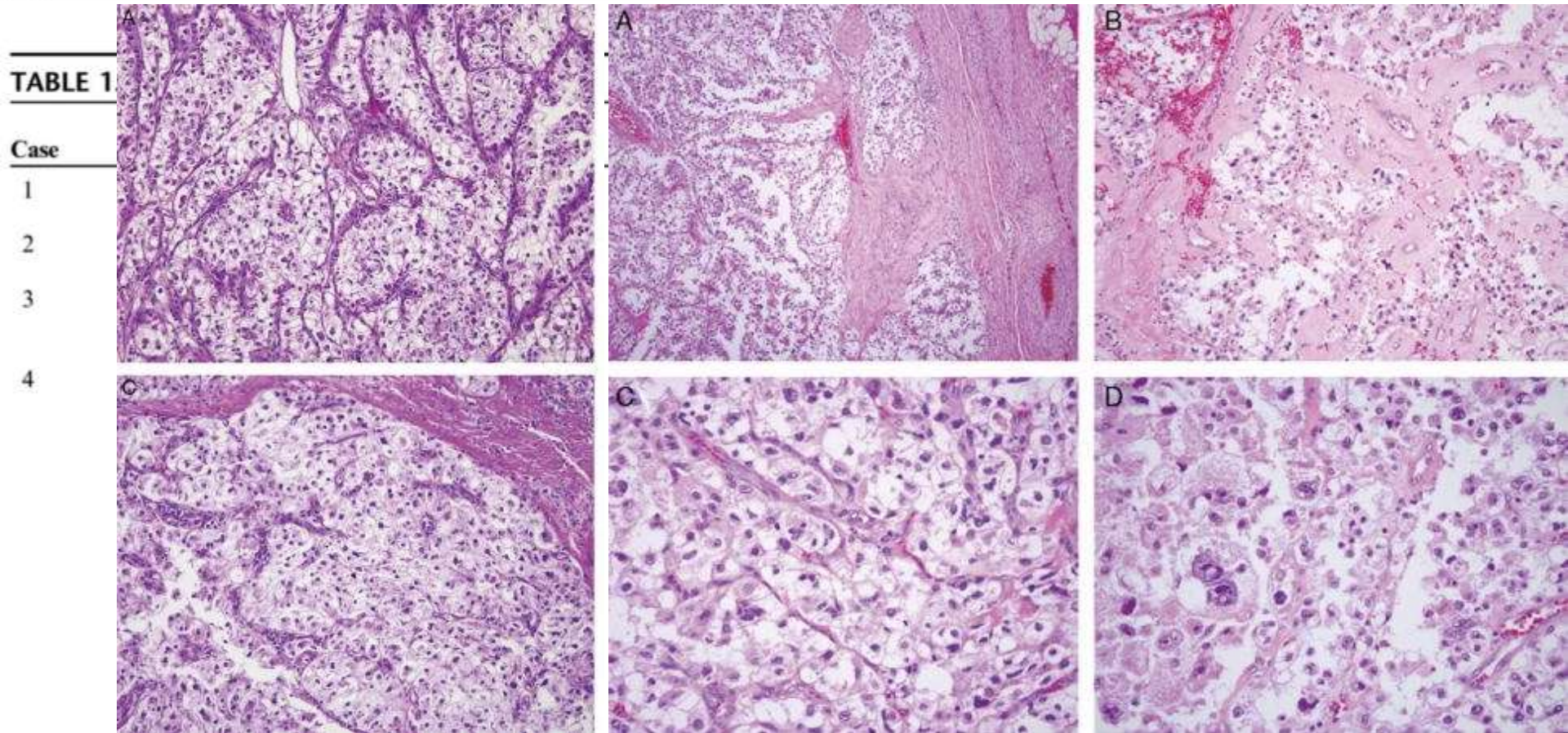
**TABLE 1.** PEComas in This Study

Case	Age/ Sex	Location, Size	TFE3 FISH	TFE3 IHC: Manual/Automated	Morphology	Other IHC
1	16/F	Colon, 1.8 cm	Balanced translocation	3+/3+	E	Cathepsin K+, <i>HMB45</i> +, <i>Melan A</i> , <i>Actin</i> , <i>Desmin</i> - <i>PAX8</i> -, <i>MitF</i> -, <i>S100</i> -
2	9/F	Uterus	Balanced translocation	3+/3+	E	Cathepsin K+, <i>HMB45</i> +, <i>Melan A</i> , <i>Actin</i> , <i>Desmin</i> -, <i>PAX8</i> -, <i>MitF</i> -, <i>S100</i> -
3	33/F	Buttock	Balanced translocation	3+/3+	E	Cathepsin K+, <i>HMB45</i> +, <i>Melan A</i> , <i>Actin</i> , <i>Desmin</i> , <i>PAX8</i> -, <i>MitF</i> , <i>S100</i> , <i>CD34</i> , <i>EMA</i> , <i>CD10</i> , <i>Cytokeratin</i> -
4	46/F	Thigh, 6.5 cm	Balanced translocation	3+/3+	E	Cathepsin K+, <i>HMB45</i> +, <i>Melan A</i> + (focal); <i>Cytokeratin</i> , <i>S100</i> , <i>Actin</i> , <i>Desmin</i> , <i>CD31</i> , <i>CD34</i> , <i>MitF</i> -

# PEComa with TFE3 gene rearrangement

Argani *et al*

*Am J Surg Pathol* • Volume 34, Number 10, October 2010



5	40/F	Lung metastasis of uterine lesion	Amplified (6–8 copies)	2+/3+	E, ANA	Cathepsin K+, Actin+ (focal), Melan A+ (focal), S100+; Cytokeratin, HMB45 –*
6	71/M	Arm (subcutaneous), 4 cm	Negative	2+/3+	E, ANA	Cathepsin K+, Desmin+, HMB45+; Cytokeratin, S100, Actin, Melan A, MiTF –
7	80/M	Scalp, 2 cm	Negative	2+/3+	E, ANA	Cathepsin K+, Actin+, Desmin+, HMB45+; Cytokeratin –, S100 –, MiTF –, Melan A –
8	63/F	Retroperitoneal, 16 cm	Negative	1+/2+	E, S	Actin+, HMB45+, Melan A+; Cytokeratin, Desmin, S100 –
9	26/F	Superficial thigh, 3 cm	Negative	1+/2+	E, F	Melan A+; Actin –
10	69/F	Pelvic	Negative	2+/2+	E	Actin+, HMB45+
11	48/F	Dorsal lateral foot	Negative	1+/0	E, S	Actin+, Desmin+ (focal), HMB45+, Melan A+
12	56/F	Uterine curettage	Negative	1+/2+	E, ANA	Actin+, Desmin+ (focal), Melan A+, HMB45+, S100+ (focal)
13	36/F	Retroperitoneal	Negative	1+/1+	E, S	Actin+, HMB45+, S100+ (focal)
14	53/F	Renal, 3 cm	Negative	2+/2+	E	Actin+, HMB45+; Cytokeratin –
15	42/F	Perirenal, 14 cm	Negative	1+/0	E, F	Actin+, HMB45+, Melan A+
16	52/F	Renal, 1.2 cm	Negative	0/1+	S, F	
17	67/M	Renal, 3 cm	Negative	1+/0	E, S, F	
18	60/F	Renal, 1.3 cm	Negative	1+/0	S, F	HMB45+, Melan A+, Actin+, Desmin +; CD34 –, S100 –
19	73/F	Renal, 1.3 cm	Negative	0/0	S, F	
20	37/F	Renal, 6.0 cm	Negative	0/0	S, E, F	
21	54/F	Renal, 2.7 cm	Negative	0/0	S	Actin+, Desmin+, HMB45+ (focal); Cytokeratin –
22	48/F	Renal, 1.8 cm	Negative	0/0	S	HMB45+ (focal)
23	55/F	Renal, 6.0 cm	Negative	0/0	S, E, F	
24	28/M	Renal, 2.5 cm	Negative	1+/0	E, S, F	
25	37/F	Renal, 10 cm	Negative	0/0	E, ANA	HMB45+, Melan A+; Cytokeratin –, EMA –
26	78/F	Renal, 6.0 cm	Negative	0/0	E	HMB45+, Melan A+; Cytokeratin –, MiTF –
27	56/F	Perirenal, 3.0 cm	Negative	0/0	E	Melan A+, Actin+ (focal), EMA+ (focal); HMB45 –, PAX8 –, Desmin –, S100 –, Cytokeratin –
28	64/M	Perirenal, 5.5 cm	Negative	0/2+	E	HMB45+, Melan A+, CD10+ (focal); S100, PAX8, PAX2 –, MiTF –, RCC Marker –, Cytokeratin –, Actin –
29	32/F	Renal	Negative	0/2+	E, ANA	HMB45+, Melan A+, CD10+ (focal); S100, PAX2, PAX8, MiTF, RCC marker –, Cytokeratin –

# Rearrangement

# Amplification

1

16/F

Colon, 1.8 cm

Balanced  
translocation



5

40/F

Lung metastasis of  
uterine lesion

Amplified (6-8  
copies)



同じ？違う？



**PEComa with  
*TFE3* gene**

**Rearrangement?**

**Amplification?**



# RNAシーケンス

gene\_overlapping\_the\_1st\_breakpoint

**ZC3H4**

exonintron\_junction\_overlapping\_the\_1st\_breakpoint

**ZC3H4.end**

gene\_overlapping\_the\_2nd\_breakpoint

**TFE3**

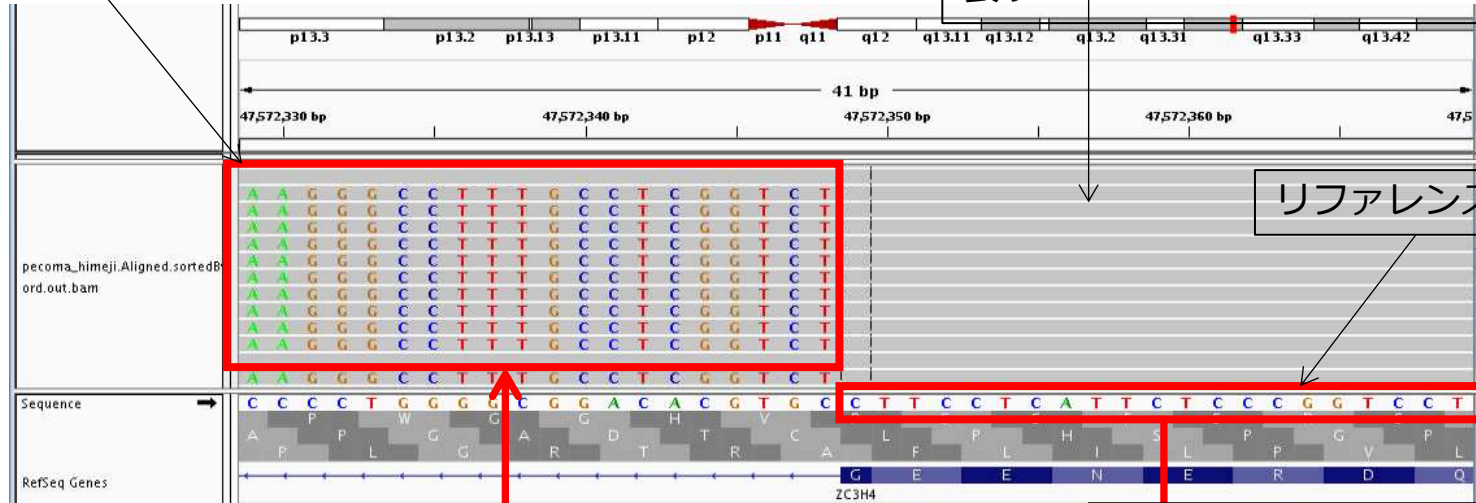
exon-intron\_junction\_overlapping\_the\_2nd\_breakpoint

**TFE3.start**

# ZC3H4-TFE3 fusion

リファレンスゲノムと異なる部分

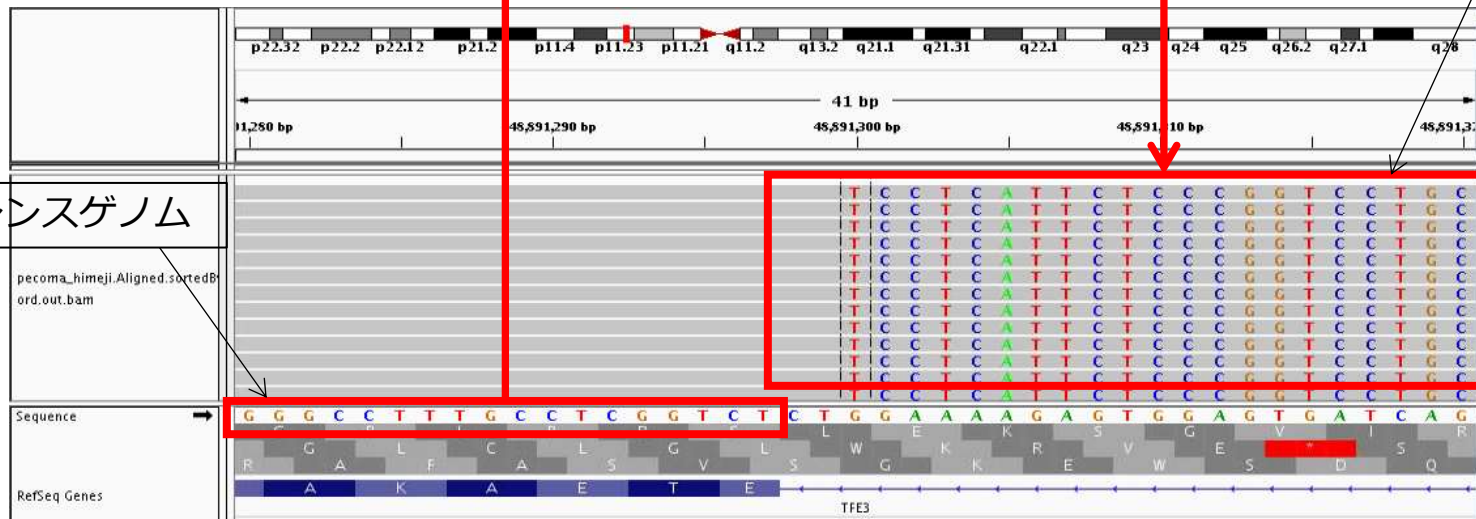
1本がシークエンスした各リードを表し、色つき部がリファレンスと異なる塩基を表す



リファレンスゲノム

リファレンスゲノムと異なる部分

リファレンスゲノム



# 演者診断

新規癒合遺伝子

ZC3H4-*TFE3*を同定した

PEComa

with *TFE3* gene rearrangement

# ZC3H4

PubMed Gene ID: 23211

(Zinc Finger CCCH-Type Containing 4)  
19q13

A member of **CCCH (C-x8-C-x5-C-x3-H type)** zinc finger domain-containing proteins.

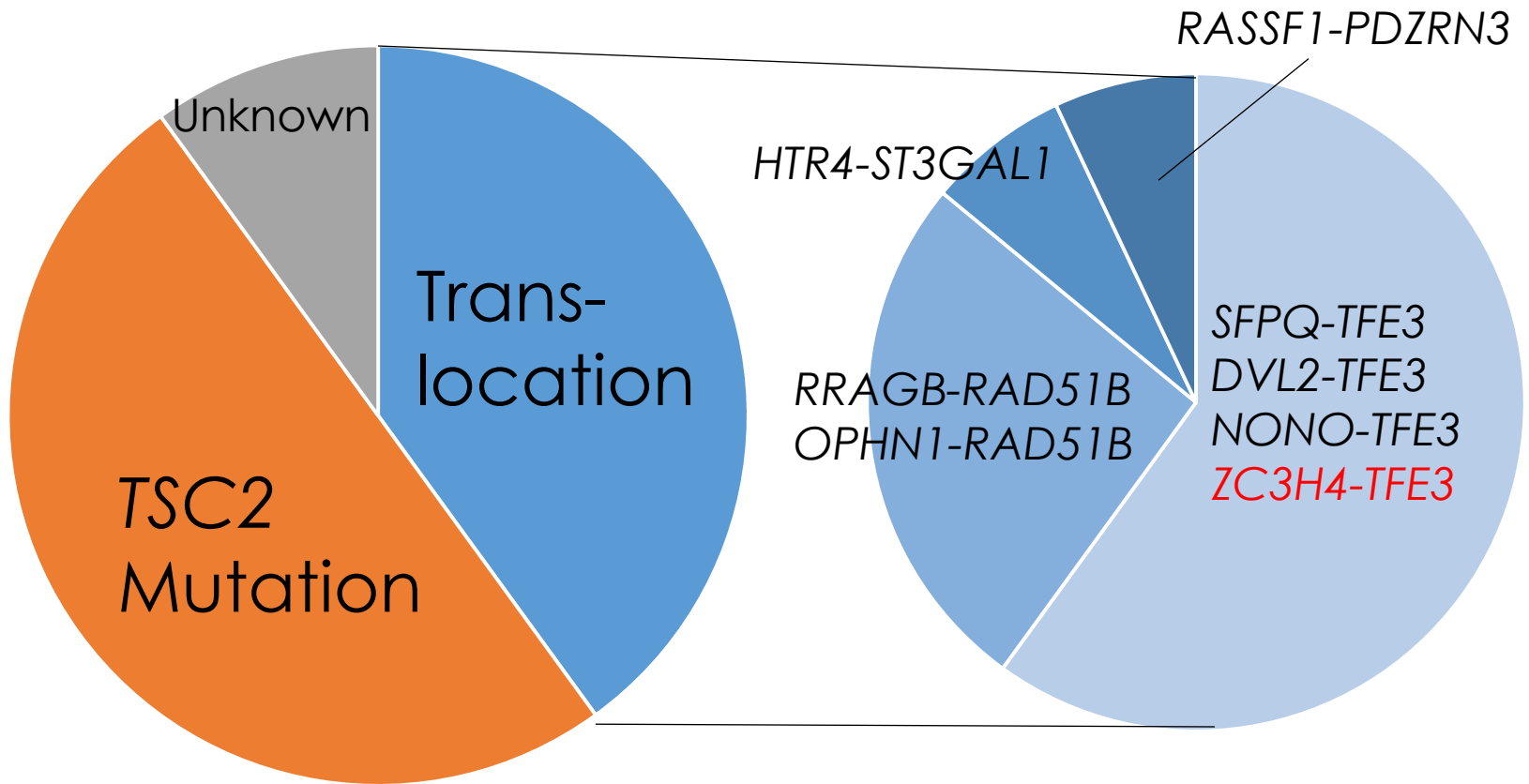
These zinc finger domains, which coordinate zinc finger binding and are characterized by **3 cysteine** residues and **1 histidine** residue, are **nucleic acid-binding**.

Other family members are known to function in post-transcriptional regulation.

# PEComa with *TFE3* fusion

- 最多数はSFPQ(PSF)-TFE3 t(X;1)  
女性に優位 6:1  
Solid nested architecture  
Epithelioid cells  
(clear to focally eosinophilic)  
No melanin pigment  
HMB45: +, Cathepsin K: +, PAX8: –  
Melan A: 4/6
- 他にDVL2-TFE3やNONO-TFE3
- まだパートナー不明も

# PEComa Genetics





# PEComa 豆知識

- 分子生物学的にも形態的にも多様な腫瘍群
- PEComaの約半数はTSC2 mutation
- TSC2 mutの45%にはTP53変異あり  
→形態的、生物学的多様性
- PEComaの23%はTFE3 fusion
- TFE3 fusion PEComaは特徴的な形態像(本例)
- HMB45がよく出る
- TFE3とTSC2は排他的