

第15回京都乳癌コンセンサス会議
リレーミニレクチャー

第6回

葉状腫瘍 Phyllodes Tumor

三上芳喜

京都大学医学部附属病院 病理診断科

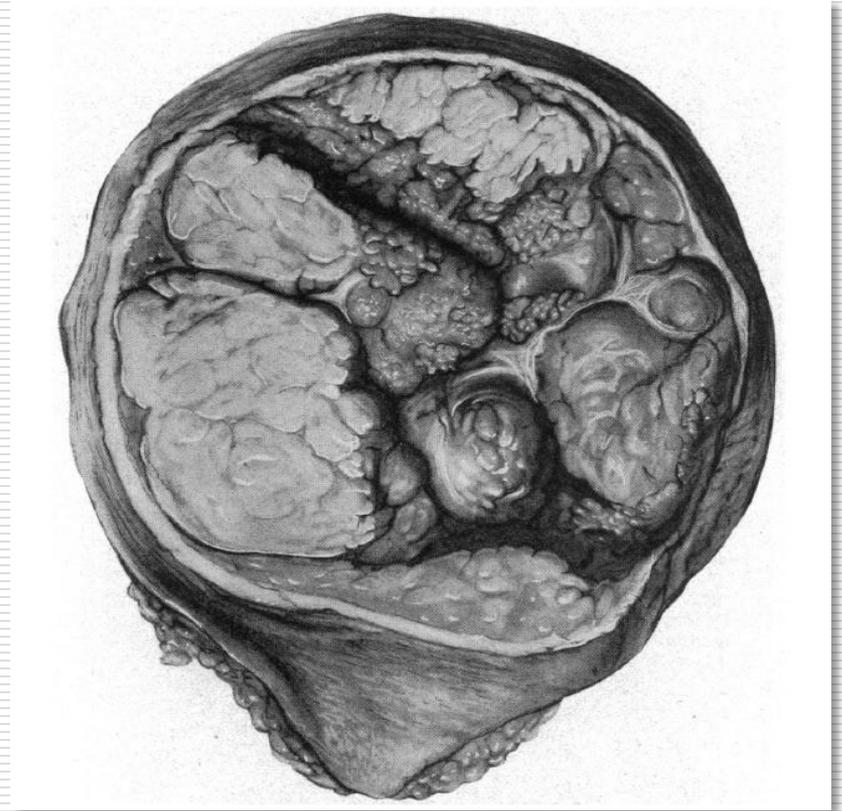
WHO2012

- Fibroepithelial tumors
 - Fibroadenoma
 - Phyllodes tumor
 - Benign
 - Borderline
 - Malignant
 - Periductal stromal tumor, low-grade
 - Hamartoma

葉状腫瘍 Phyllodes Tumor

- 定義

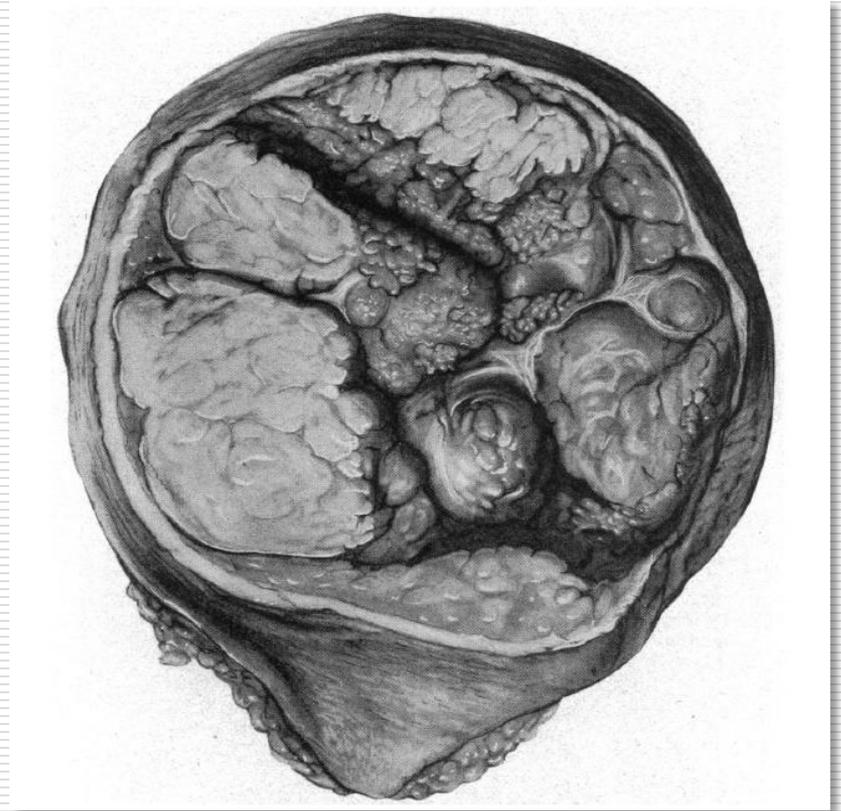
2層の上皮成分で被覆された裂隙とそれを取り囲む間質・間葉系成分から構成され、葉状構築を示す、管内型線維腺腫に類似した線維上皮性腫瘍
(WHO2012)



葉狀腫瘍 Phyllodes Tumor

- 同義語

Cystsarcoma
phyllodes



葉狀腫瘍 Phyllodes Tumor

- 同義語？

“Giant fibroadenoma”

“Juvenile fibroadenoma”

“Cellular fibroadenoma”

葉狀腫瘍 Phyllodes Tumor

- 同義語？

“Glandular fibroadenoma”

“Juvenile fibroadenoma”

“Cellular fibroadenoma”



Cystsarcoma phyllodes

- Chelius が1828年に最初に記載



Maximilian Joseph von Chelius

2013/5/29
16. Januar 1794 in Mannheim; † 17. August 1876 in Heidelberg) war

Cystsarcoma phyllodes

- Johannes Peter Muller
と Rudolph Virchow が
1838年に cystsarcoma
phyllodes と命名



Johannes Peter Müller (14 July 1801 – 28 April 1858),
was a [German physiologist](#), [comparative anatomist](#),
[ichthyologist](#), and [herpetologist](#), known not only for his
discoveries but also for his ability to synthesize knowledge.

HEBER
DEN FEINERN BAU
UND
DIE FORMEN
DER KRANKHAFTEN
GESCHWULSTE
—
JOHANNES MÜLLER
1838

Heber
den feinem Bau
...
die Formen
der krankhaften Geschwülste

Dr. Johannes Müller.

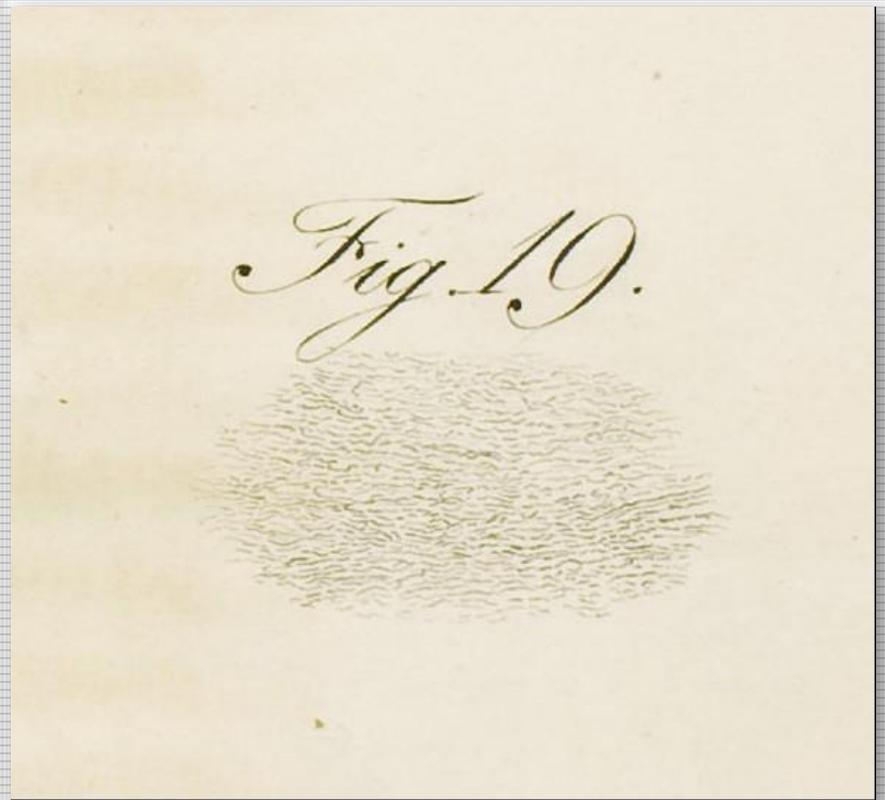
und Oberst-Physikus der Anatomie und Chirurgie, Erster der Königl. anatomischen Institute und anatomischer Theater in Berlin, Ritter des Königl. Preuss. Ordens der Ehre von Grossen, Mitglied der Königl. Academie der Wissenschaften in Berlin und Göttingen, Correspondent der Kaiserl. Russischen Academie der Wissenschaften in St. Petersburg, der Königl. Academie der Wissenschaften in Turin, Mitglied der Königl. Societät der Wissenschaften in Göttingen und Leipzig.

In zwei Lieferungen.

Erste Lieferung.

Seiten 1-12 mit Tafel 1-10.

Berlin.
Verlag und Vertheilung bei G. Reimer
1838



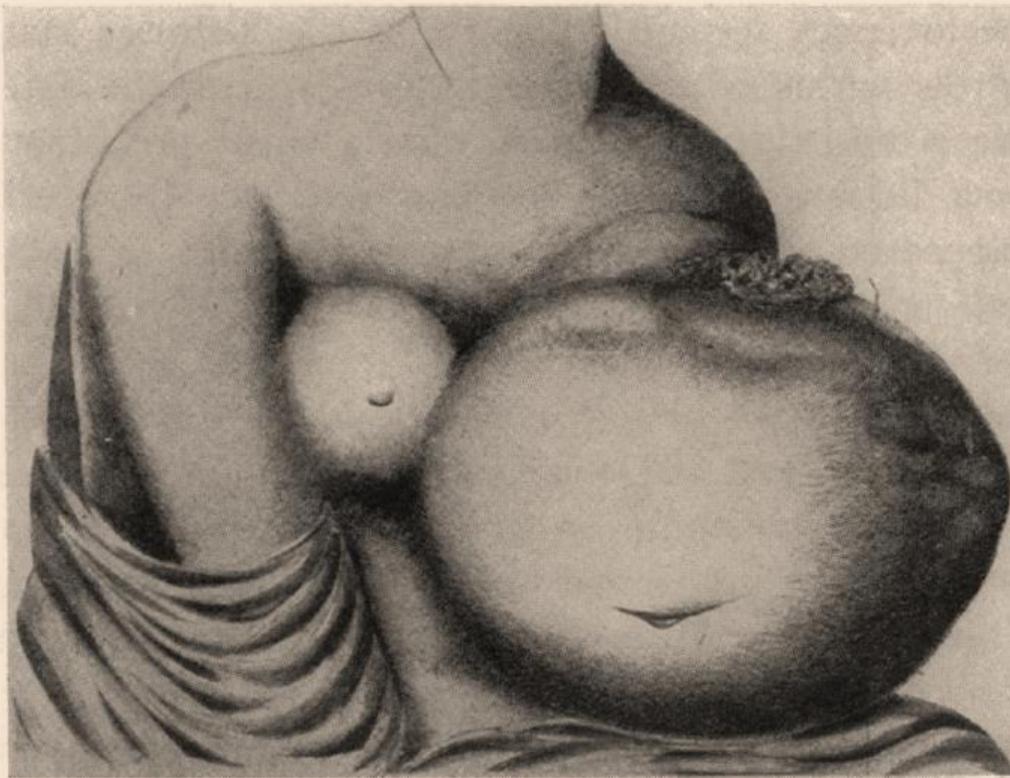
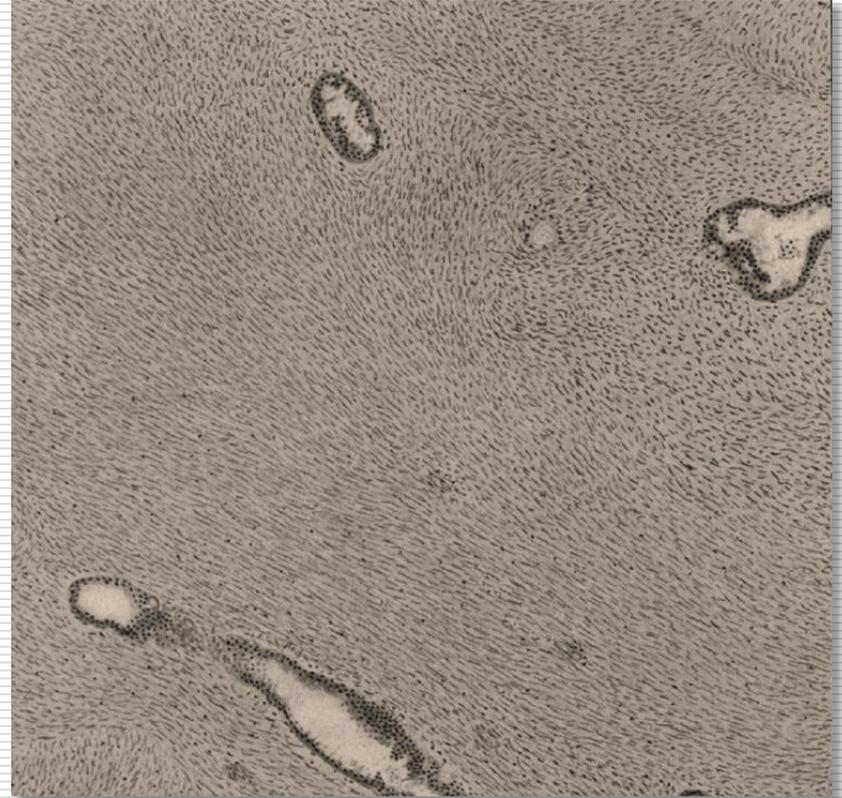


FIG. 1.—Case report by von Graefe (1838). The patient was a Russian woman, thirty-nine years of age. She had nursed her five children without lactational difficulties. After her last childbirth, a small nodule the size of a filbert (fibro-adenoma?) was felt in the right breast. This nodule never increased in size. In 1836, a new tumor appeared in the left breast and grew slowly until 1838, when it exhibited an increased impetus of growth. It ruptured spontaneously and twelve hours later a large cauliflower vegetation pro-lapsed through the ruptured skin. This enormous tumor covered the entire chest, displaced the right breast and a local mastectomy was done without anæsthesia. While an assistant supported the breast, two surgeons with three knives amputated the breast by three slashes in less than thirty seconds. Immediate hæmostasis was obtained by compressing nine large severed vessels between the fingers. The breast and its content of tumor weighed twenty-two pounds and eight ounces. A cure was effected.



FIG. 2.—Case report by Helmuth (1871). The patient was a woman, aged sixty-eight years, who first observed a small tumor in her right breast twenty years previously. This tumor gradually increased in size until it extended from the clavicle to below the waist and from the sternum beyond the axilla to the scapular line. The integument over the tumor was tense and bluish; the tumor mass was nodular, circumscribed and fluctuant. Treatment consisted entirely of injection of carbolic acid. The patient died several months later.

First Case of Metastatic Phyllodes Tumor



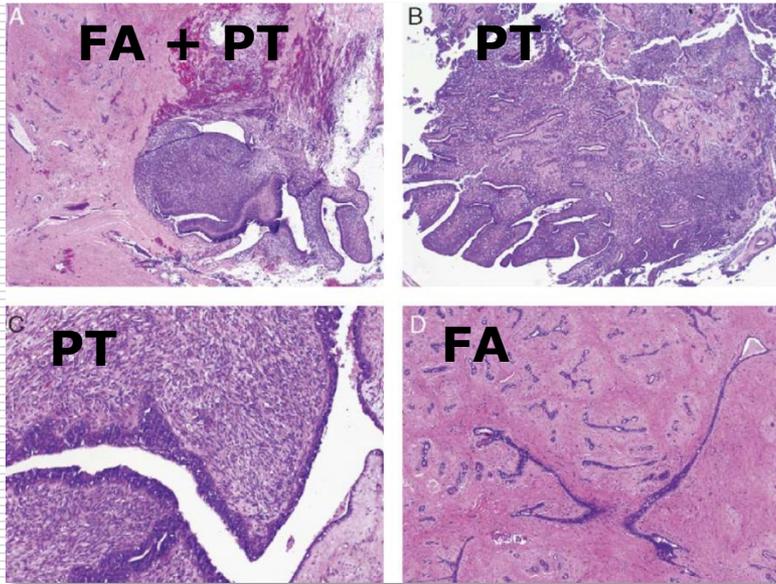
GIANT INTRACANALICULAR MYXOMA OF THE BREAST: THE SO-CALLED
CYSTOSARCOMA PHYLLODES MAMMAE OF JOHANNES MULLER.

[Lee BJ](#), [Pack GT](#). [Ann Surg](#). 1931 Jan;93(1):250-68.

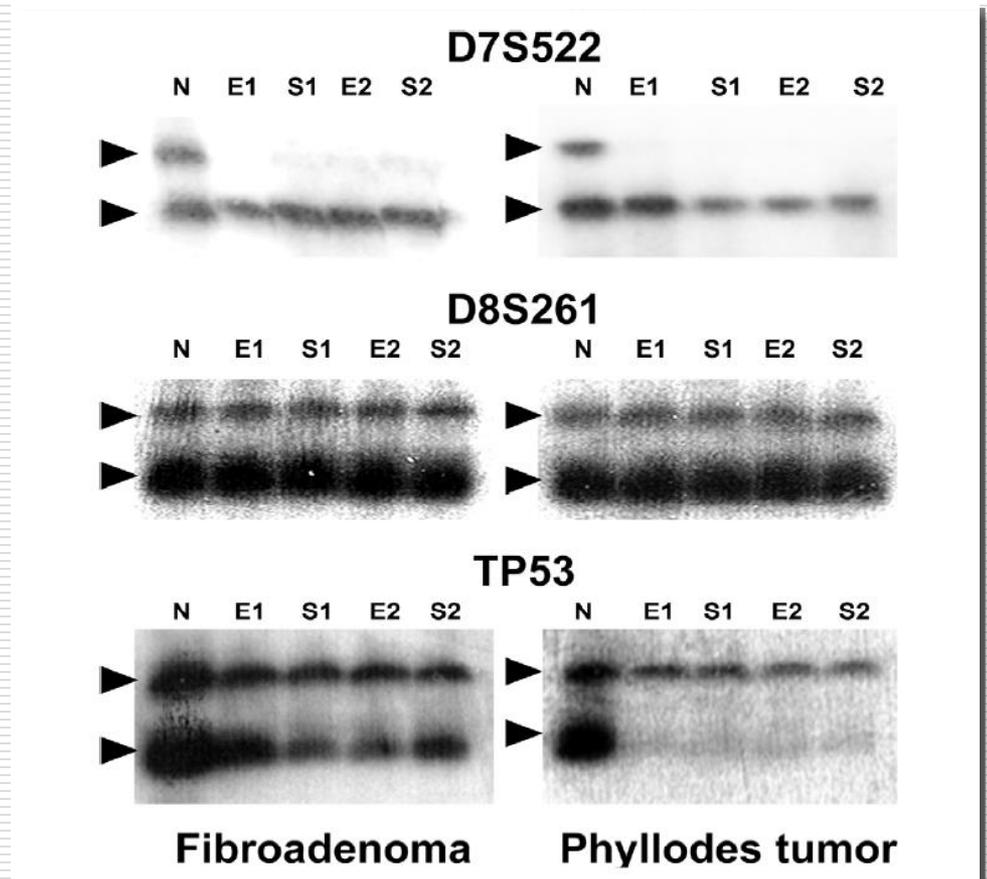
葉状腫瘍 Phyllodes Tumor

- 発生起源
 - 小葉内ないし乳管周囲間質
 - 殆どは de novo
 - 線維腺腫の悪性化例

Evidence for transformation of fibroadenoma of the breast to malignant phyllodes tumor



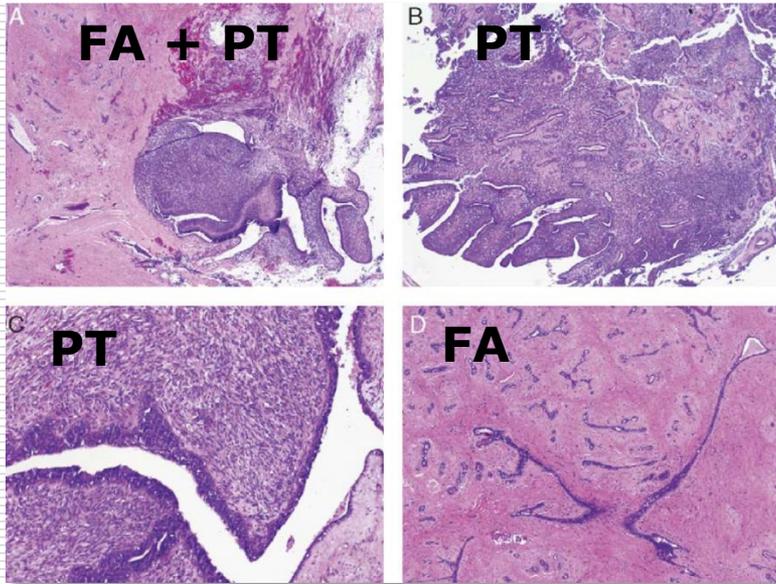
23-year-old woman
Synchronous FA and PT



Hodges et al. Appl Immunohistochem Mol Morphol

2013/5/29
2009; 17: 345-50.

Evidence for transformation of fibroadenoma of the breast to malignant phyllodes tumor



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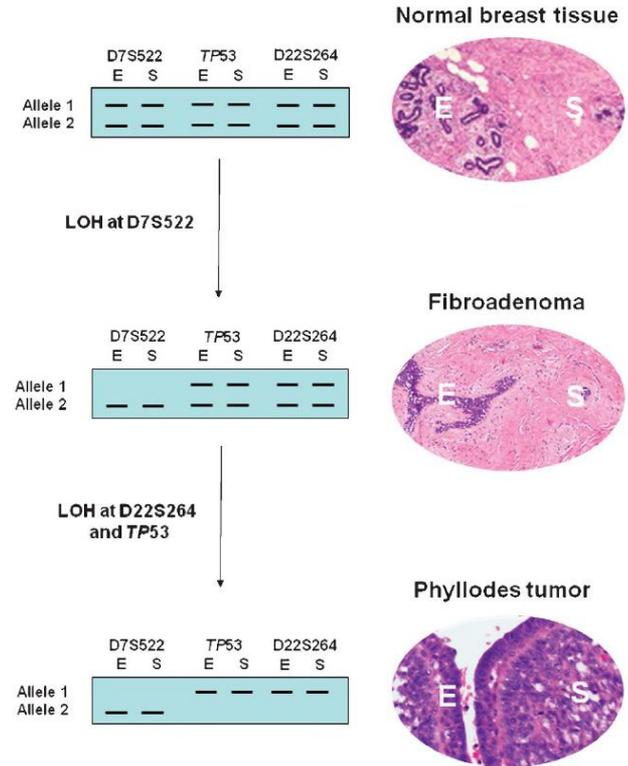
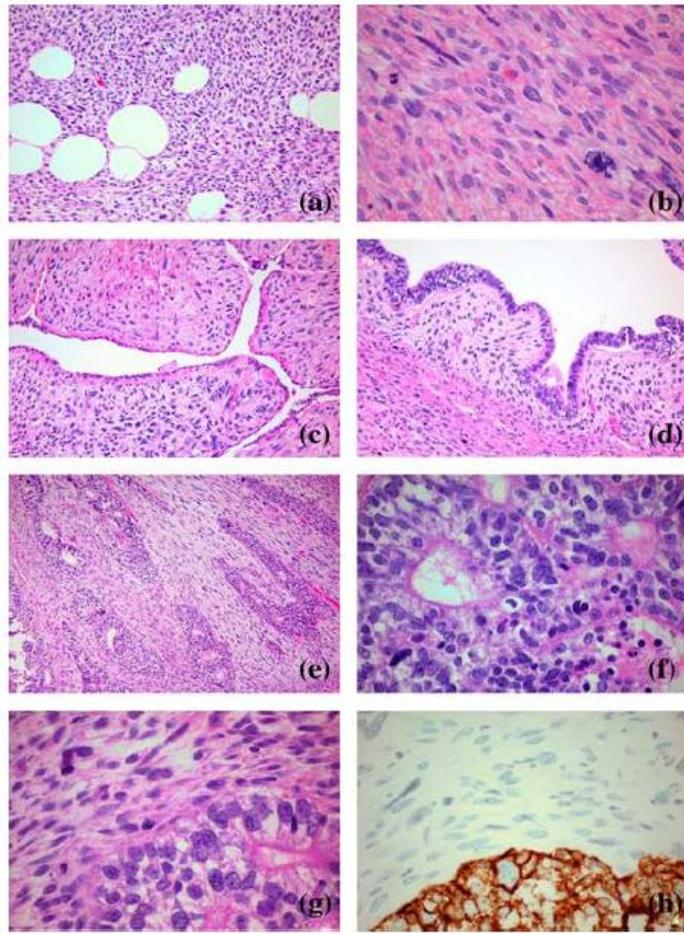


FIGURE 4. Schematic illustration of genomic events involved in the progression of malignant phyllodes tumor of the breast from coexisting fibroadenoma. LOH at D7S522 occurred in both epithelial and stromal components of the breast fibroadenoma, but TP53 gene is still intact as shown in the blue box (upper allele of D7S522 was lost in both epithelial and stromal components). Additional allelic losses at TP53 and D22S264 may lead to progression of fibroadenoma to phyllodes tumor. E indicates epithelial cells; S, stromal cells.

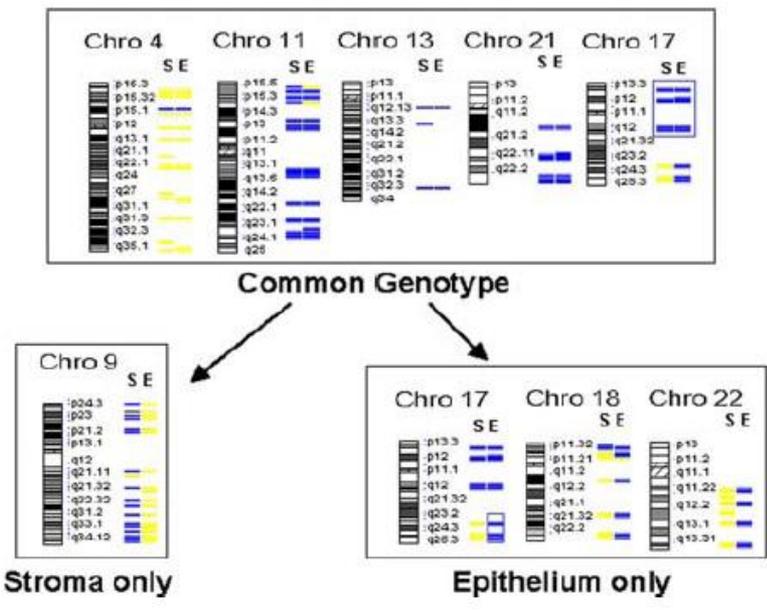
Hodges et al. Appl Immunohistochem Mol Morphol

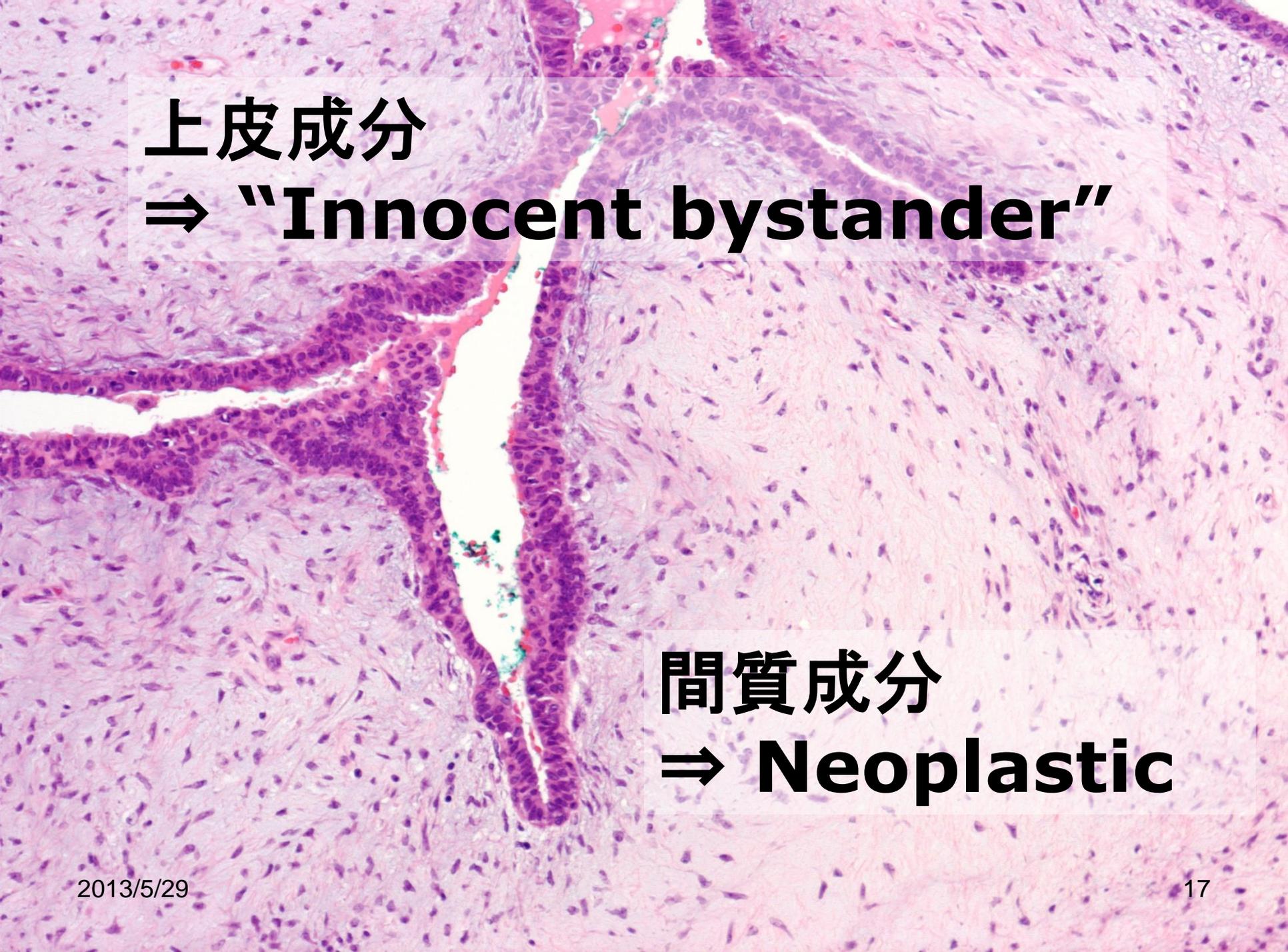
2013/5/29
2009; 17: 345-50.

Shared LOH pattern in both the stromal and the co-existing epithelial malignancy, suggesting a common precursor cell for the biphasic malignant components



Genome-wide LOH analysis of phyllodes tumor 307



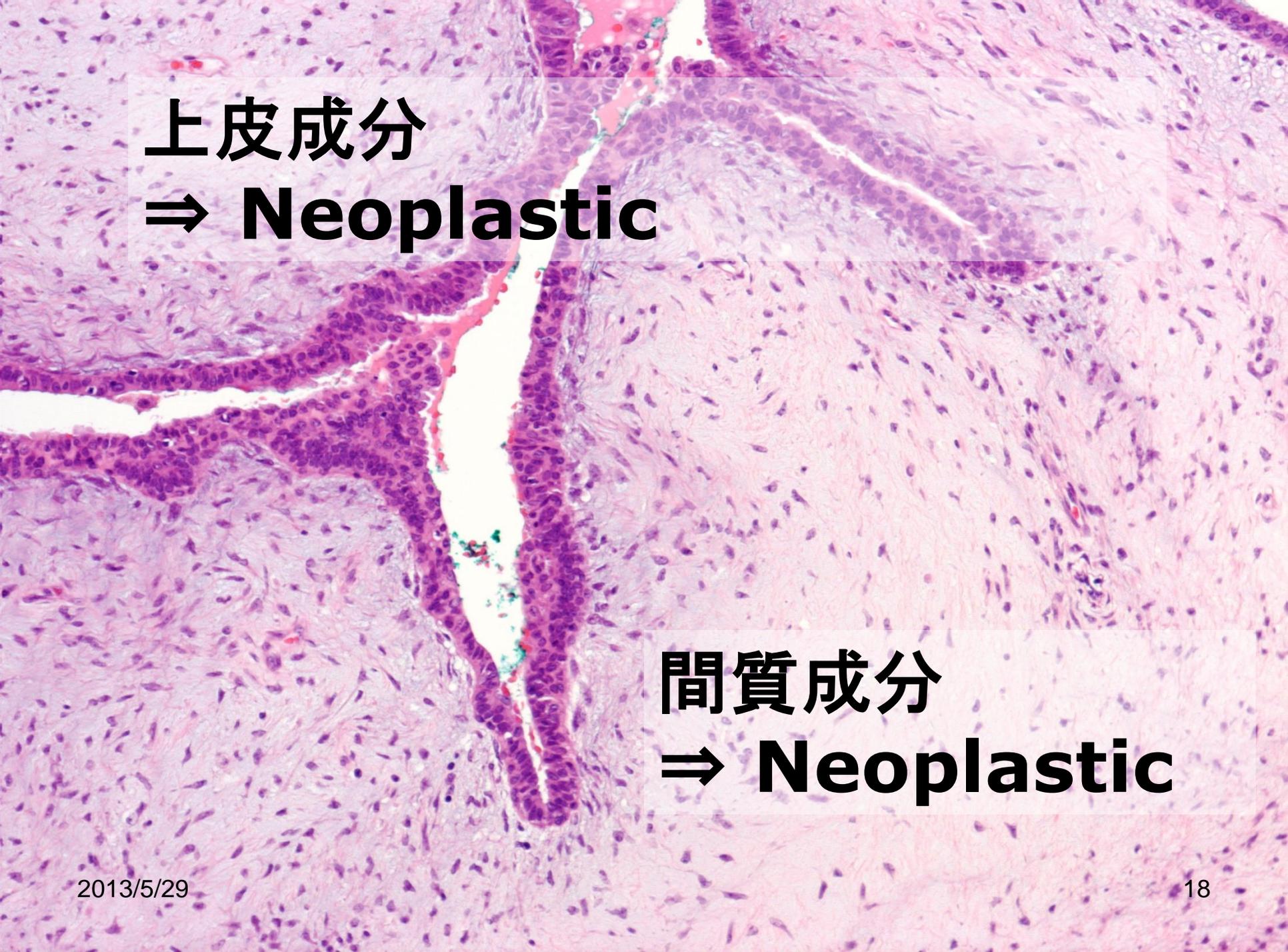


上皮成分

⇒ “Innocent bystander”

間質成分

⇒ Neoplastic



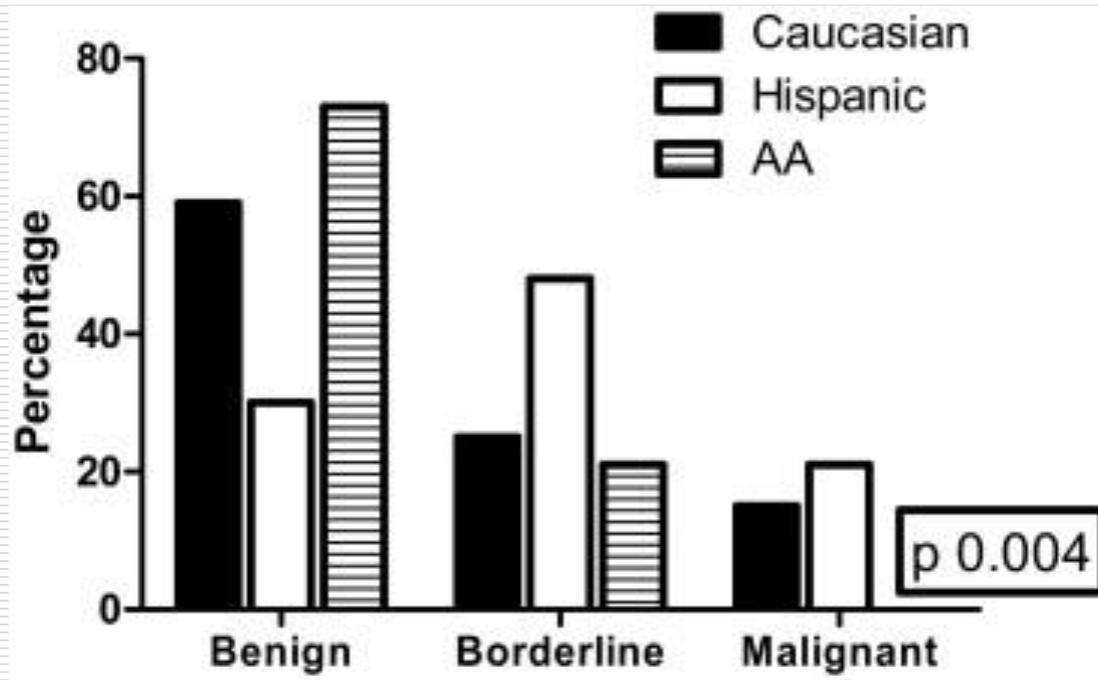
上皮成分
⇒ Neoplastic

間質成分
⇒ Neoplastic

葉状腫瘍 Phyllodes Tumor

- 乳腺腫瘍の0.3~1%以下
- 線維上皮性腫瘍全体の2.5% (1/40)
- 年齢：中央値 45歳
(10~86歳、25歳以下は稀)
 - 線維腺腫より15~20歳高齢
 - アジアでは若年の傾向 (平均25~30歳)
 - 若年でも悪性例あり
 - ときに妊娠時に発生

High-grade 葉状腫瘍はヒスパニック系 (特に中央、南アメリカ)で高頻度である



Histologic classification of phyllodes tumor by race. AA, African American.

Jose M et al. Phyllodes Tumors: Race-Related Differences

2013/5/29 Journal of the American College of Surgeons 2011; 213: 537-542.

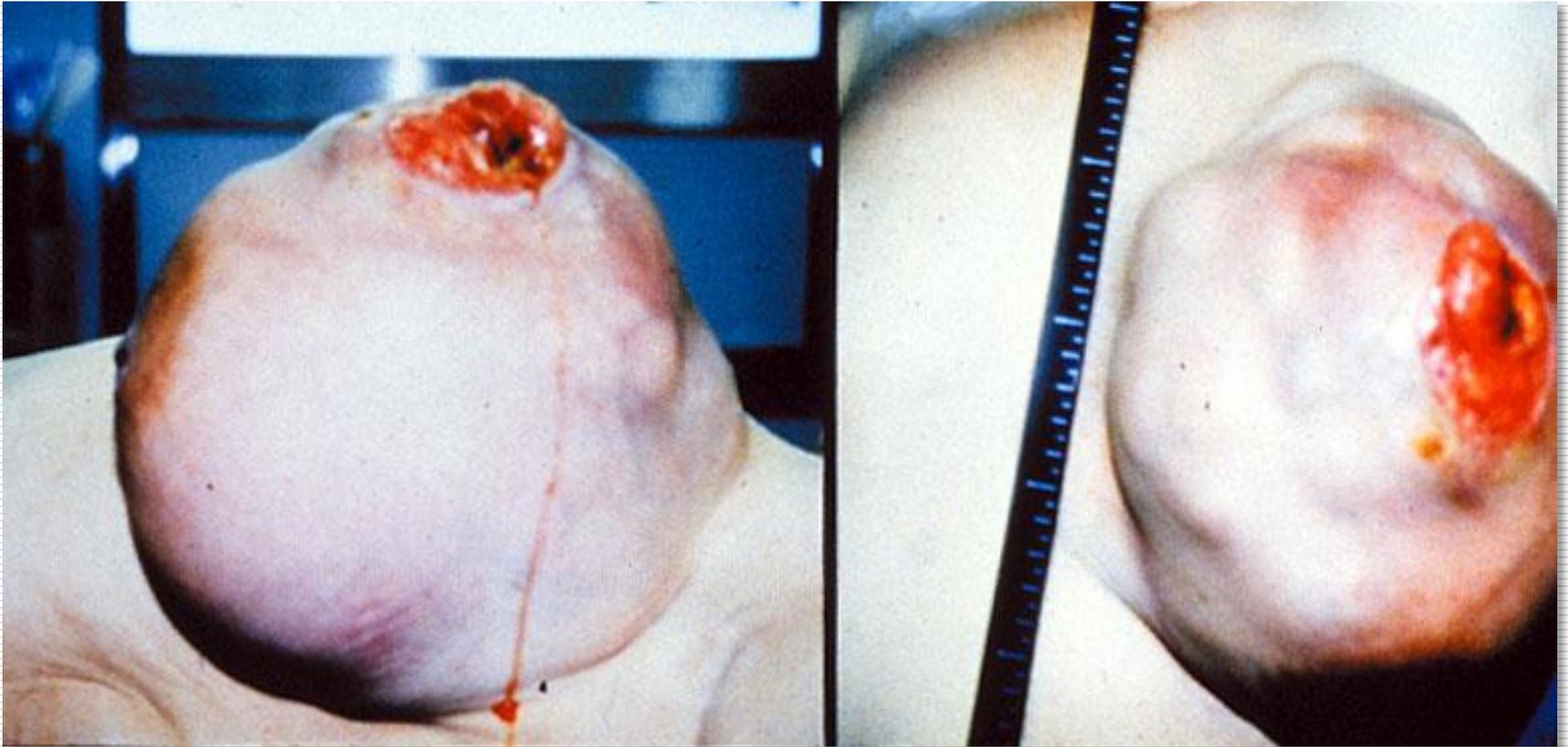
葉状腫瘍 Phyllodes Tumor

- 臨床像
 - 片側性の硬い腫瘍
 - 皮膚との連続性なし
 - 急速増大
 - 稀に多発



2013/5/29

Phyllodes tumor, borderline



恶性葉状腫瘍

Phyllodes tumor, malignant

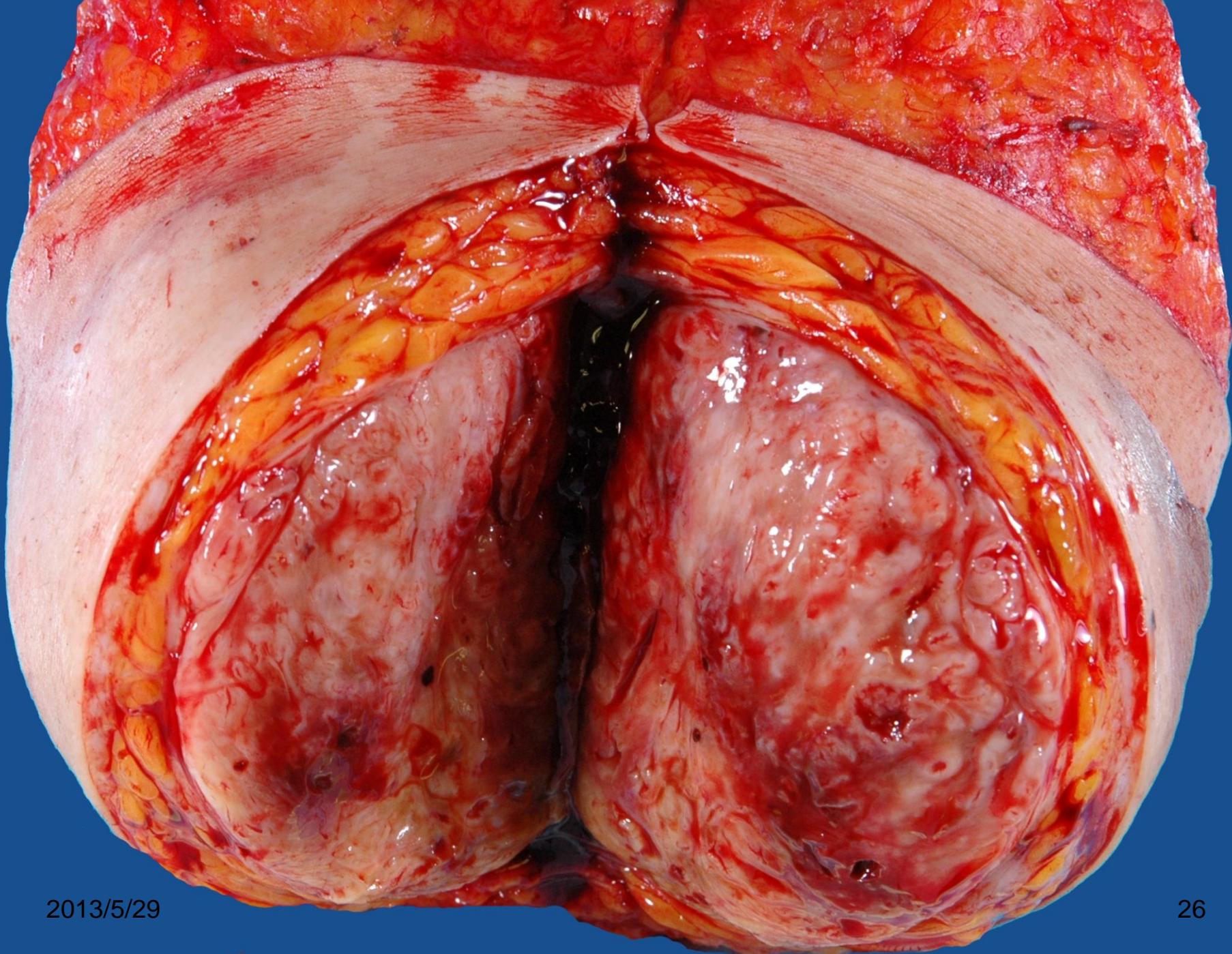
葉状腫瘍 Phyllodes Tumor

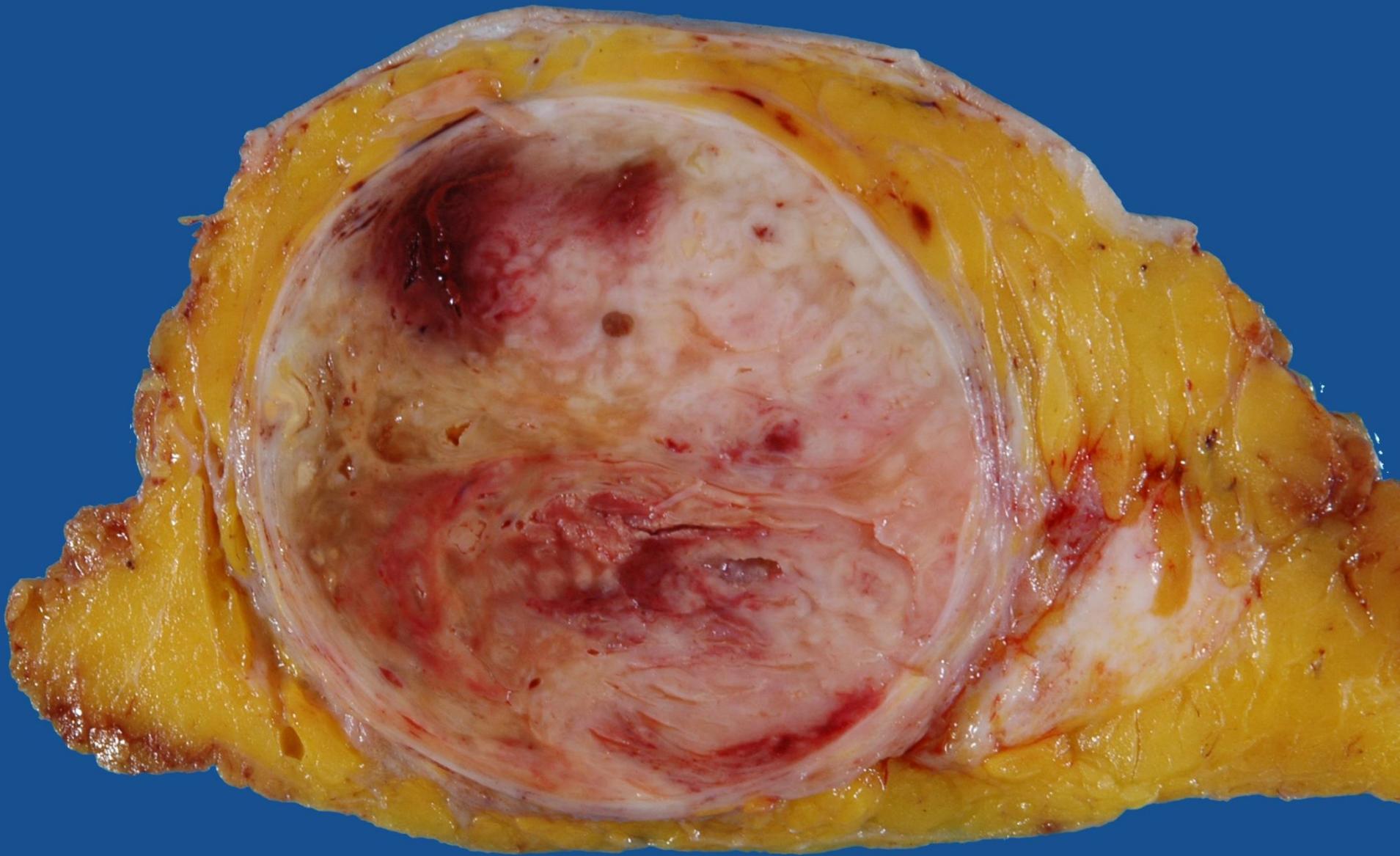
- 肉眼像
 - 円形、弾性硬の境界明瞭な腫瘤
 - 腫瘍径は平均4～5cm(悪性は大きい)
 - “shelled-out”
 - 充実性、灰白色～白色調、裂隙状空隙
 - 出血・壊死(悪性)



2013/5/29

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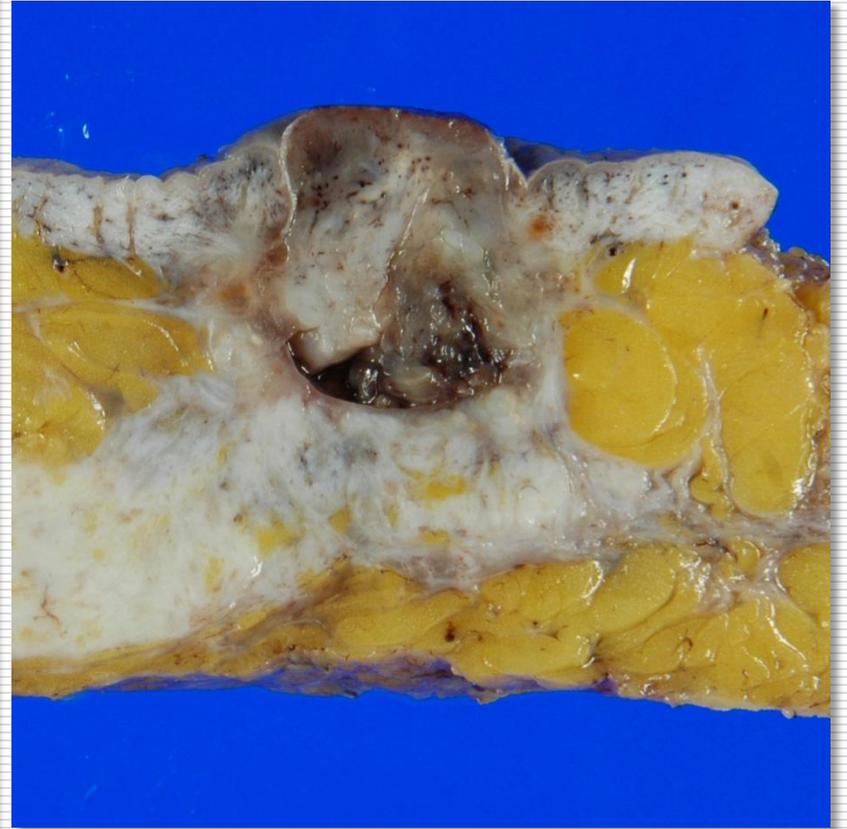




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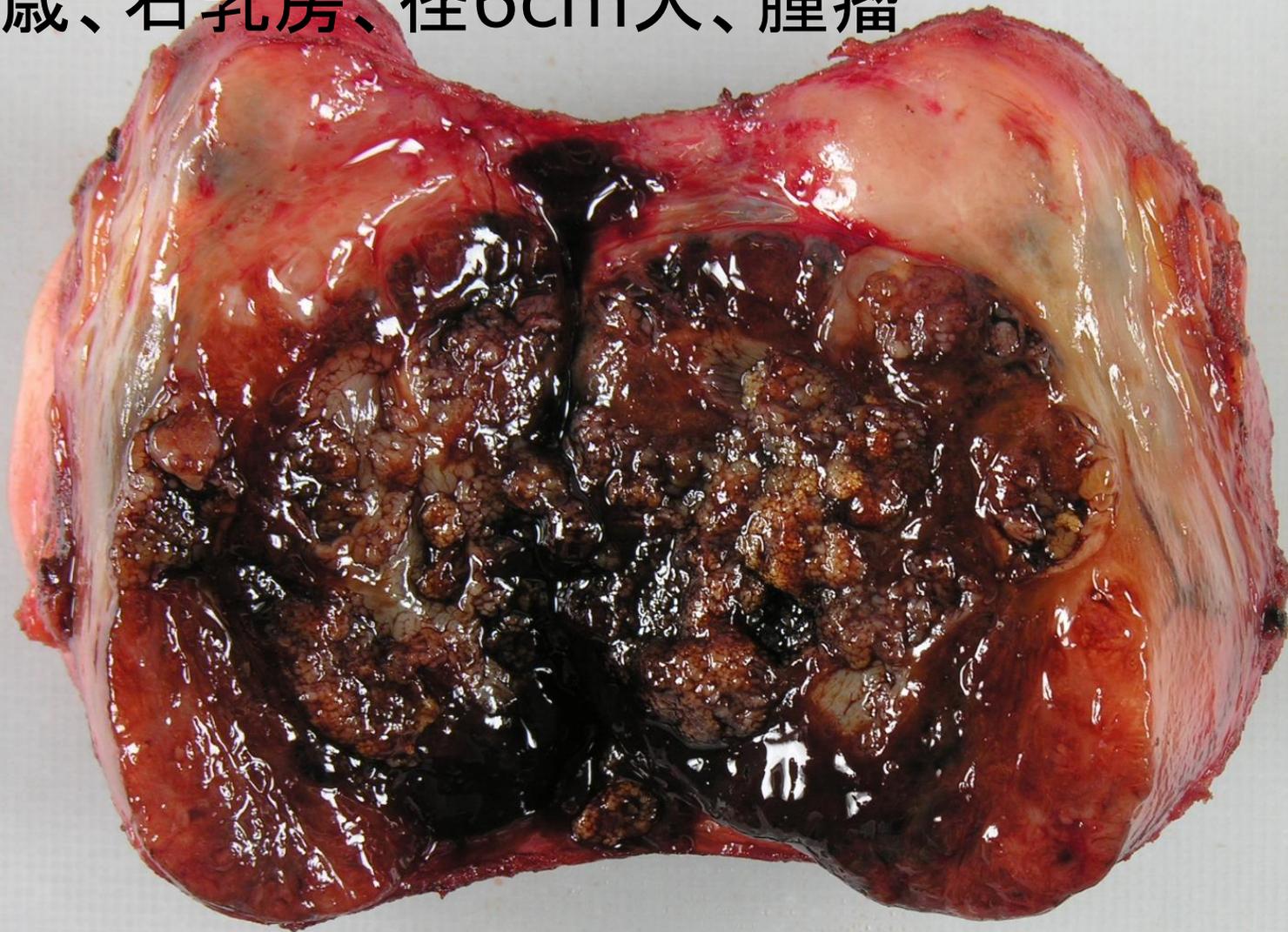
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2013/5/29

15歳、右乳房、径6cm大、腫瘤



2013/5/29

KUHP0603574
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葉状腫瘍 Phyllodes Tumor

- 組織像

- 良性上皮成分

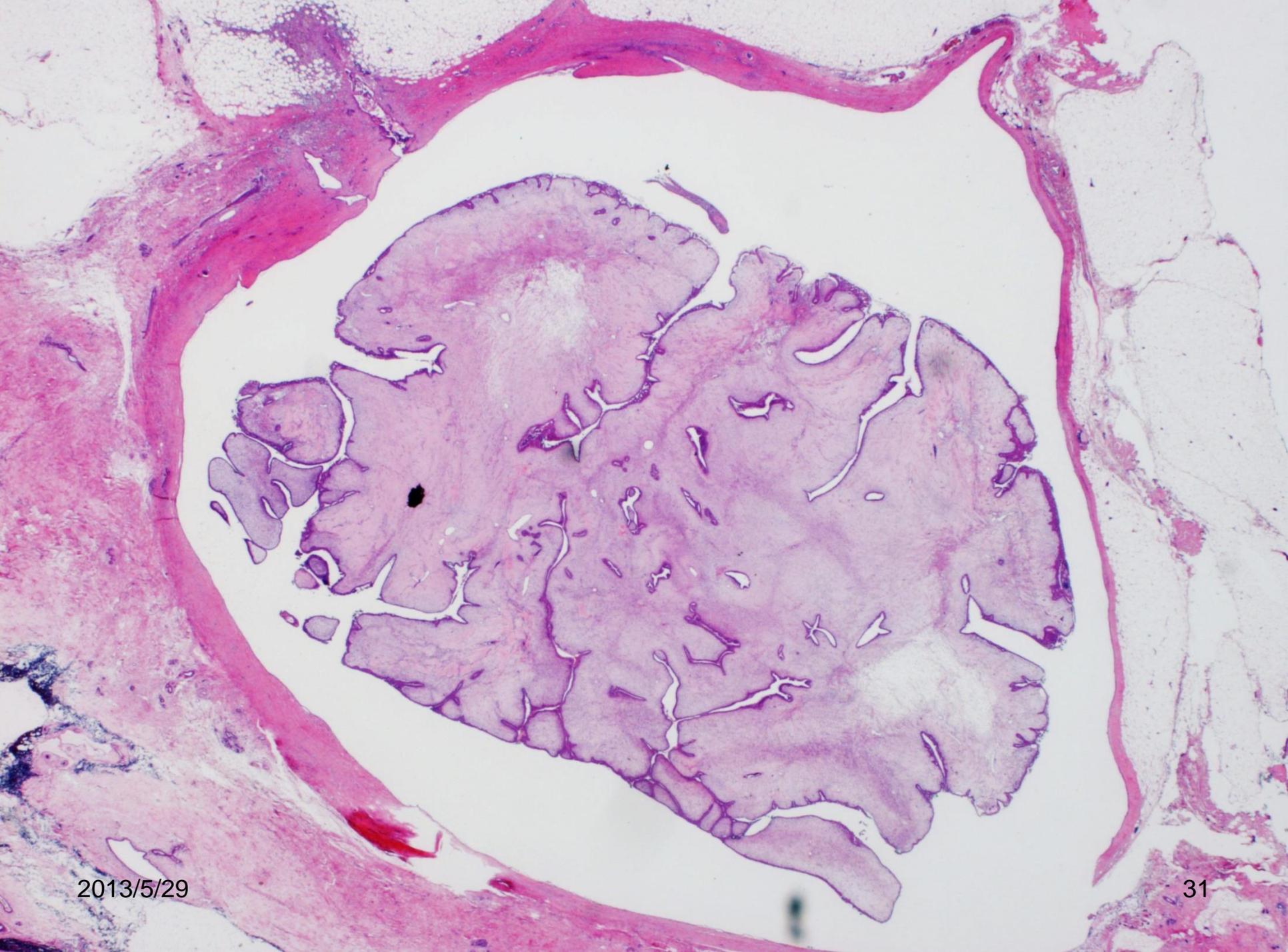
- ✓ 乳管上皮過形成、ADH、DCIS、LCIS

- 細胞密度の高い間質成分(程度は様々)

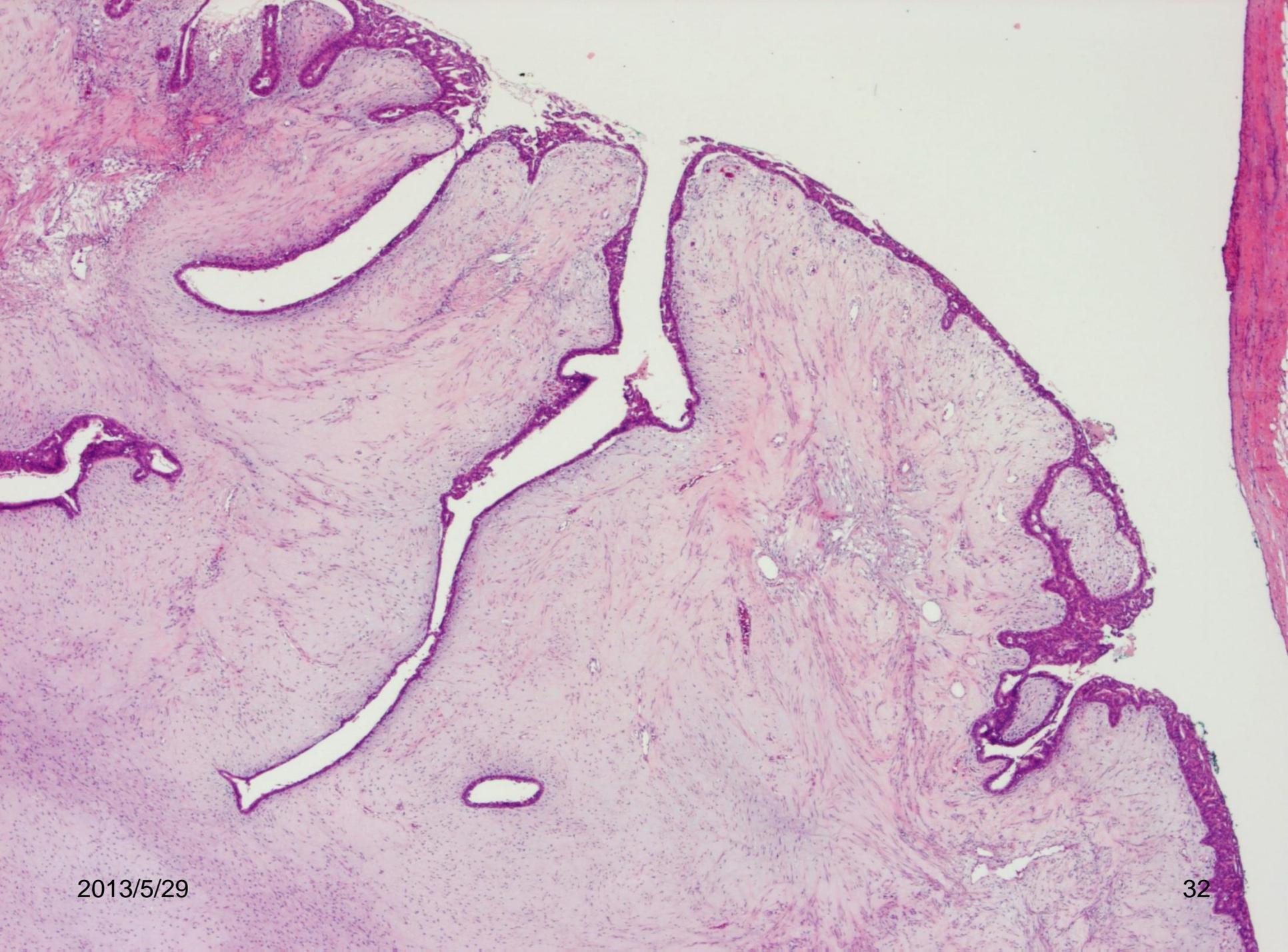
- ✓ 間質細胞の形態には幅広いスペクトラム

- ✓ 良性～悪性

- ✓ 異所性肉腫成分(血管肉腫、骨肉腫、軟骨肉腫、脂肪肉腫、平滑筋肉腫など)

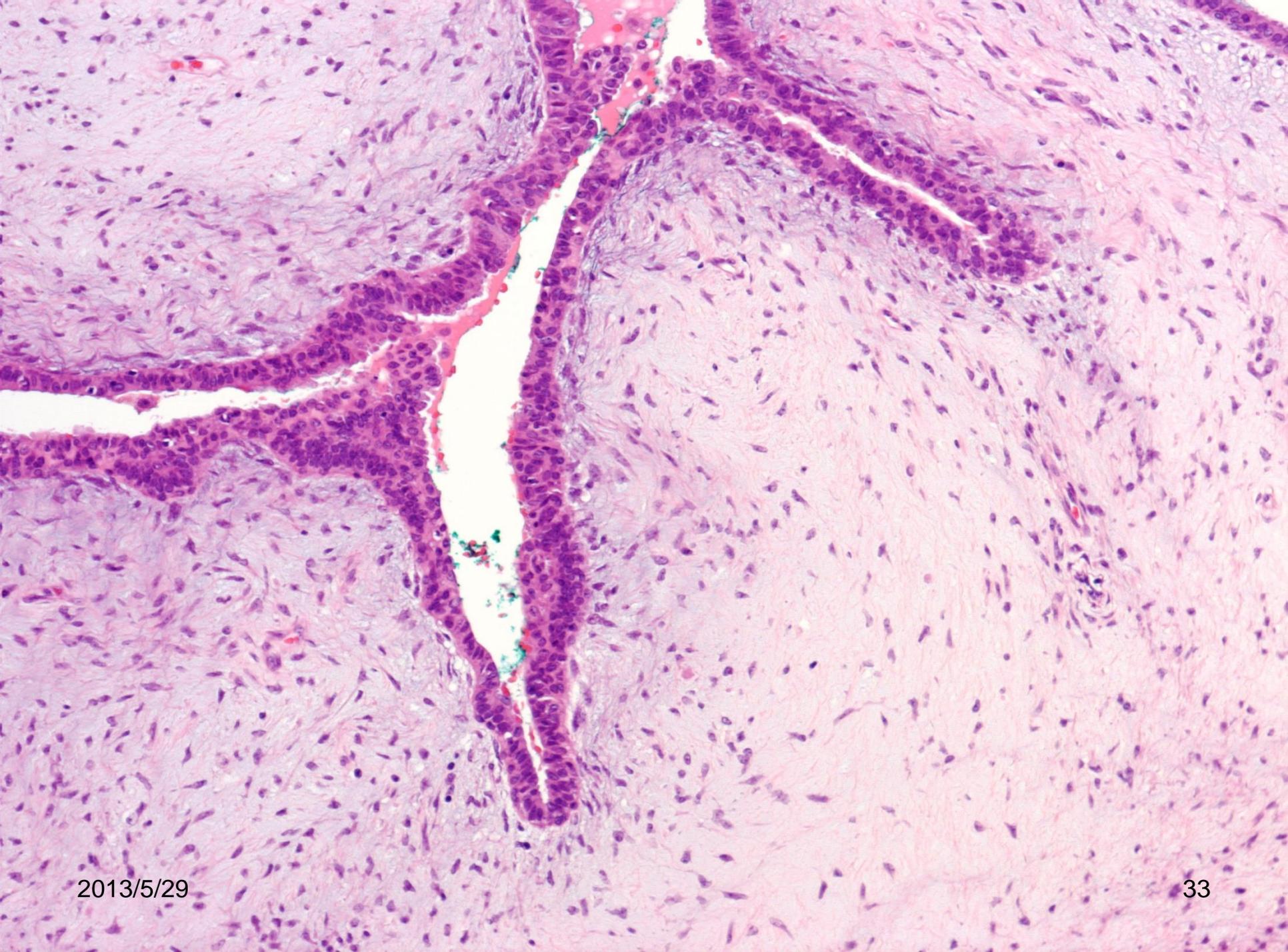


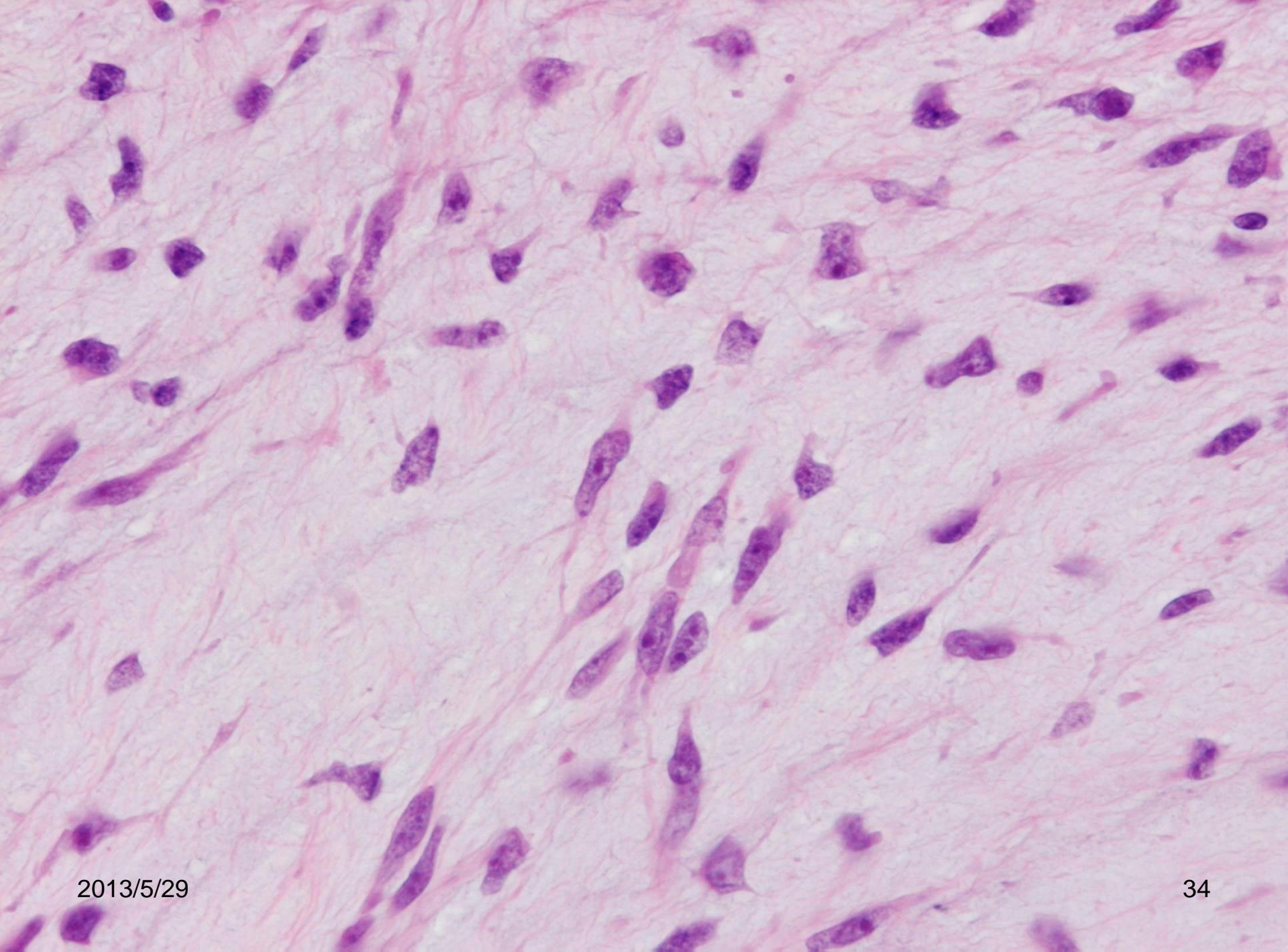
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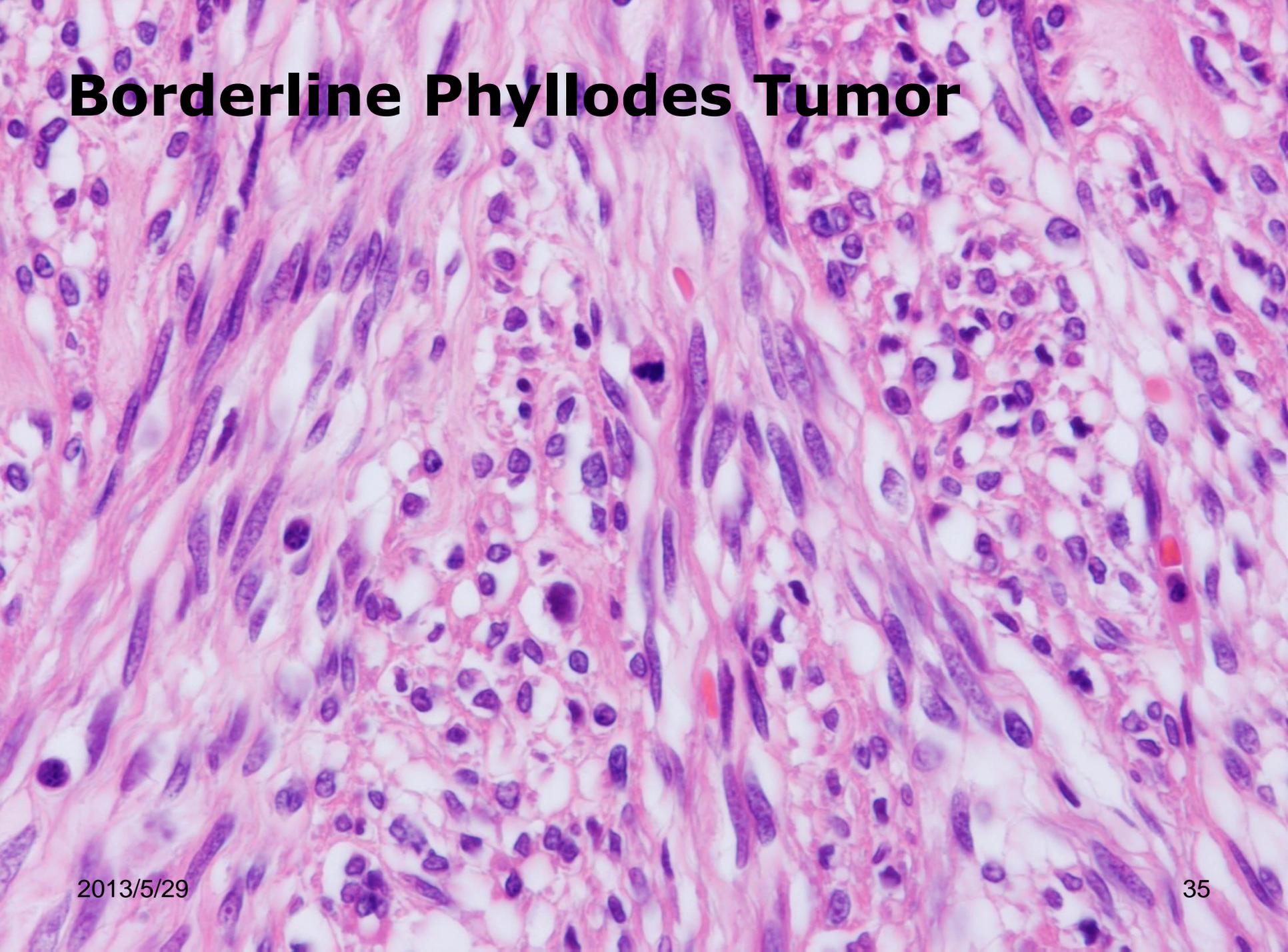
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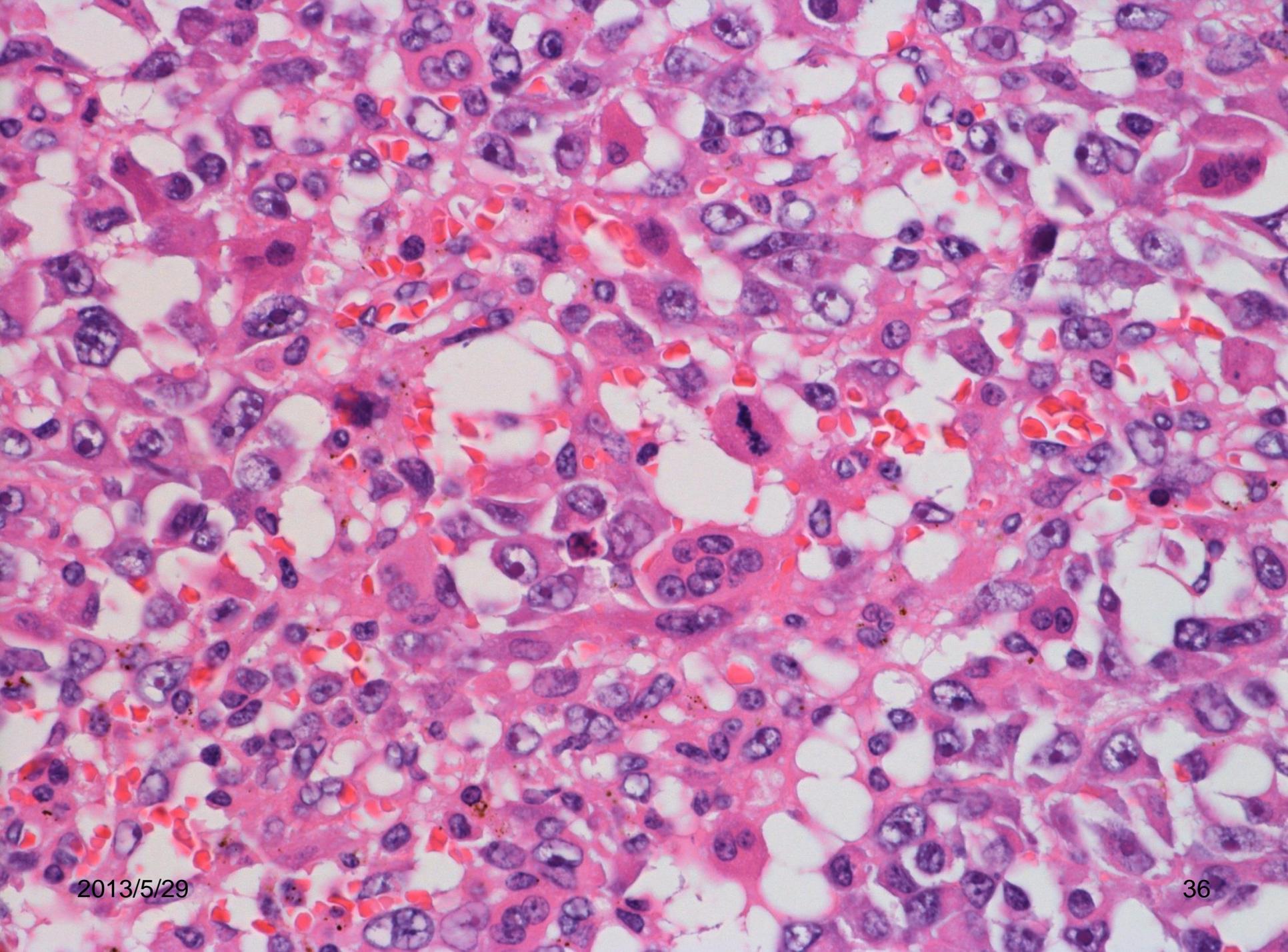
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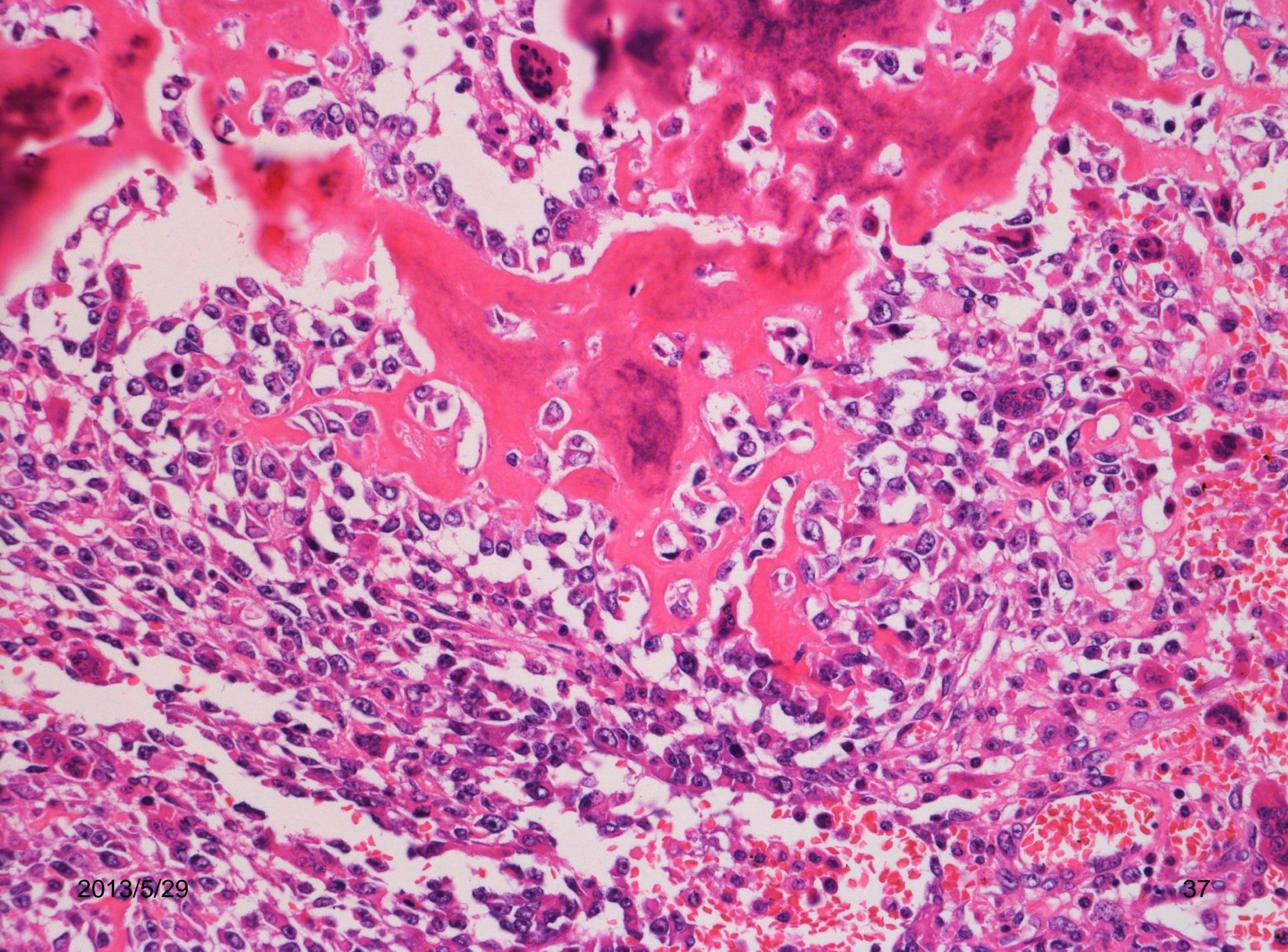




Borderline Phyllodes Tumor

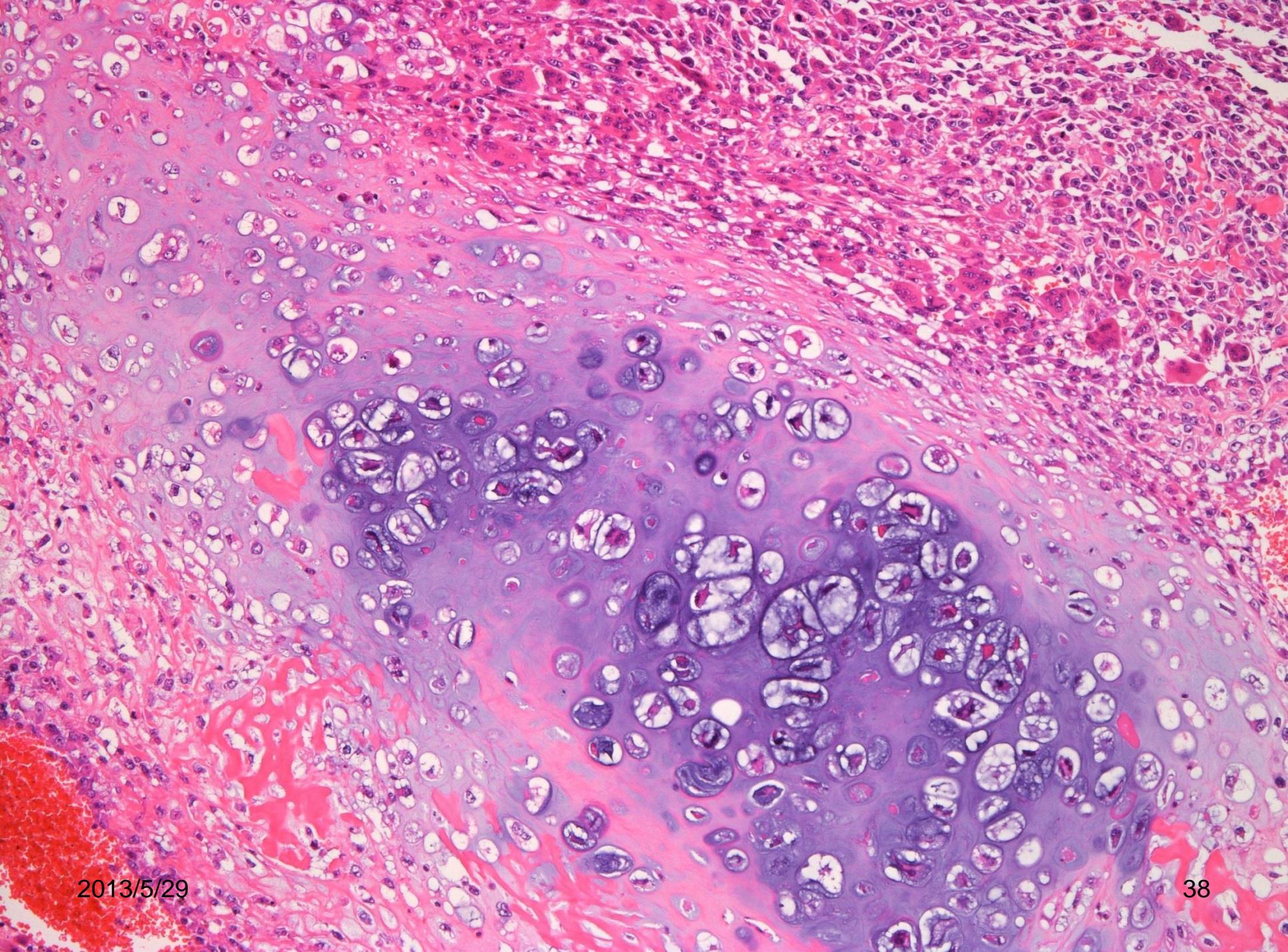




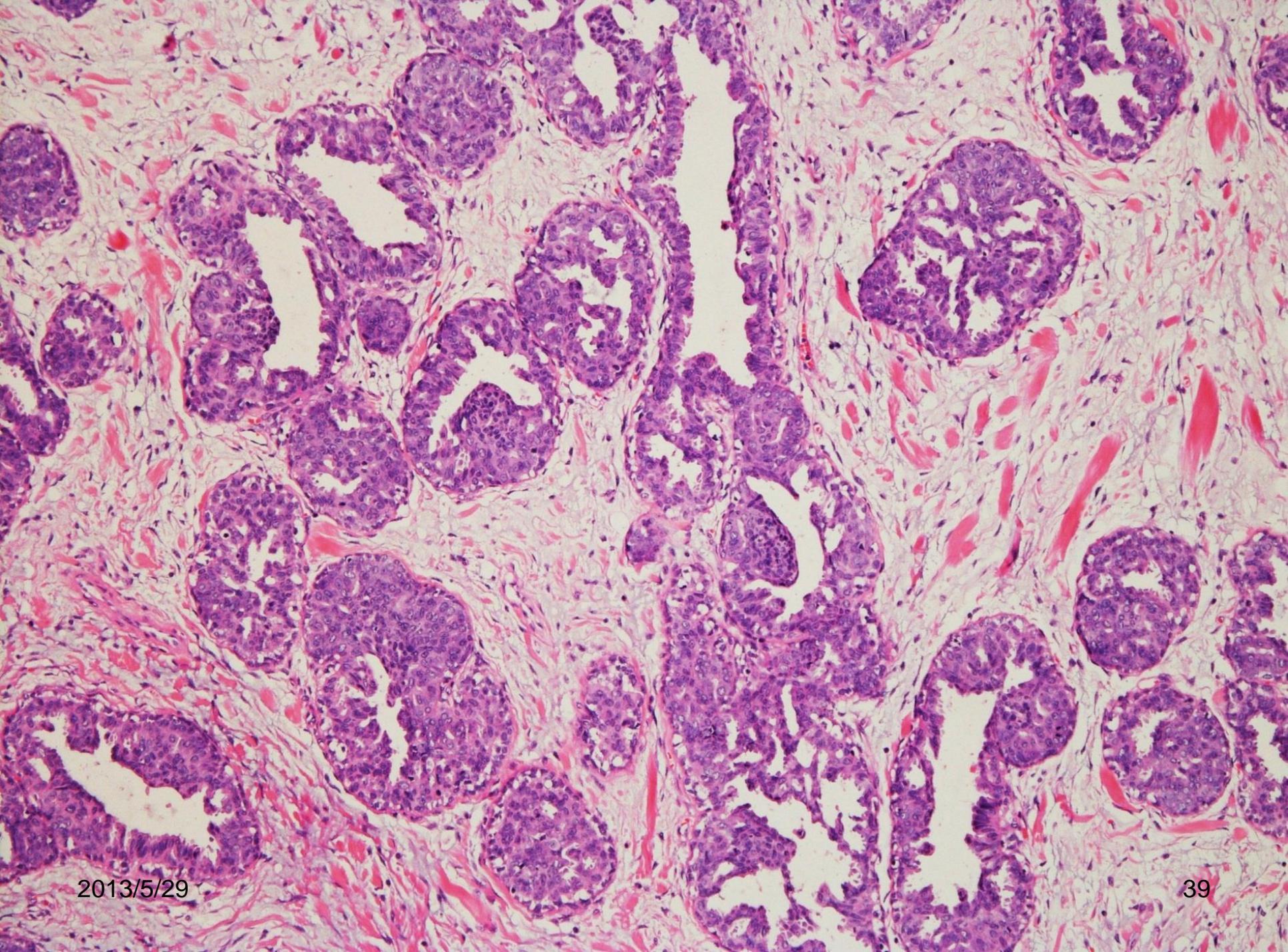


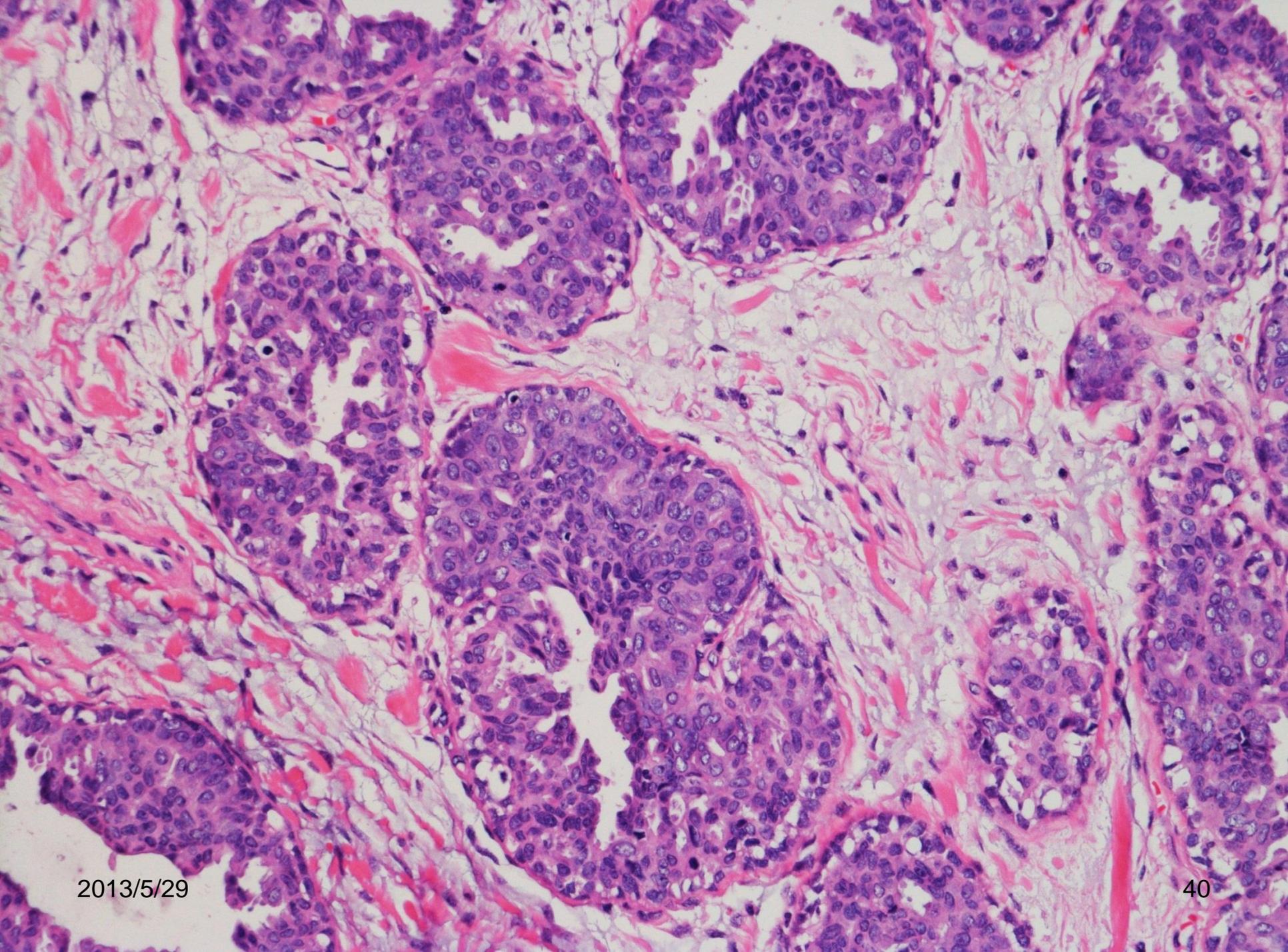
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2013/5/29





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40

葉状腫瘍 Phyllodes Tumor

- 組織像

- 間質細胞はPR陽性(ER陰性)
- 化生性軟骨、脂肪化生、骨、骨格筋(稀)
- 線維腺腫の併存(～40%)

間質の過剰増殖

Stromal overgrowth

- 少なくとも弱拡大1視野を占める間質成分のみの領域

葉状腫瘍 Phyllodes Tumor

- 悪性を示唆する所見

- ① 核分裂像 $> 10/10\text{HPF}$

- ② 高度の細胞異型

- ③ 浸潤性発育 (周囲脂肪織の巻き込み)

- ④ 間質の過剰発育

- ⑤ 壊死

- ⑥ 出血

葉状腫瘍の分類 (WHO2012)

	良性 Benign	境界悪性 Low-grade	悪性 High-grade
辺縁	圧排性	圧排性、ときに一部侵入性	侵入性
細胞密度	低	中等度	高
間質細胞の異型	なし~軽度	軽度~中等度	高度
核分裂 (/10HPF)*	<5	5-9	≥10
間質過剰増殖	なし	なし~ごく一部	しばしば
悪性異所性成分	なし	なし	ときに存在
葉状腫瘍中の割合	60~75%	15~20%	10~20%

* 対物40X、接眼10X、0.196mm²; ** 1弱拡大視野

2013/5/29

Grading

WHO2012

Benign	Benign	Low-grade
Borderline	Low-grade	Intermediate
Malignant	High-grade	High-grade

葉状腫瘍 Phyllodes Tumor

- バイオマーカー

- p53
- Ki-67
- CD117 (KIT)
- EGFR
- VEGF
- Microvessel density
- p16
- pRb
- HOXB13

葉状腫瘍の予後

- 5年生存率
 - 90%
- 局所再発
 - 20% (8~40%)、多くは3年以内
- 転移
 - 2%未満 (1~21%)

葉状腫瘍の再発率

良性	10~17%
境界悪性	14~25%
悪性	23~30%
全体	21%

再発率

	切除、lumpectomy 後(20 文献)	最低1~2cmの マージンで切除さ れた局所切除後 (13文献)
良性	21% (111/540)	8% (17/212)
境界悪性	46% (18/39)	29% (20/68)
悪性	65% (26/40)	36% (16/45)

Barth et al. Breast Cancer Res Treat 1996; 57:

291-295

Risk Factors for Local Recurrence

Table 5. Univariate and Multivariate Survival Analysis Comparing Age, Tumor Size, and Grade

	Univariate analysis	p	Multivariate analysis	p-value
Age	RR = 1 (0.97–1.05)	0.56		
Size	RR = 1.02 (0.99–1.04)	0.07	RR = 1.01 (0.99–1.03)	0.07
Grade	RR = 2.4 (3.36–6.64)	0.08	RR = 2.1 (0.73–6.04)	

RR = relative risk.

- Histologic grade
- Tumor size

- Incomplete excision
- Invasive tumor border
- Secondary tumor nodules at the periphery

Guillot et al., The Breast Journal 2011;

2013/5/29 17: 129-137

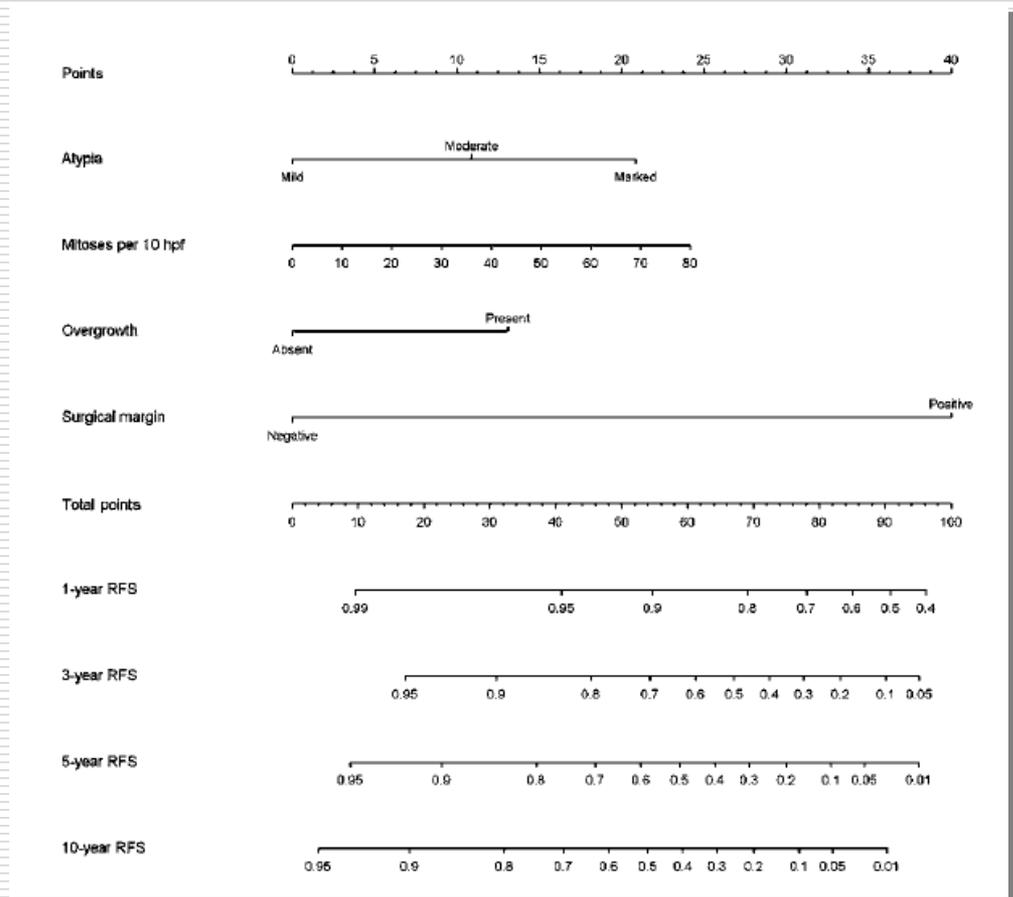
Table 2. Factors Associated with Local Recurrence in Patients with Phyllodes Tumors

Factor	p Value
Tumor size	<0.01
Close margins (<2 mm)	0.04
Histologic classification	0.01
Mitotic rate	<0.01
Race	0.89

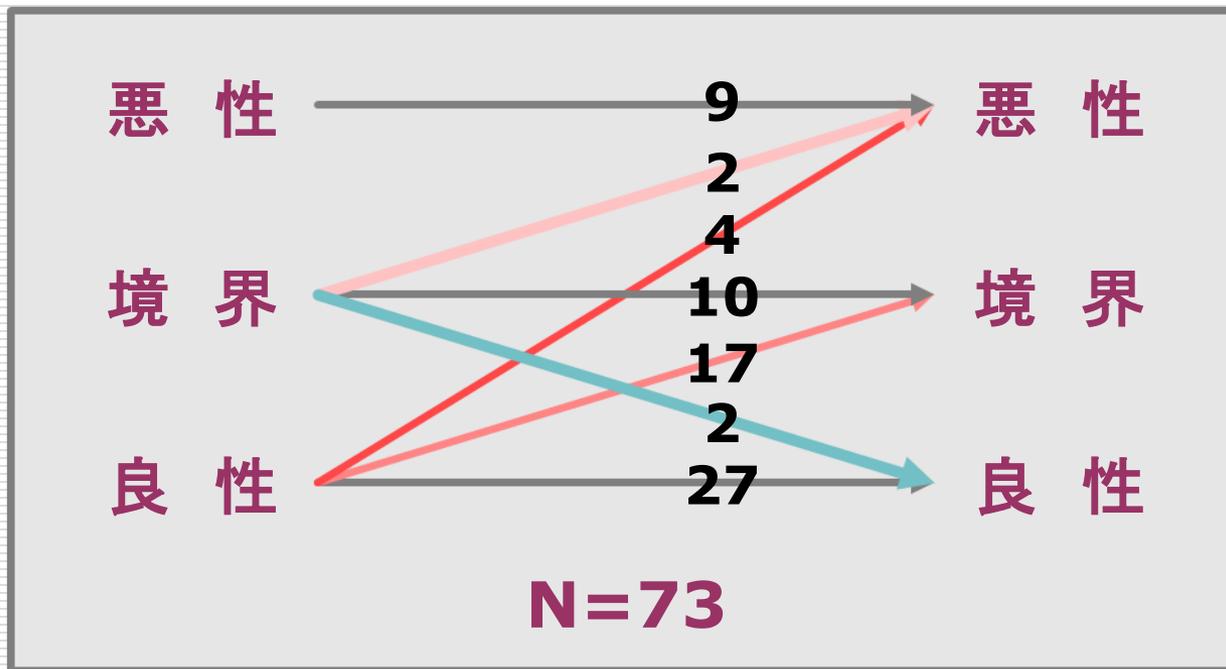
Jose M et al. Phyllodes Tumors: Race-Related Differences
Journal of the American College of Surgeons 2011; 213: 537-542.

Nomogram for predicting recurrence-free survival

- 異型
- 核分裂数
- 間質過剩発育
- 切除断端



原発腫瘍と転移巣の Grade



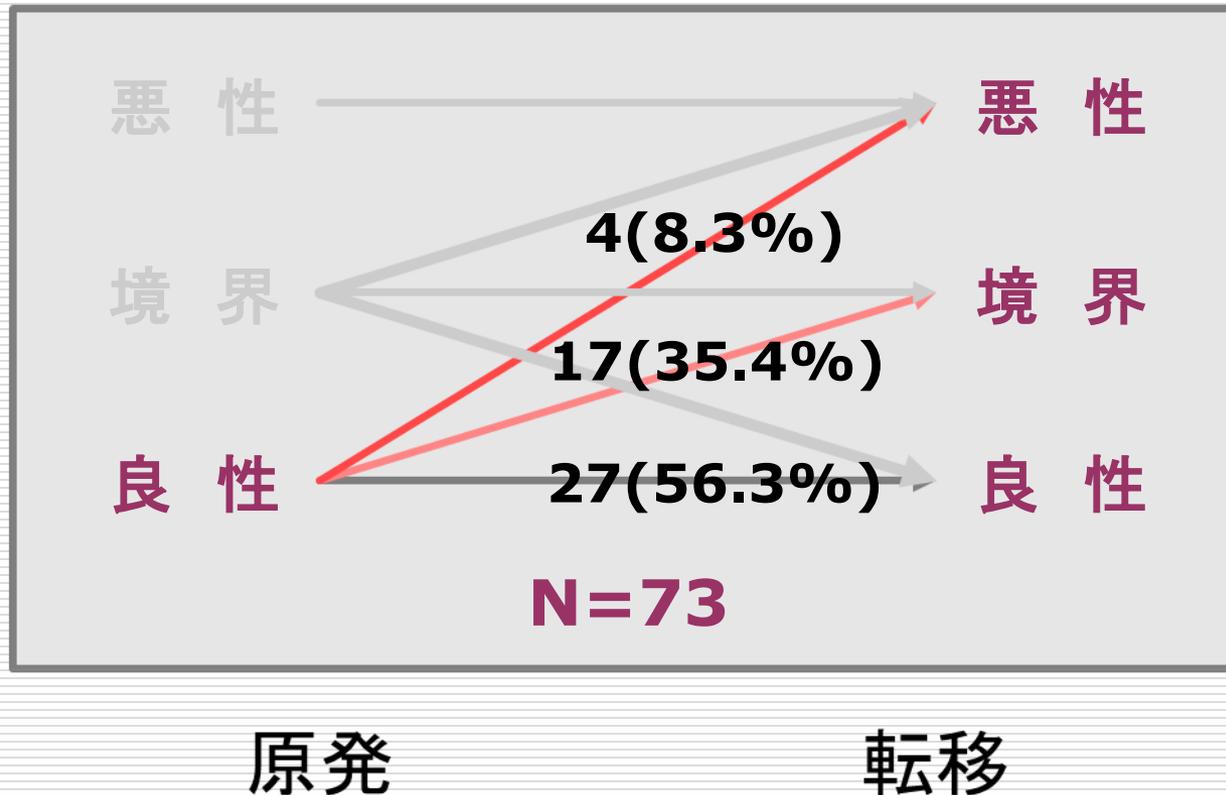
原発

転移

Tan PH et al; Phyllodes Tumour Network Singapore.
Predicting clinical behaviour of breast phyllodes tumours: a
nomogram based on histological criteria and surgical margins.

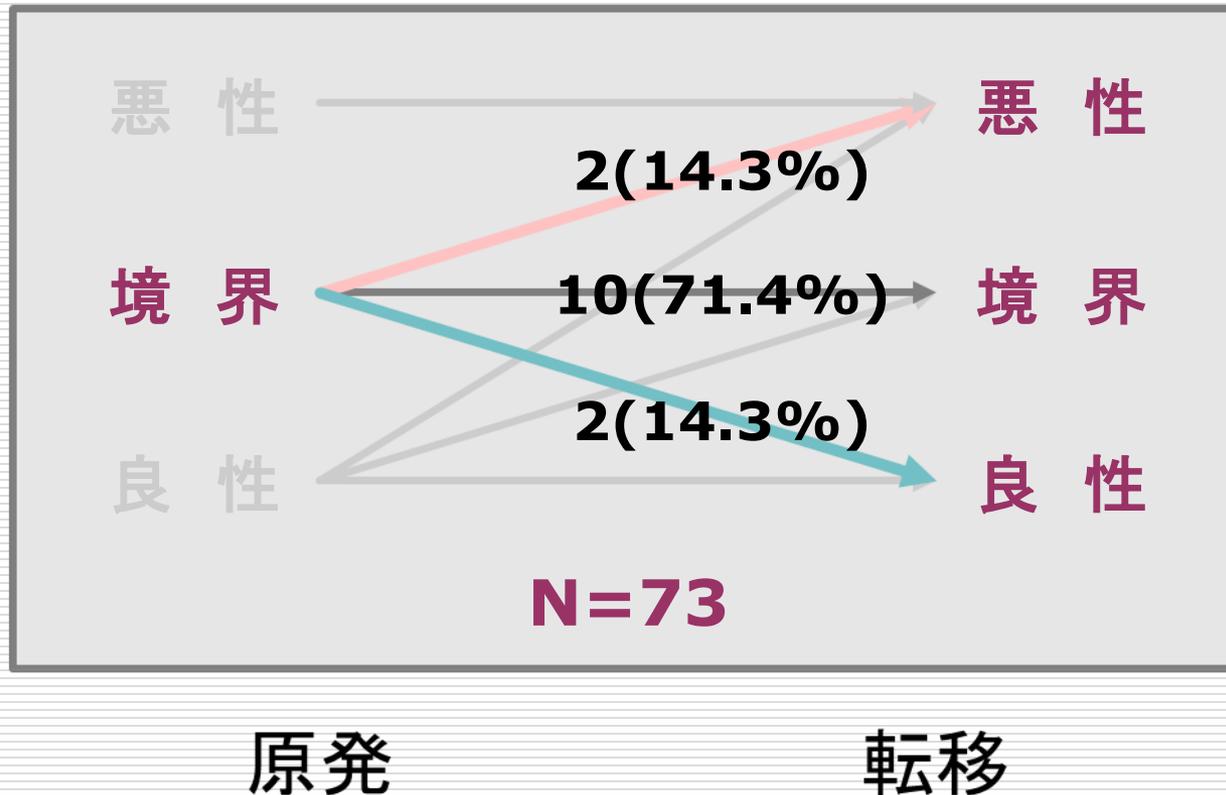
2013/5/29 J Clin Pathol 2012; 65: 69-76.

原発腫瘍と転移巣の Grade



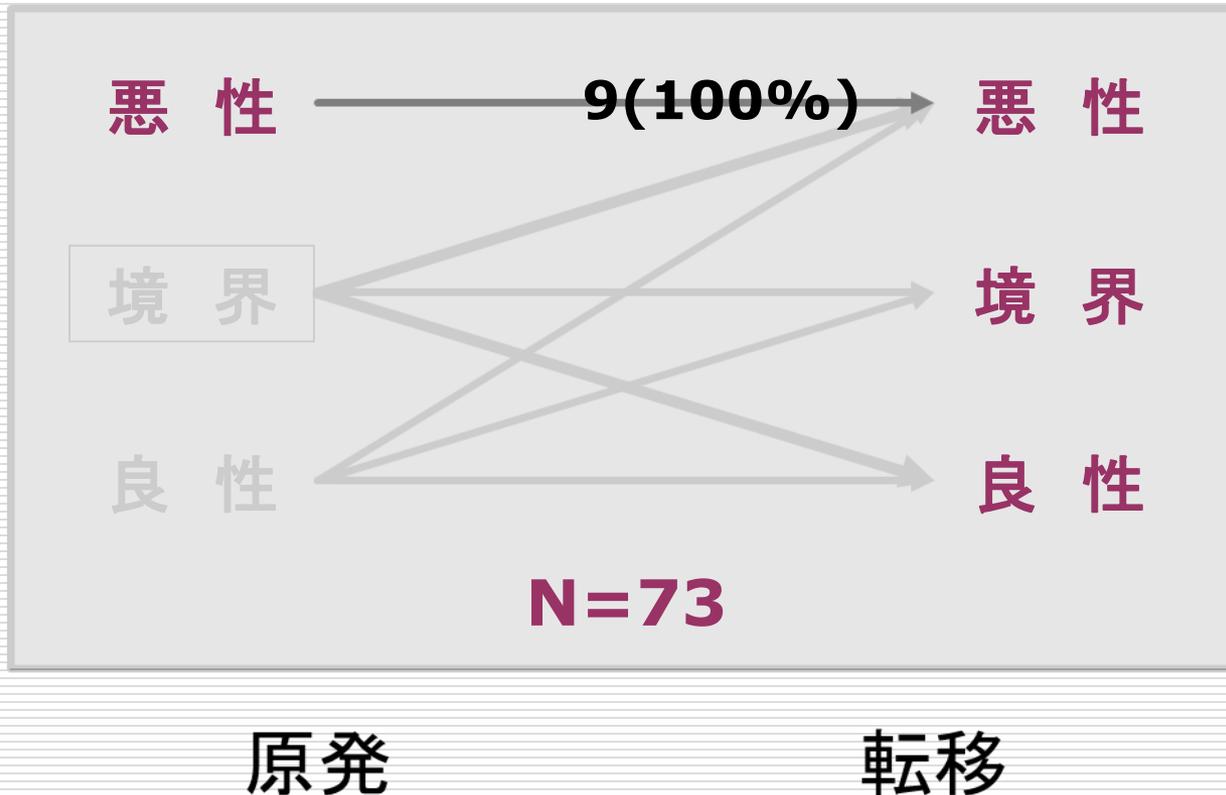
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葉状腫瘍における転移

良性	2% (3/138)
境界悪性	9% (5/57)
悪性	23% (24/105)

Barth et al., 1999

葉状腫瘍における転移

- 肺
- 骨
- 心臓

腋窩リンパ節転移

悪性葉状腫瘍 (high-grade) の1%未満

腫瘍死

良性	0.3% (2/600)
境界悪性	6.6% (7/107)
悪性	20% (48/240)

Barth et al. Breast Cancer Res Treat 1996;
57: 291-295

悪性葉状腫瘍の疾患特異的生存率 (821例、SEER)

5 years	91%	Median F/U 5.7 years
10 years	89%	
15 years	89%	

Macdonald et al. Cancer 2006; 107: 2127-2133

Management

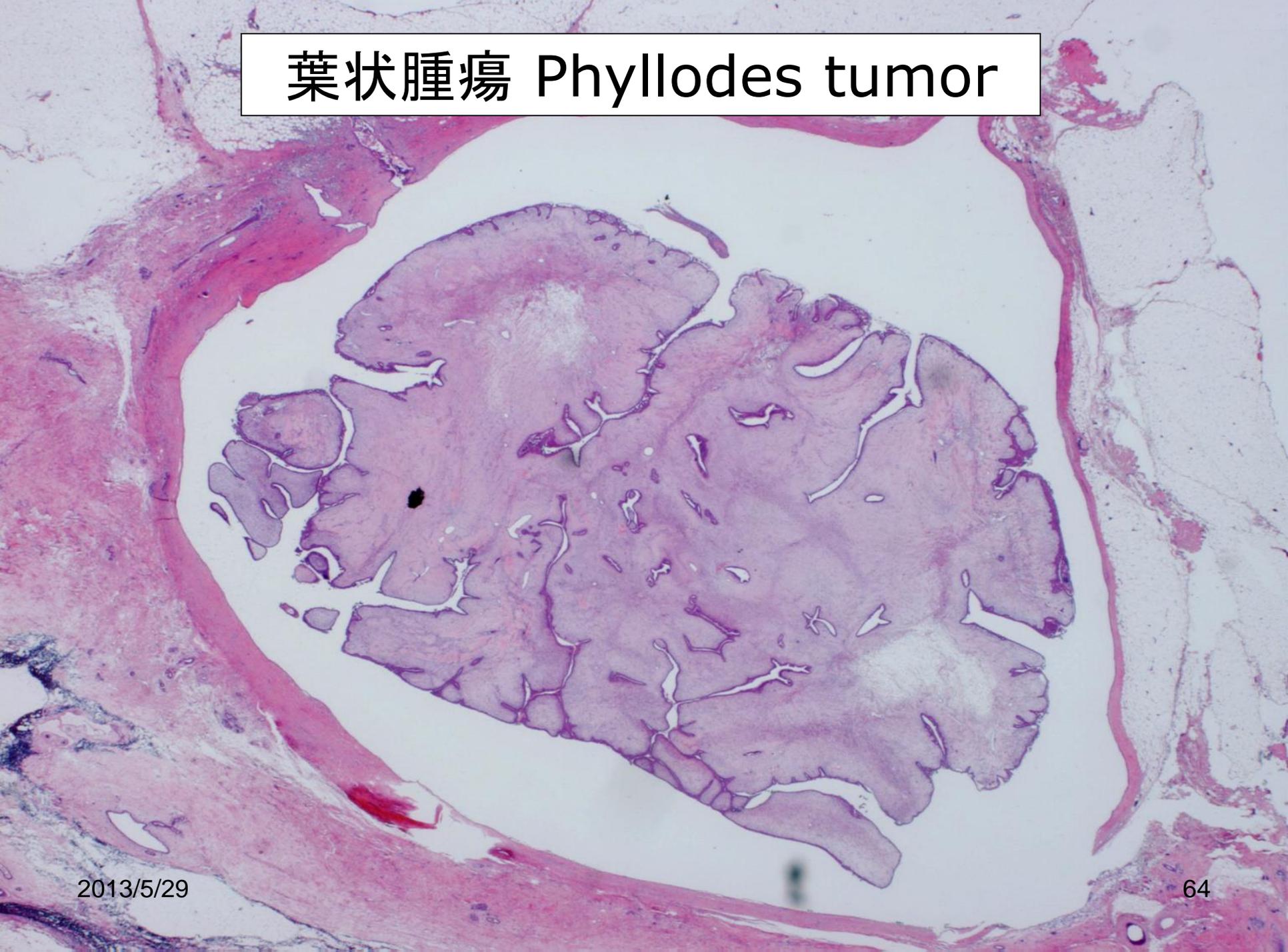
- Excision with a safe surgical margin
- Mastectomy for borderline or malignant phyllodes tumors or in cases of local tumor recurrence

Guillot et al., The Breast Journal
2011; 17: 129-137

鑑別診断

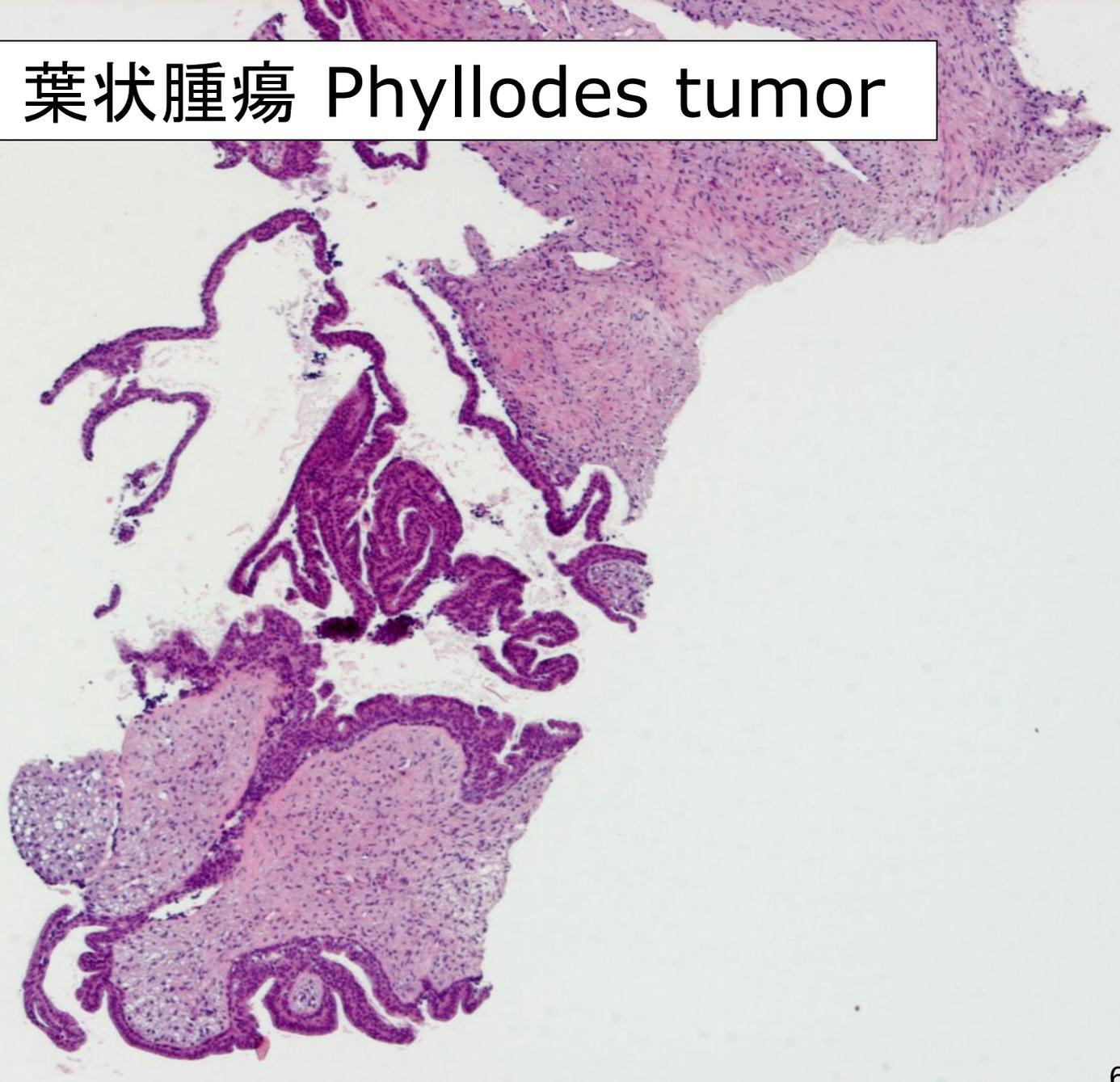
- 線維腺腫
- Pseudoangiomatous stromal hyperplasia (PASH)
- 化生癌（紡錘細胞癌）
- 間質肉腫
- その他の肉腫

葉状腫瘍 Phyllodes tumor

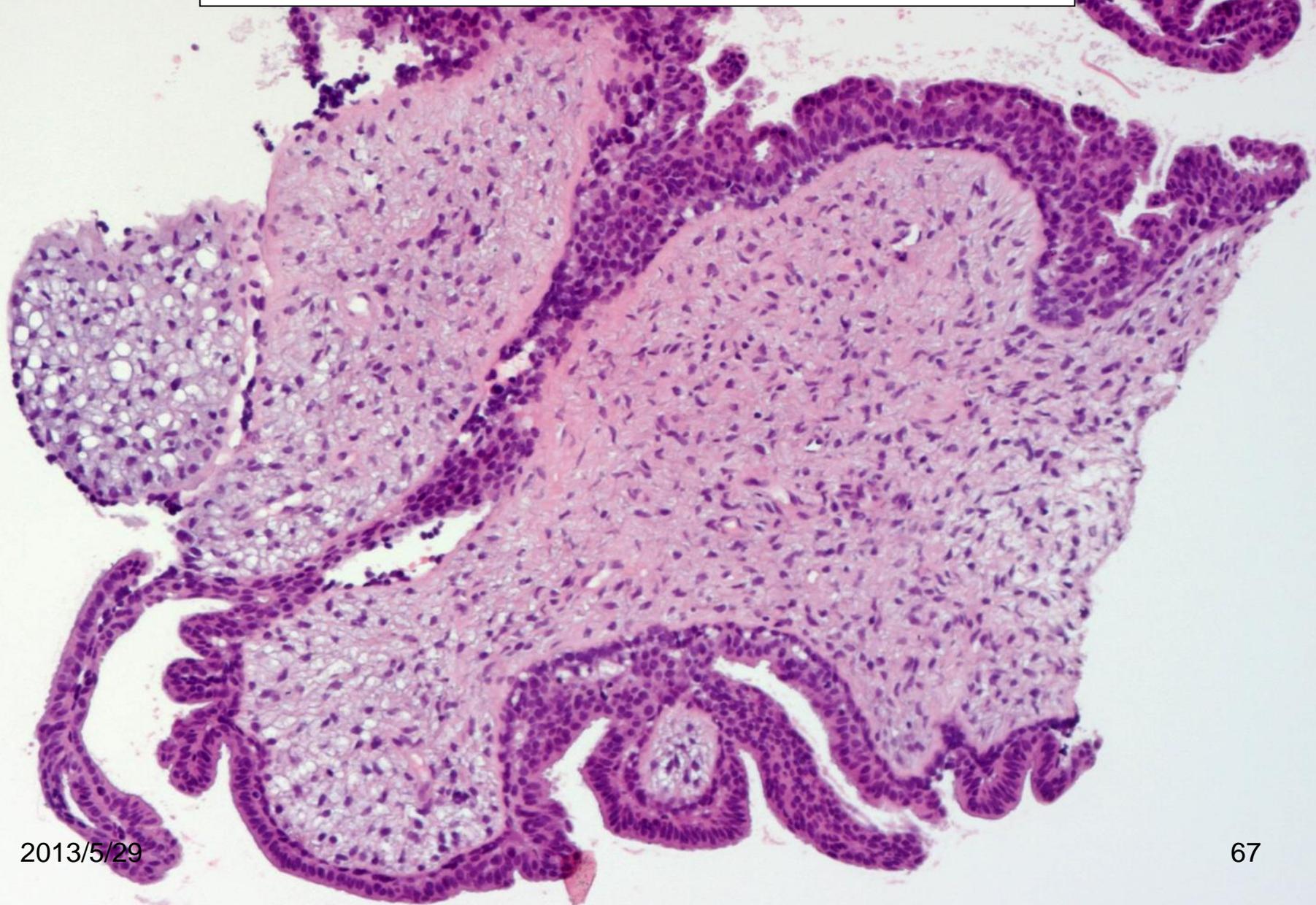




葉狀腫瘍 Phyllodes tumor

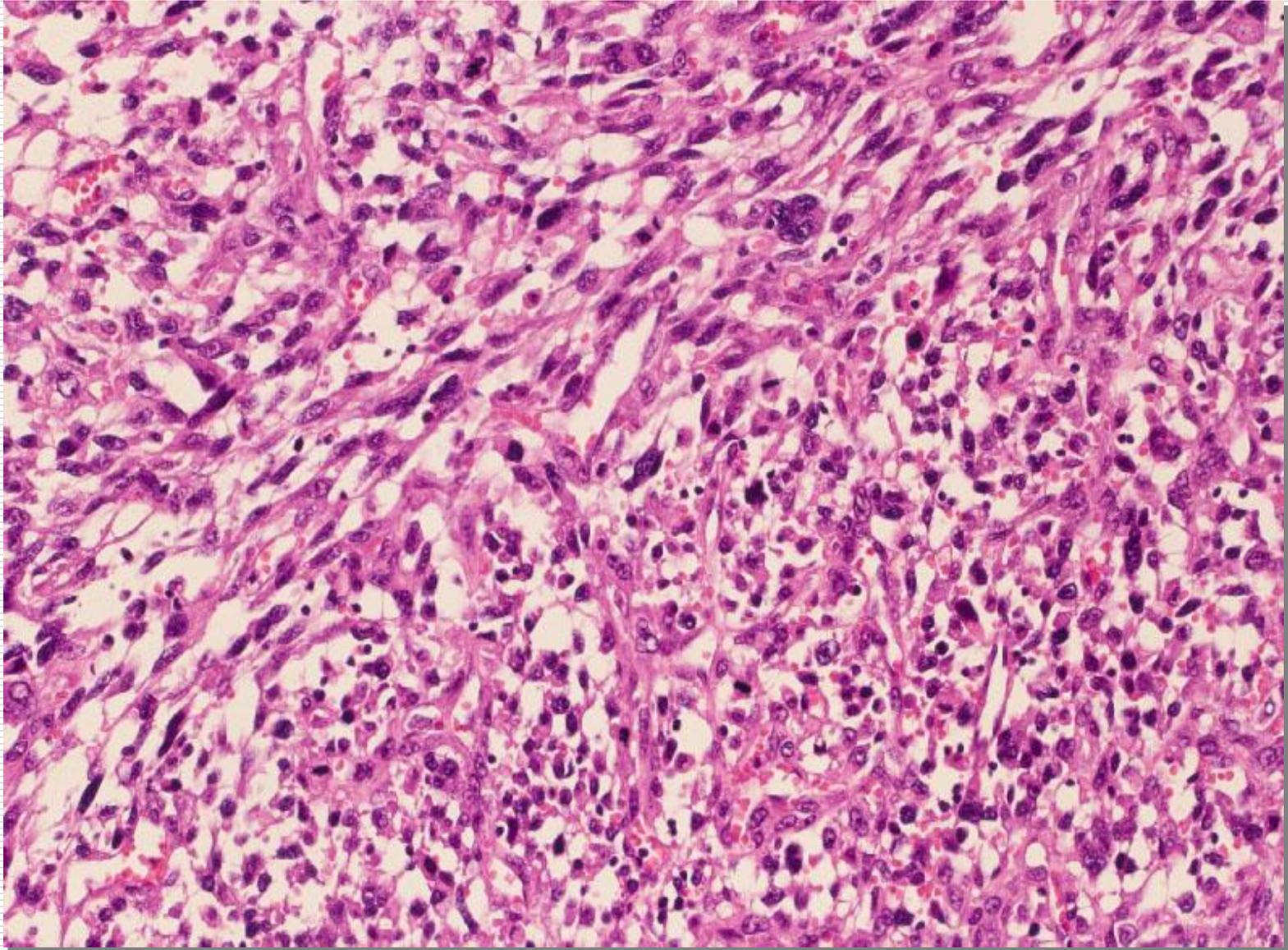


葉狀腫瘍 Phyllodes tumor

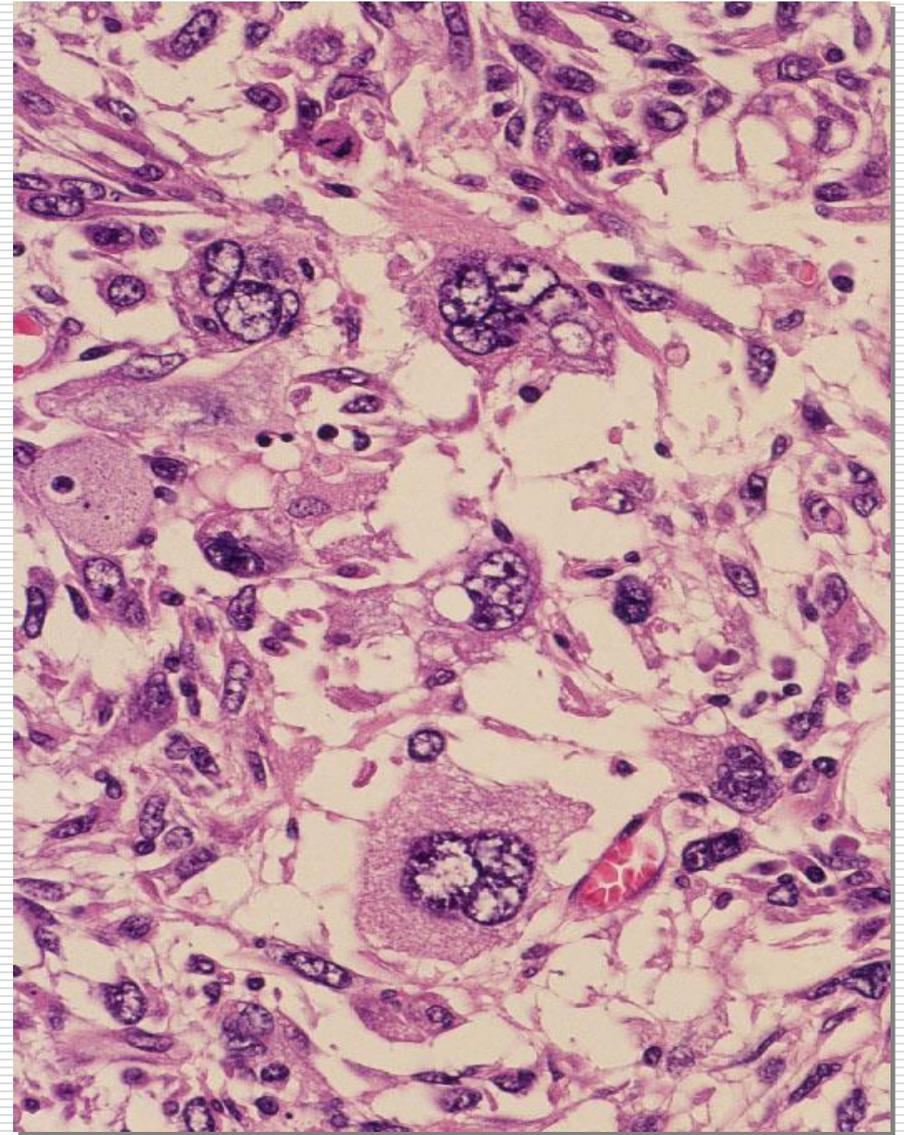
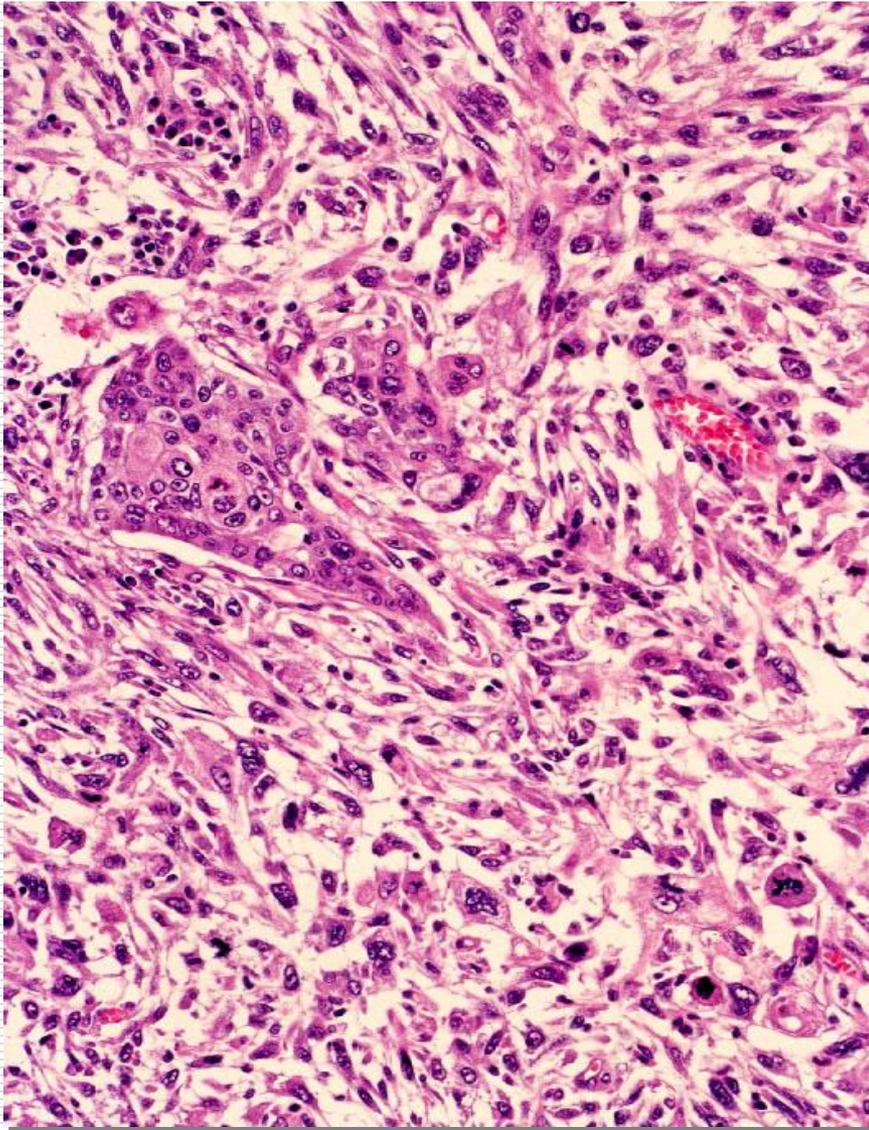


VS 線維腺腫

- Favor phyllodes
 - 細胞密度の増加
 - 間質過剰増殖
 - 断片化
 - 間質内に脂肪細胞が混在



2013/5/29 Sarcomatoid (spindle cell) carcinoma 69



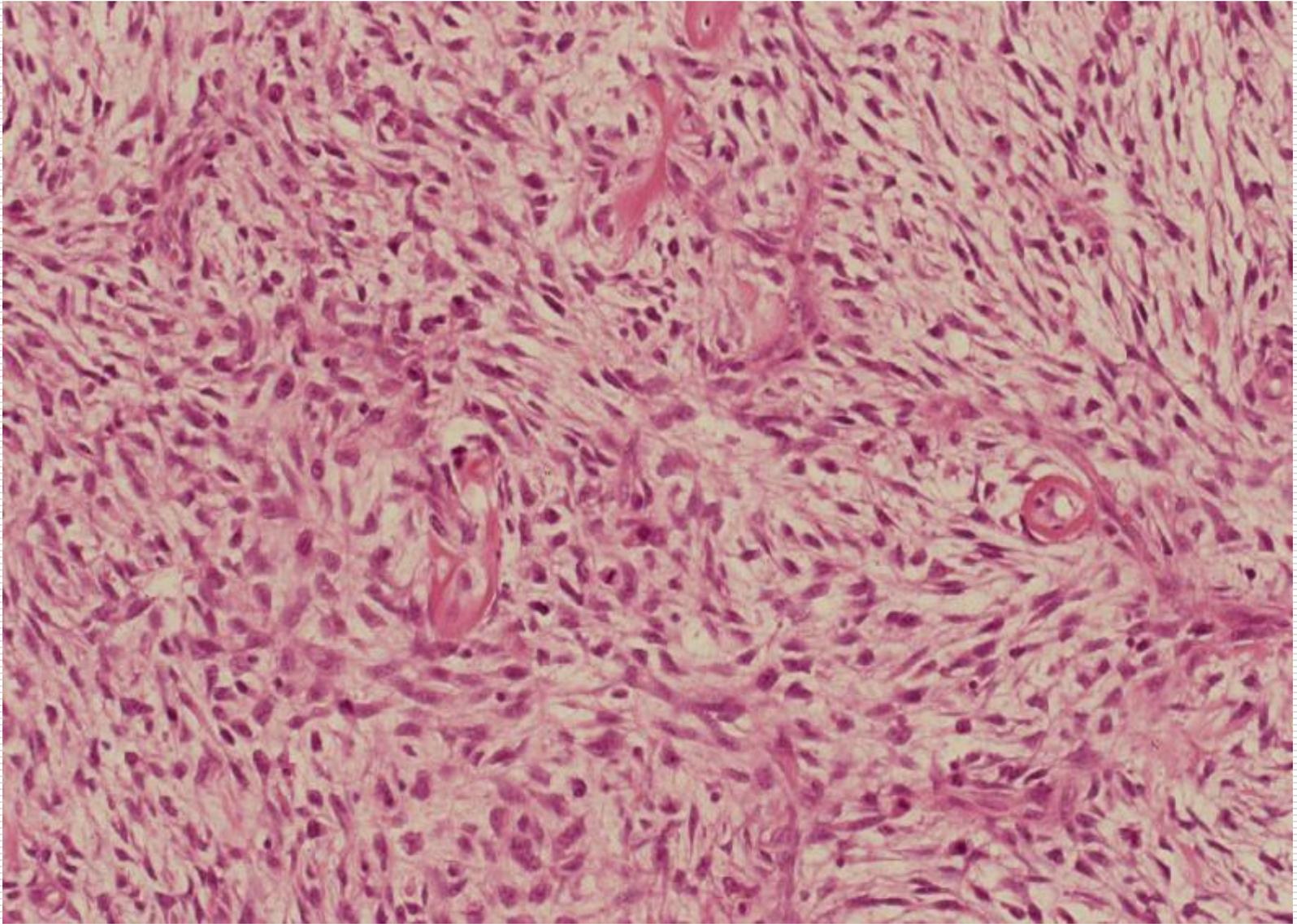
2013/5/29 Sarcomatoid (spindle cell) carcinoma 70



間質肉腫 Stromal sarcoma

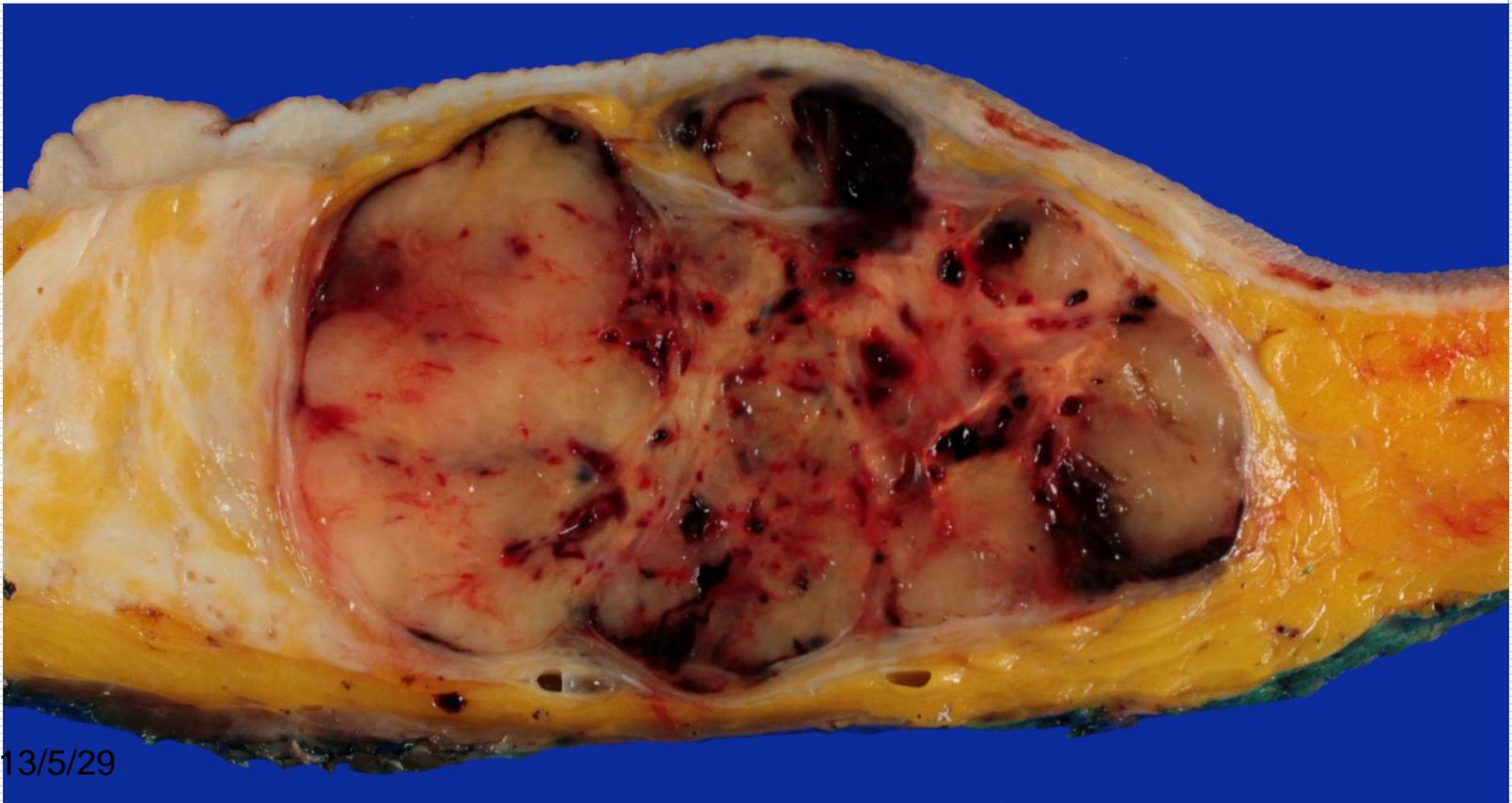
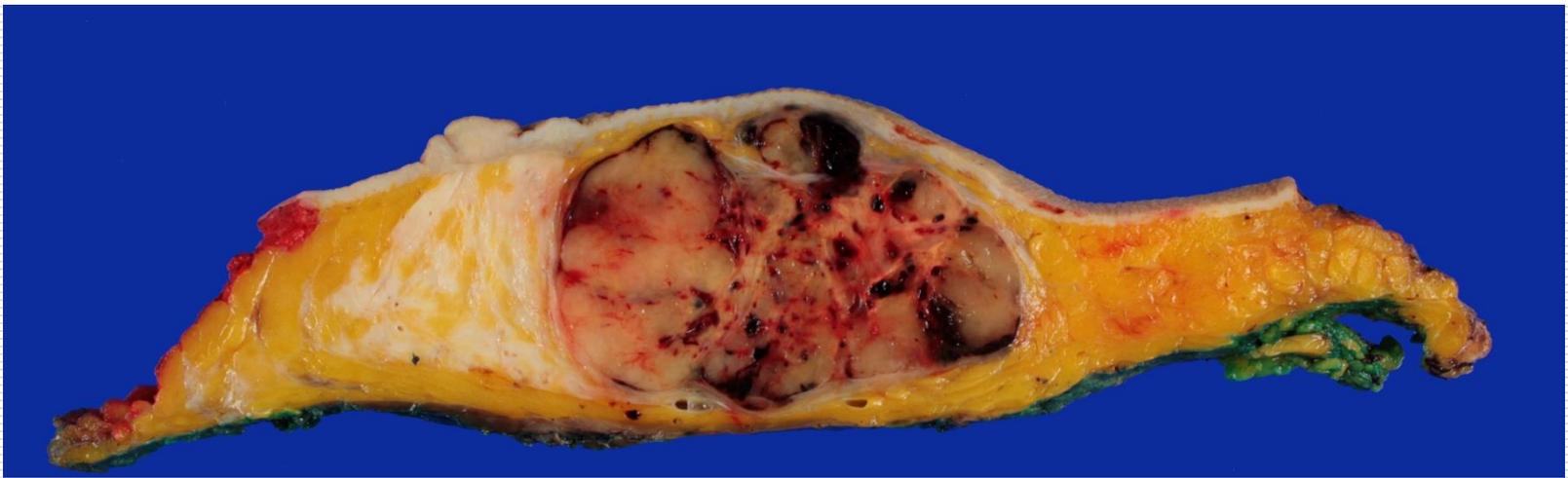
間質肉腫 Stromal sarcoma

- 乳腺特有の悪性軟部腫瘍
- 肉腫成分のみで、上皮成分は欠如
- ホルモン反応性の特殊な乳管周囲間質から発生
- 紡錘形細胞からなる線維肉腫様形態



2013/5/29

間質肉腫 Stromal sarcoma

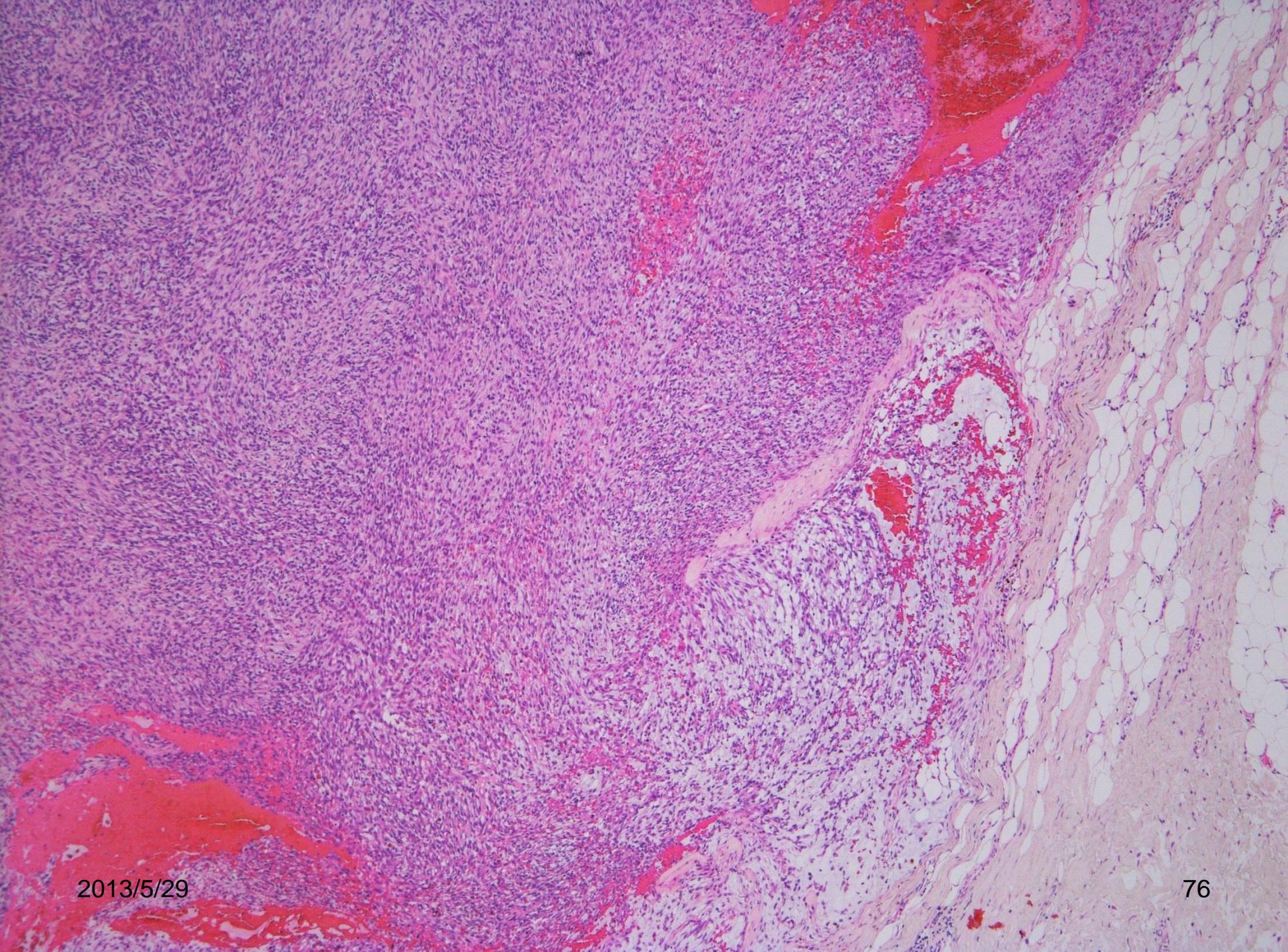


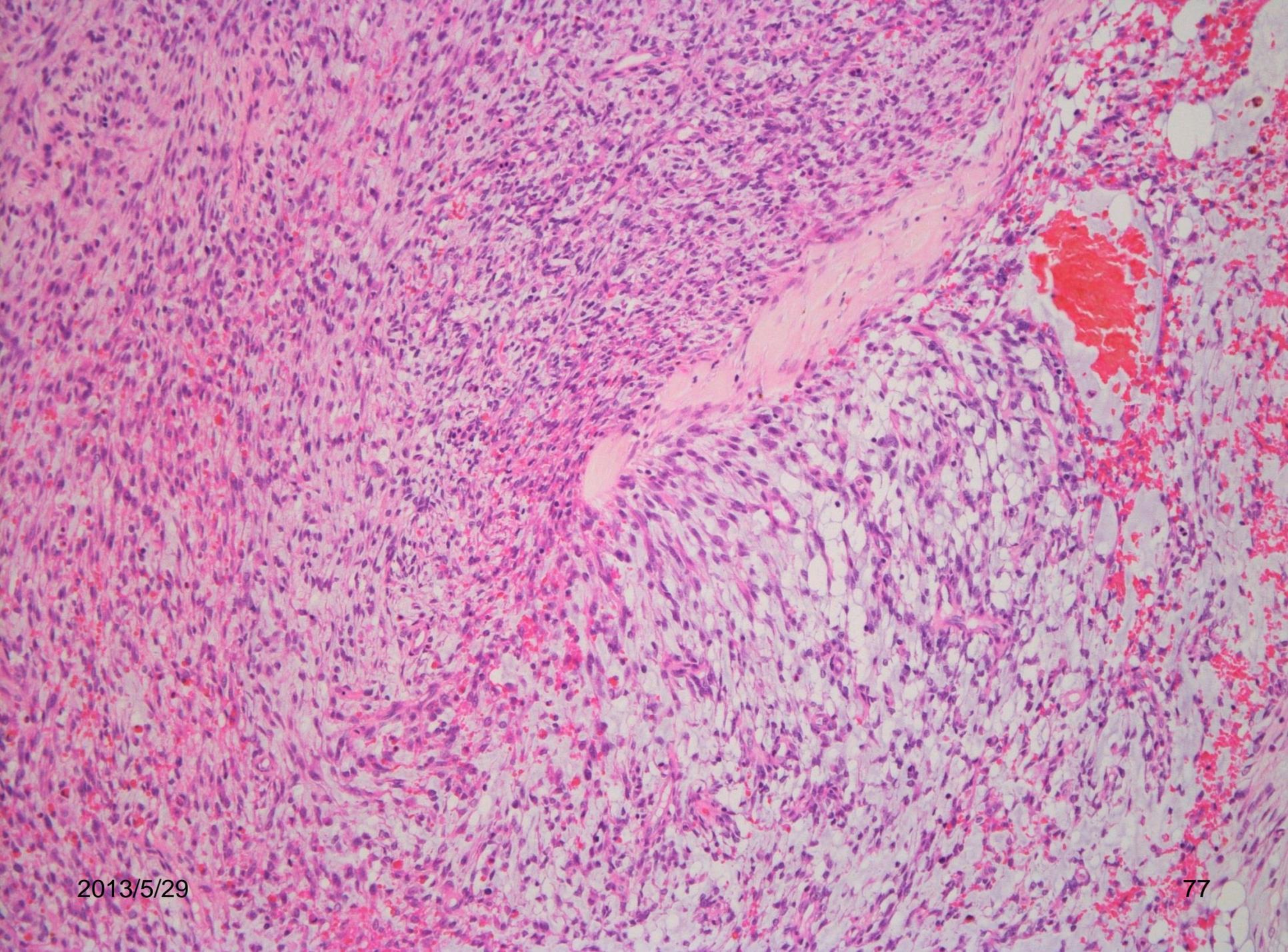
Case

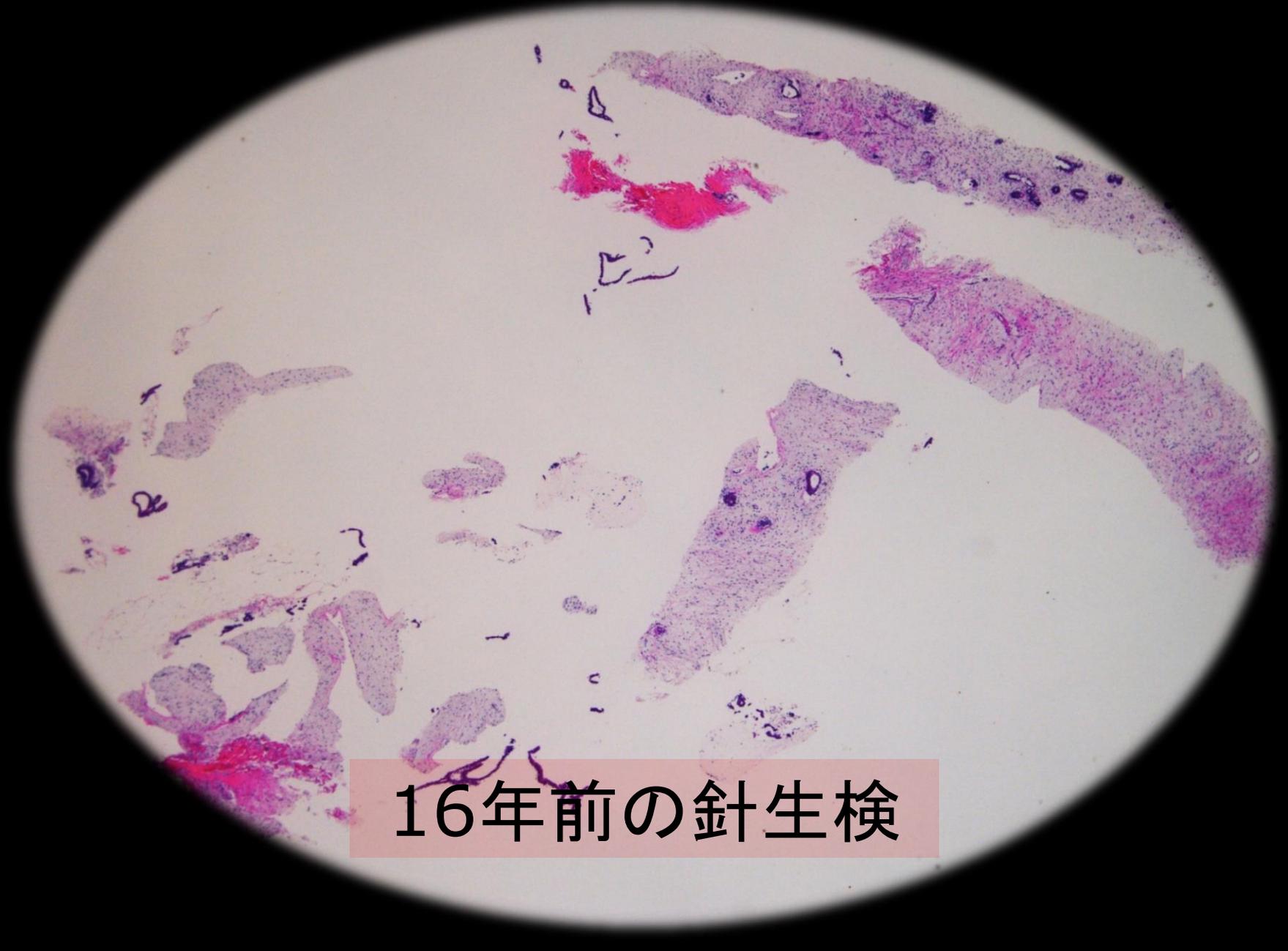
58歳、女性

右乳房腫瘍、乳房全摘

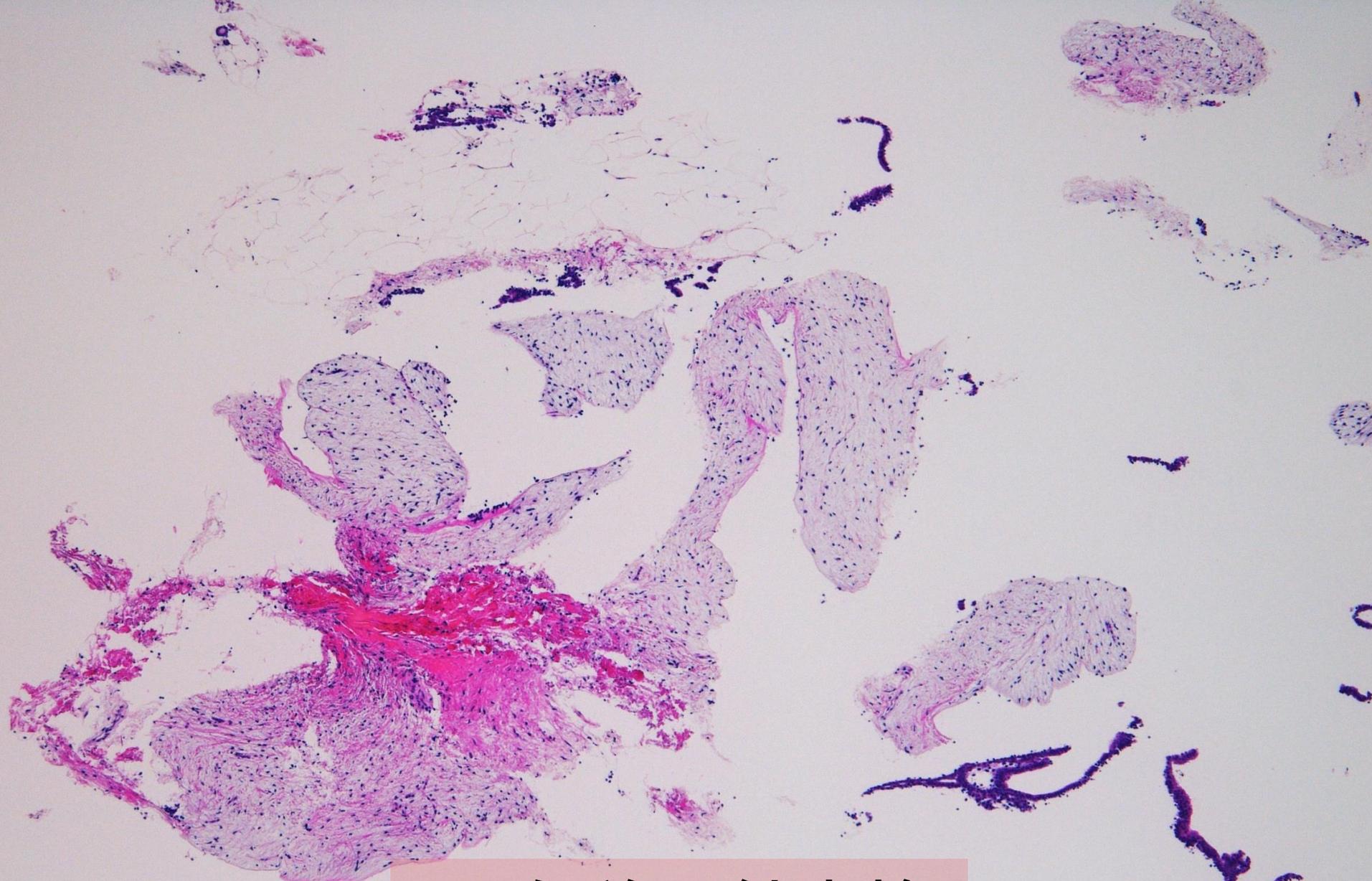






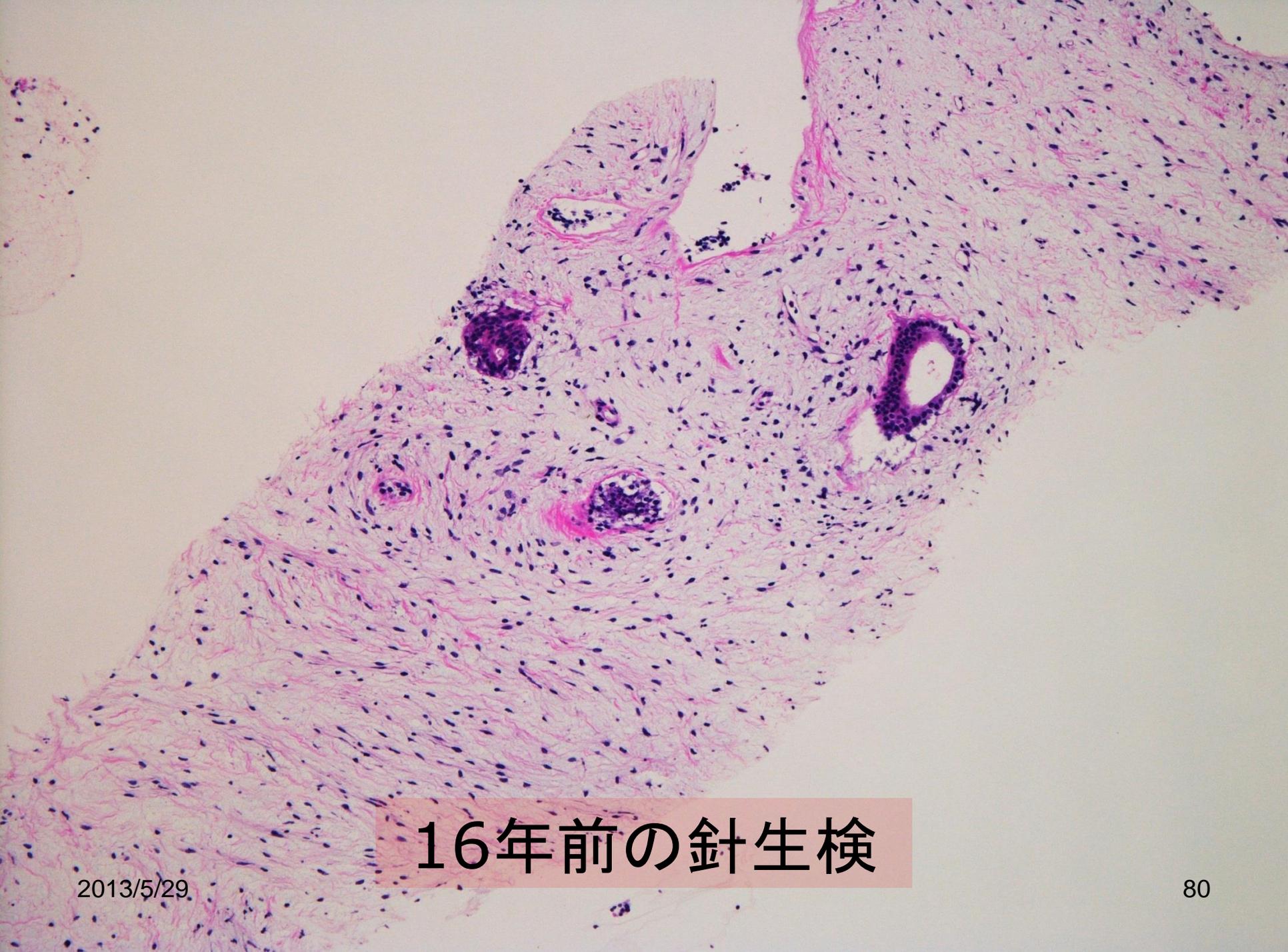


16年前の針生検



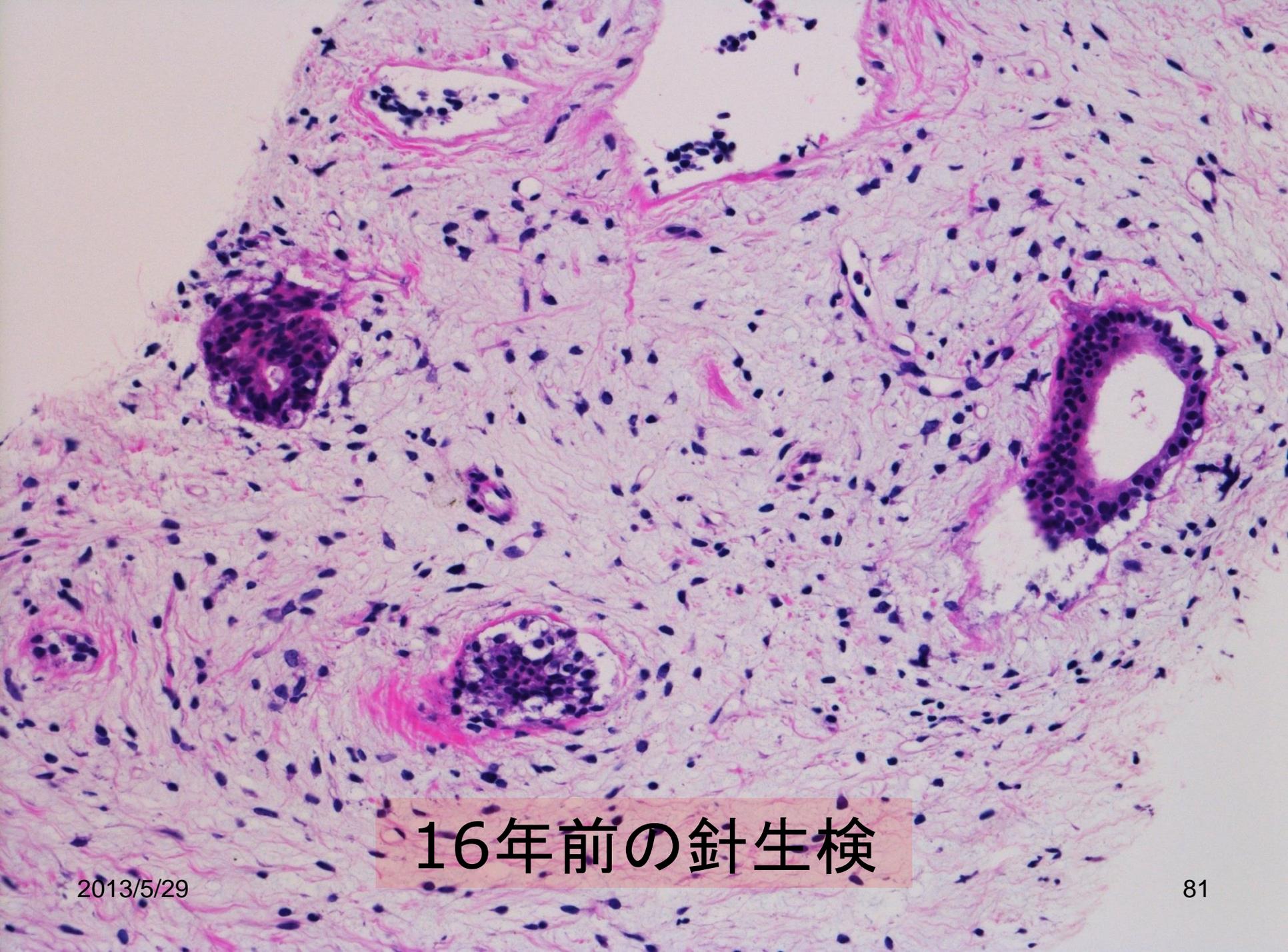
16年前の針生検

2013/5/29



16年前の針生検

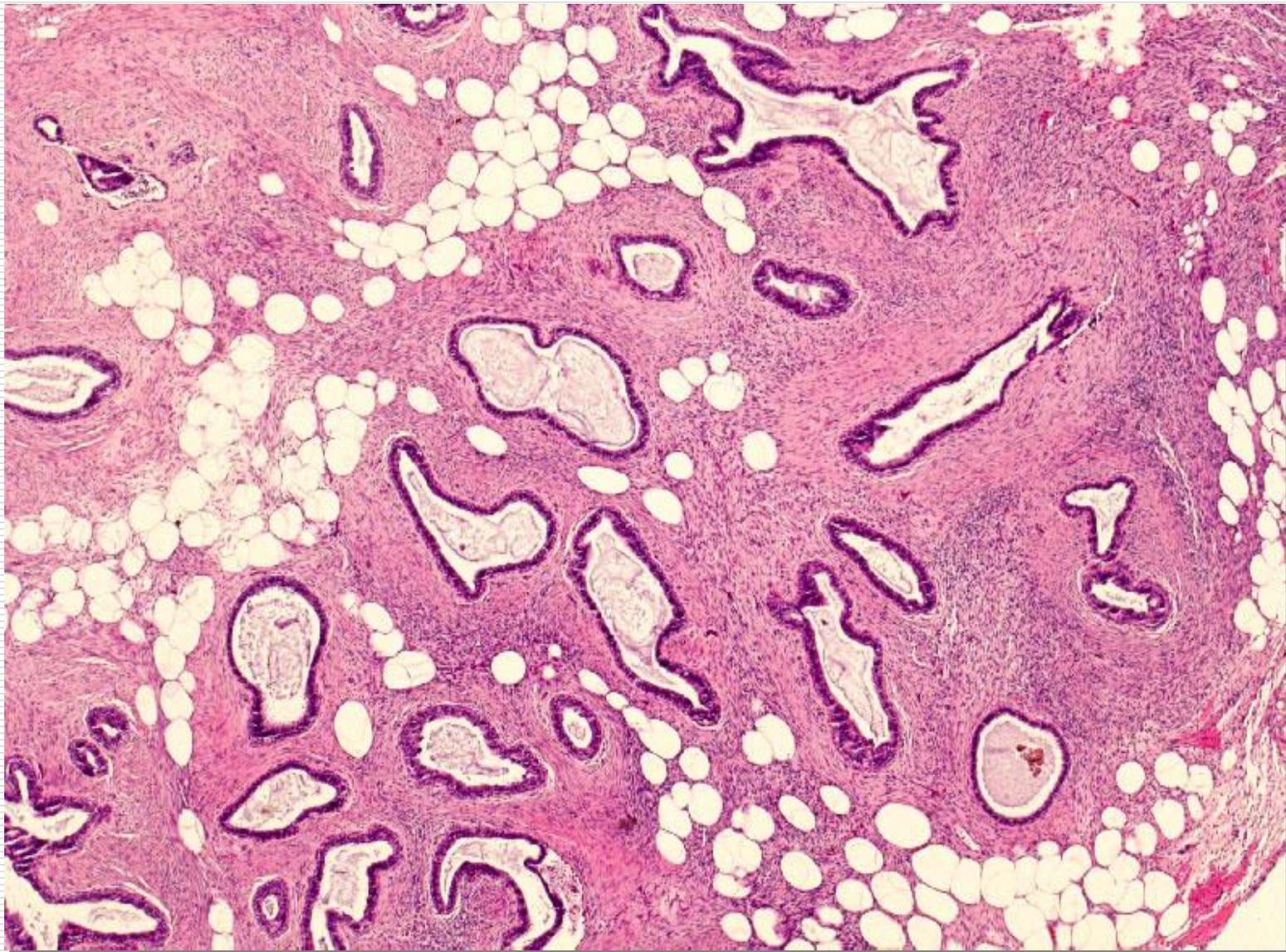
2013/5/29



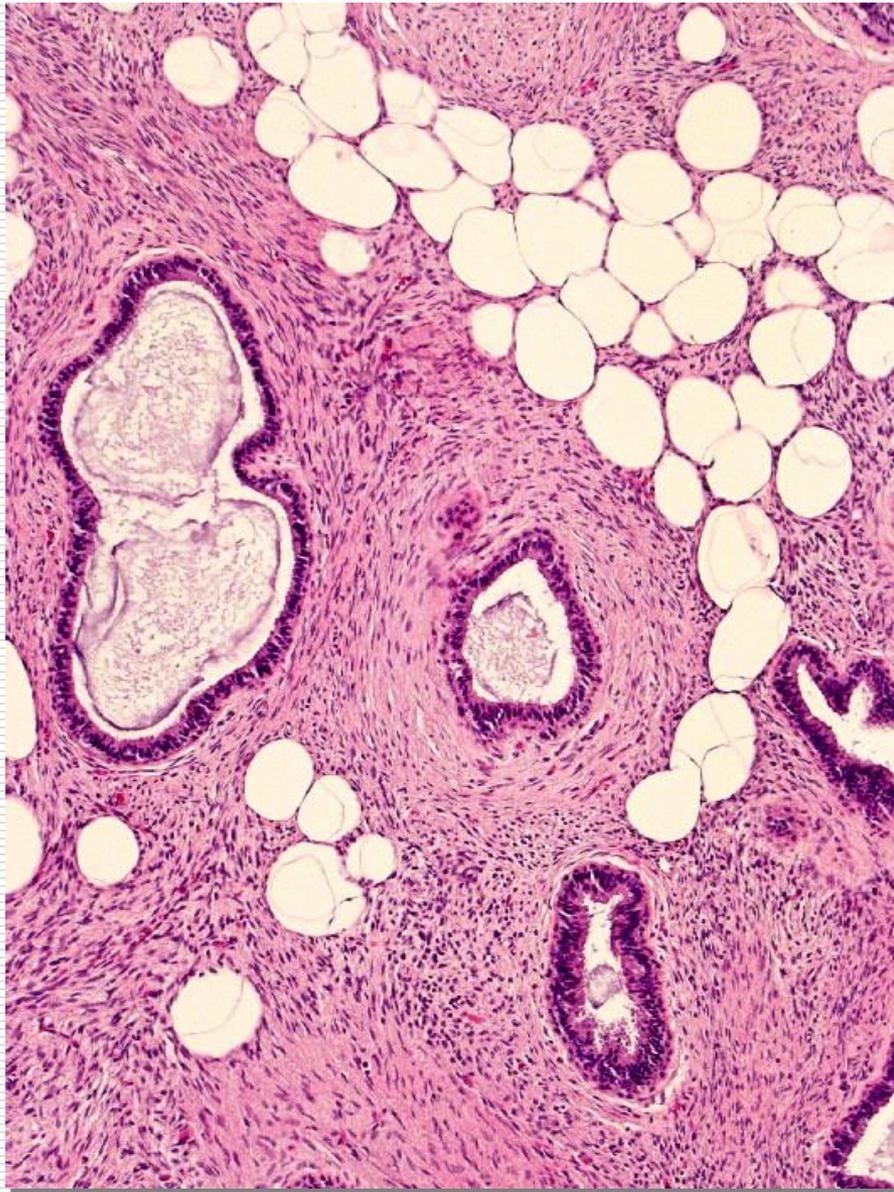
16年前の針生検

2013/5/29

81



乳管周圍間質肉腫
Periductal Stromal Sarcoma



2013/5/29

乳管周圍間質肉腫

ご清聴ありがとうございました



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