Breast Pathology Course 2020@21

Case 23

63 year old Chinese female underwent left mastectomy for a 17cm tumour.

Division of Pathology
Singapore General Hospital

SingHealth DukeNUS ACADEMIC MEDICAL CENTRE
PATHOLOGY

IAP International Academy of Pathology Singapore Division

Breast Pathology Course 2020@21

F63, 7 month history of enlarging mass in left breast occupying the entire lateral aspect extending into the axilla.

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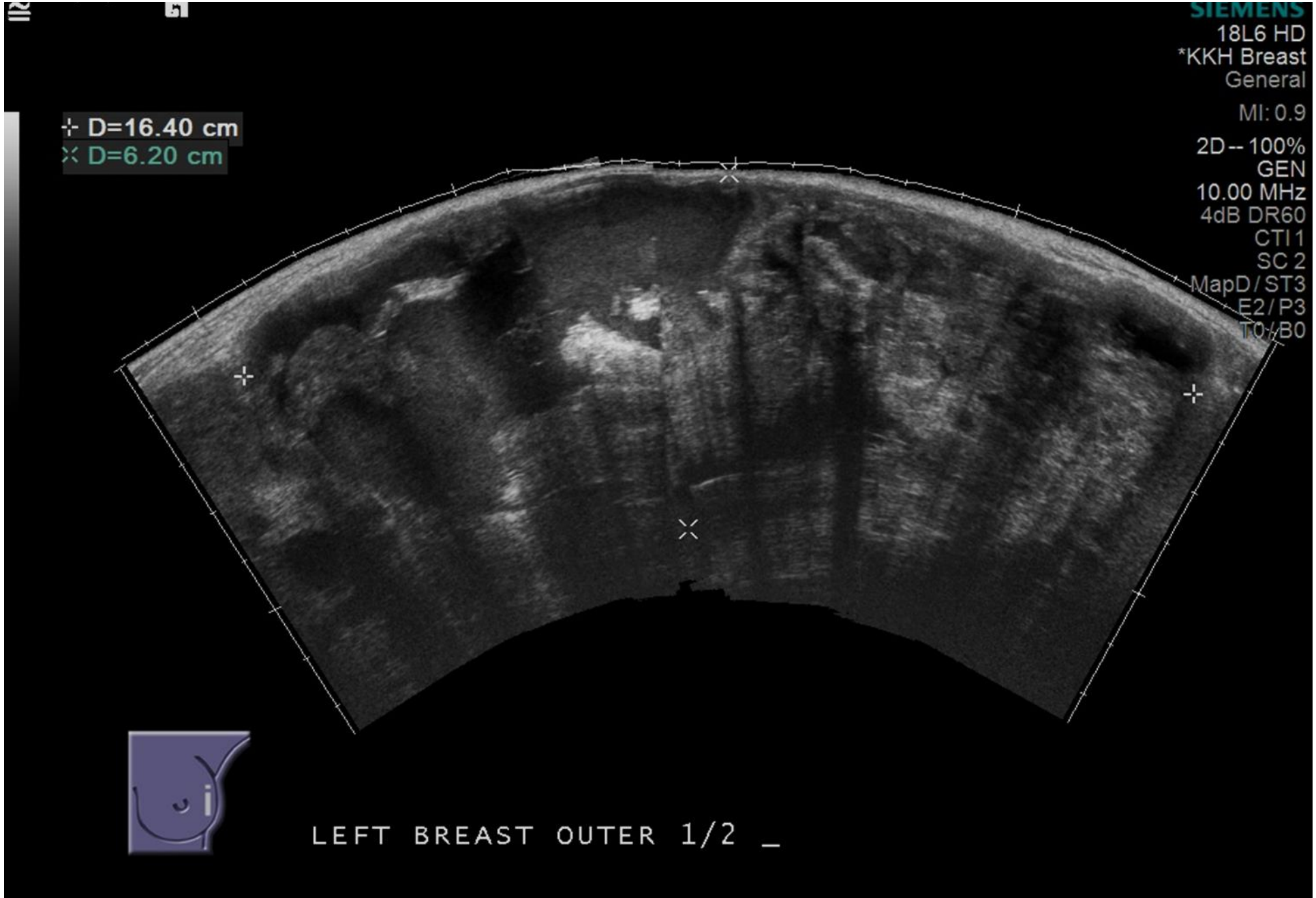
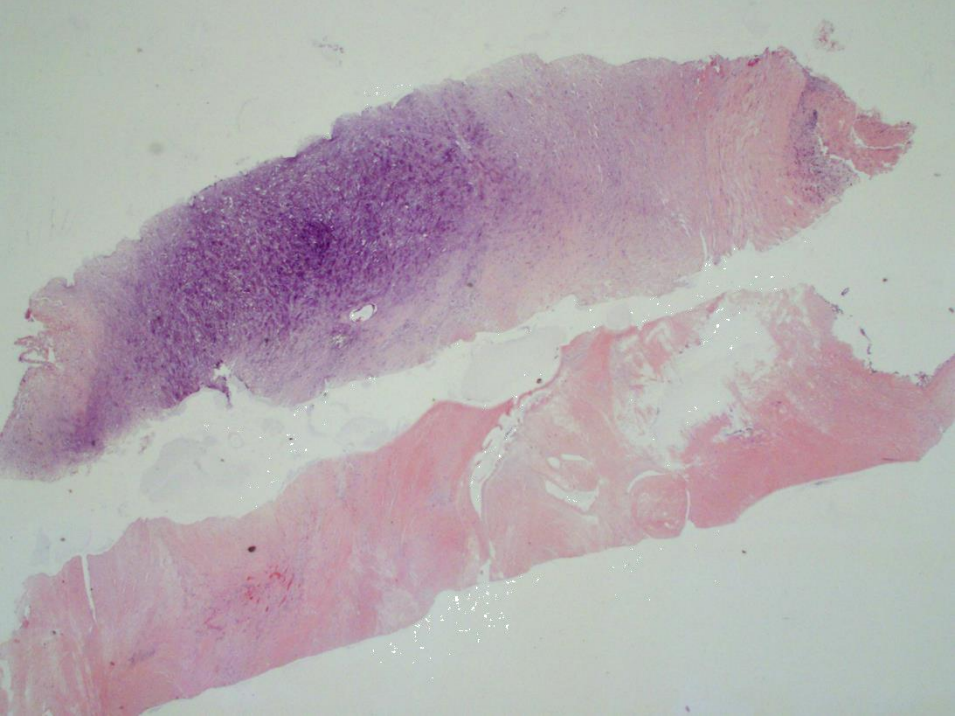
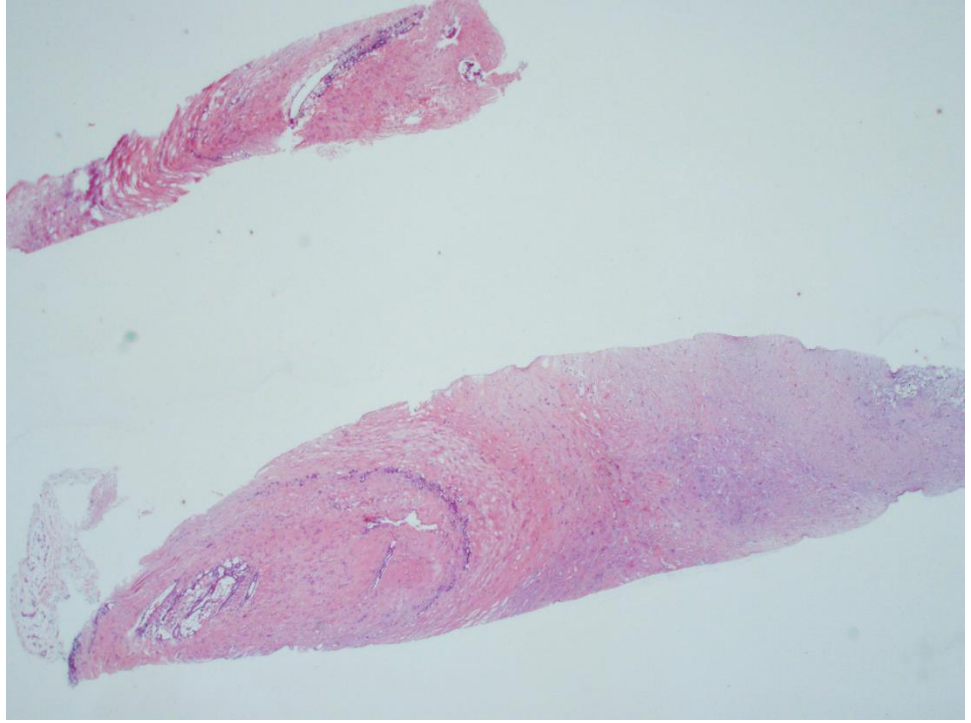
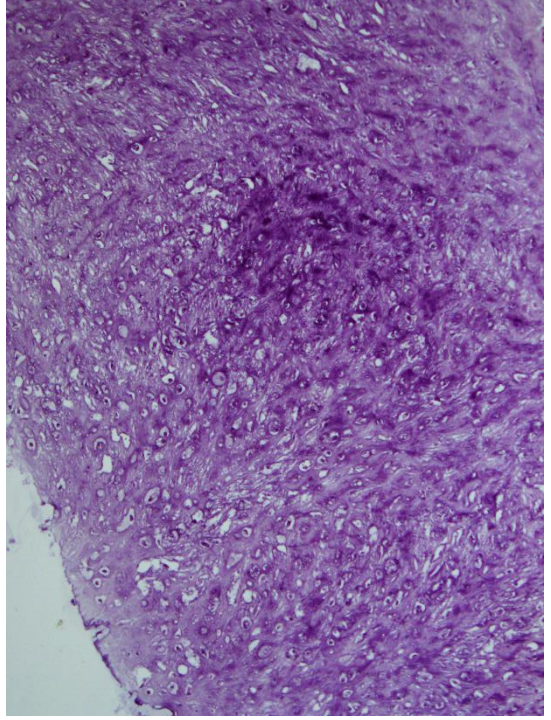

D=16.40 cm
D=6.20 cm
SIEMENS
18L6 HD
*KKH Breast
General
MI: 0.9
2D -- 100%
GEN
10.00 MHz
4dB DR60
CTI 1
SC 2
MapD / ST3
E2 / P3
T0 / B0
LEFT BREAST OUTER 1/2 _

The strips of tissue show a nodular mass which is composed largely of hyalinised and myxoid stroma with low cellularity. Areas of infarction/necrosis are seen focally. A few compressed ductal slits are present in one strip.

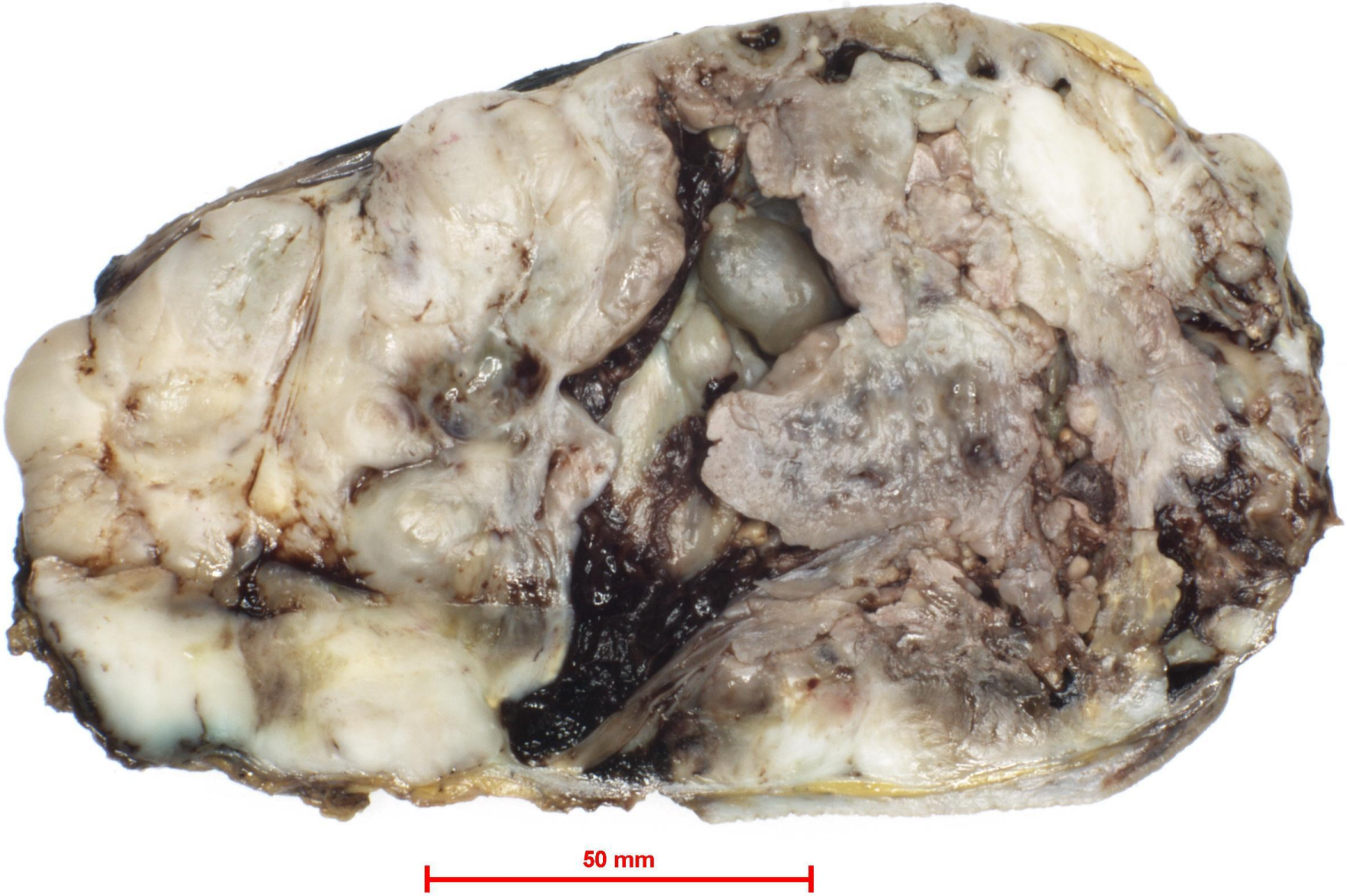
Immunohistochemistry performed shows the following characteristics of the lesion:

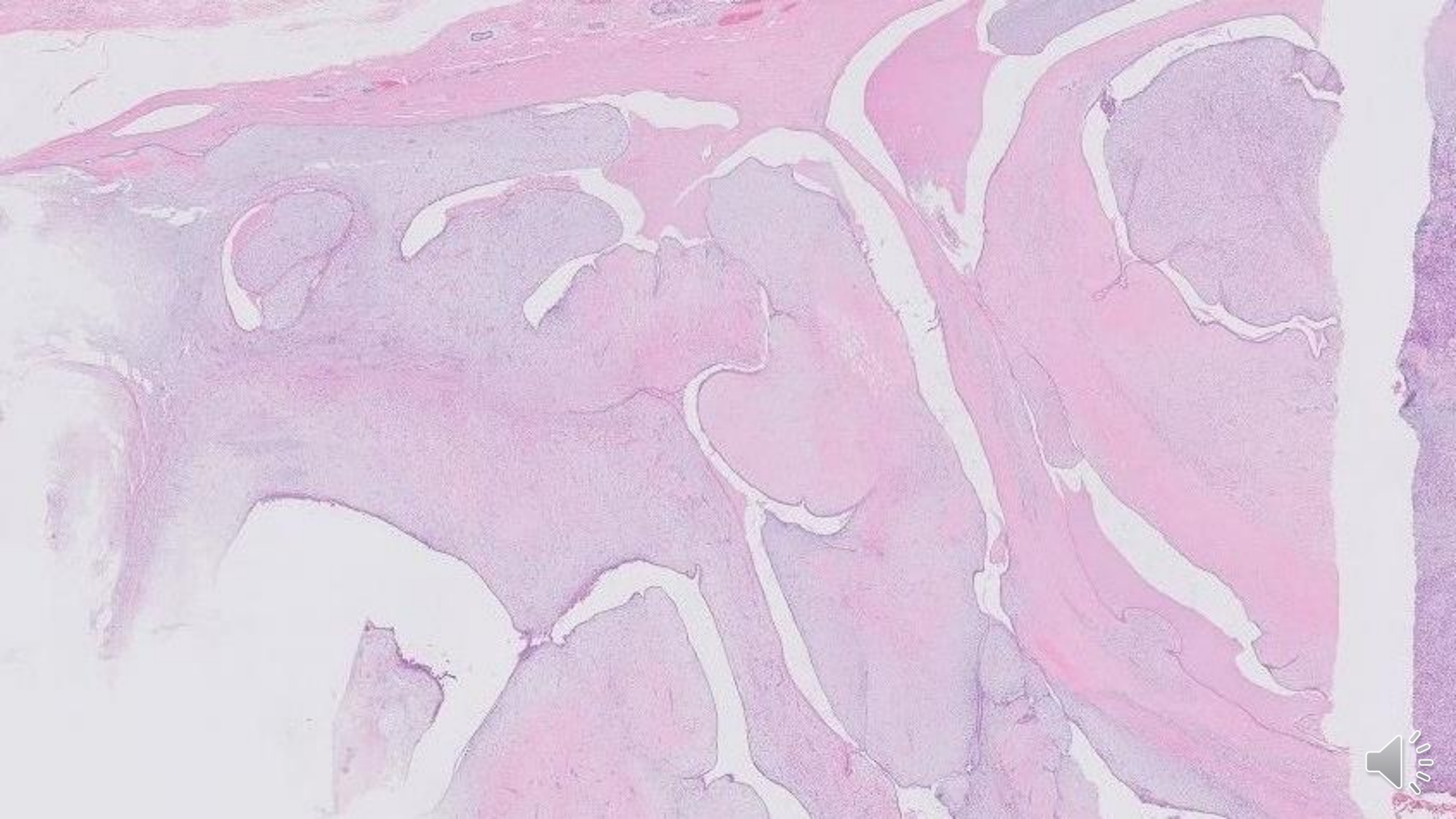
MNF 116:	Negative
AE 1/3:	Focal positive
S-100 protein:	Negative

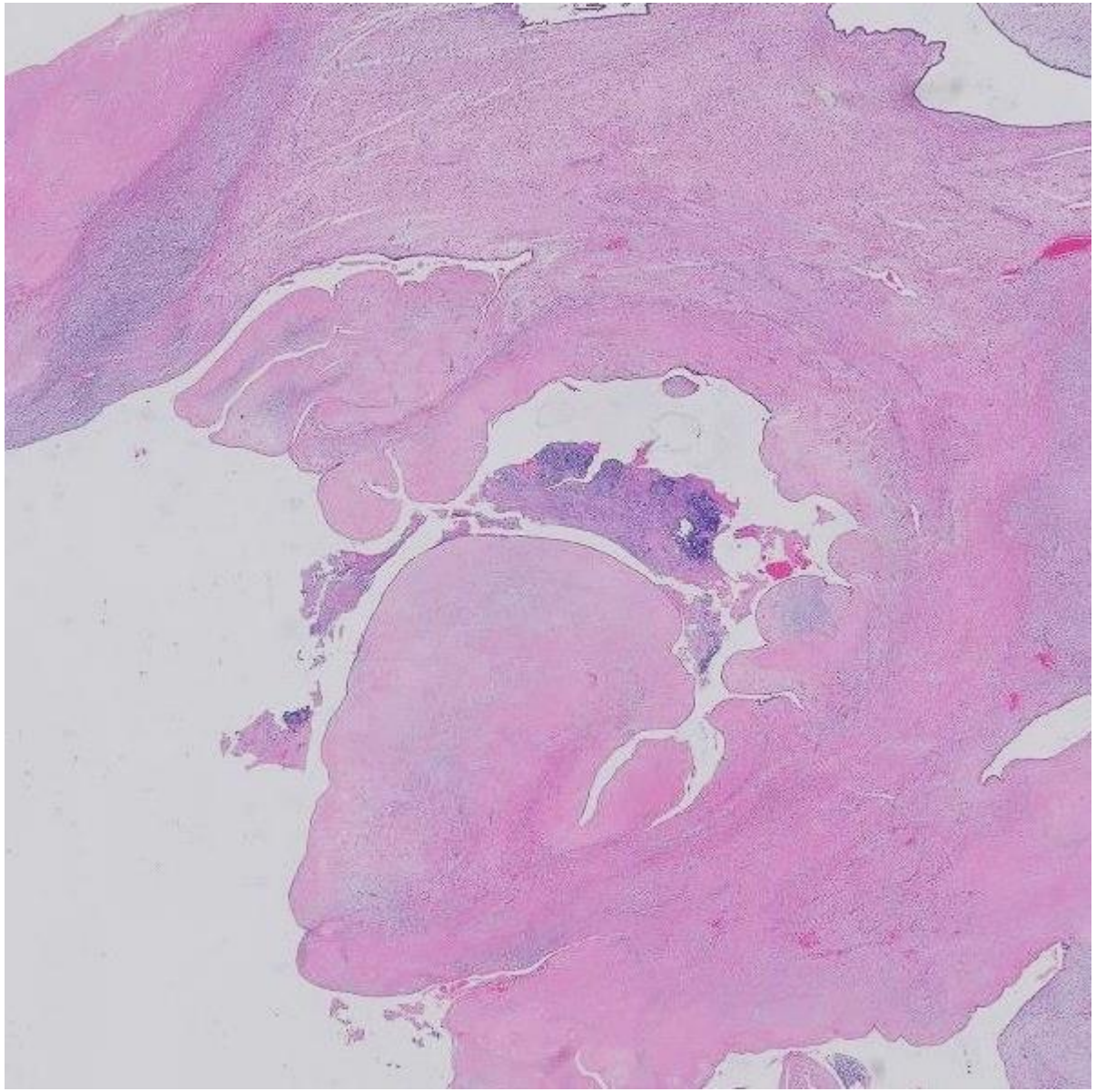
Deep sections cut from the paraffin blocks do not show additional features.

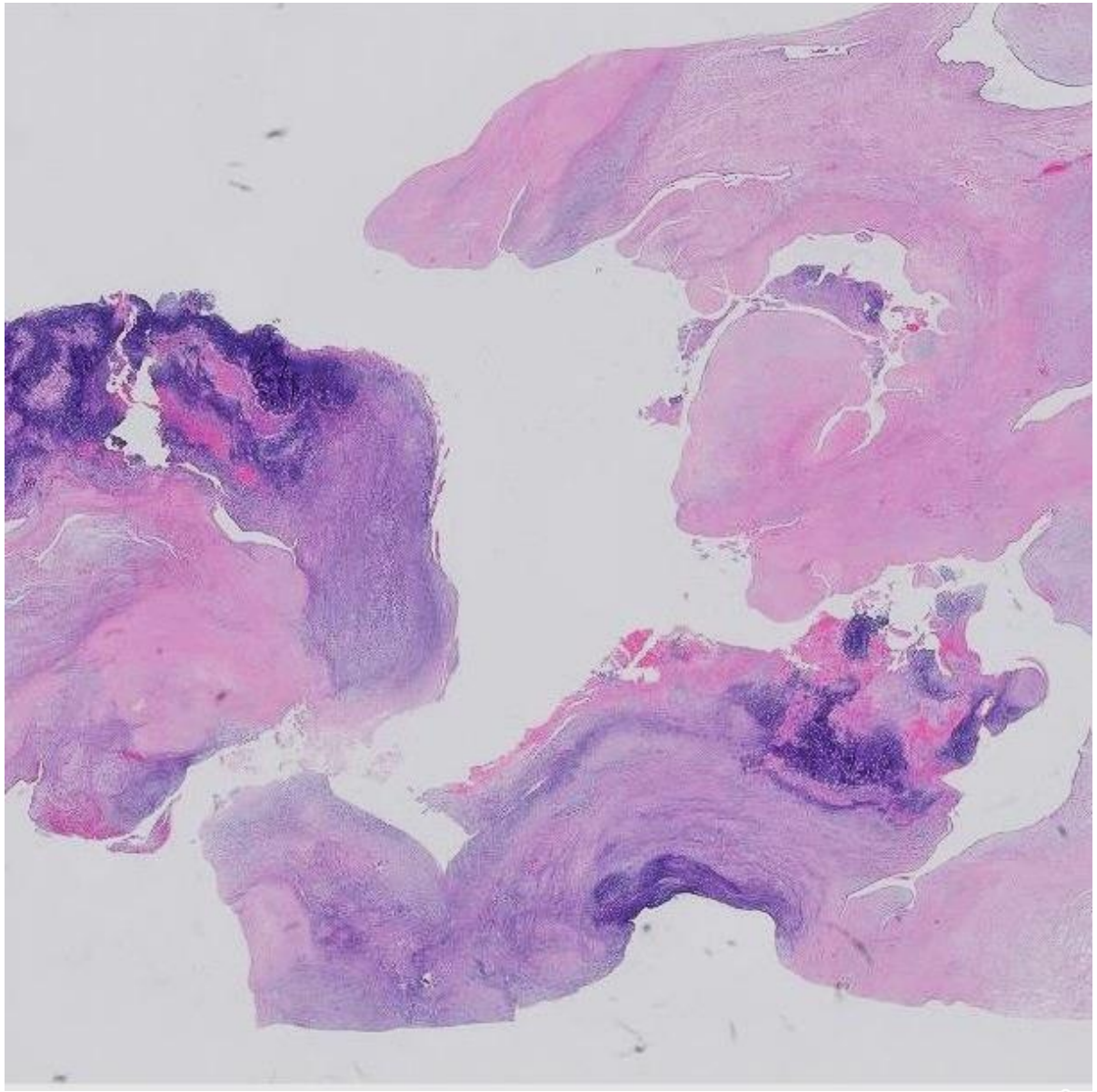
Histology Final Diagnosis

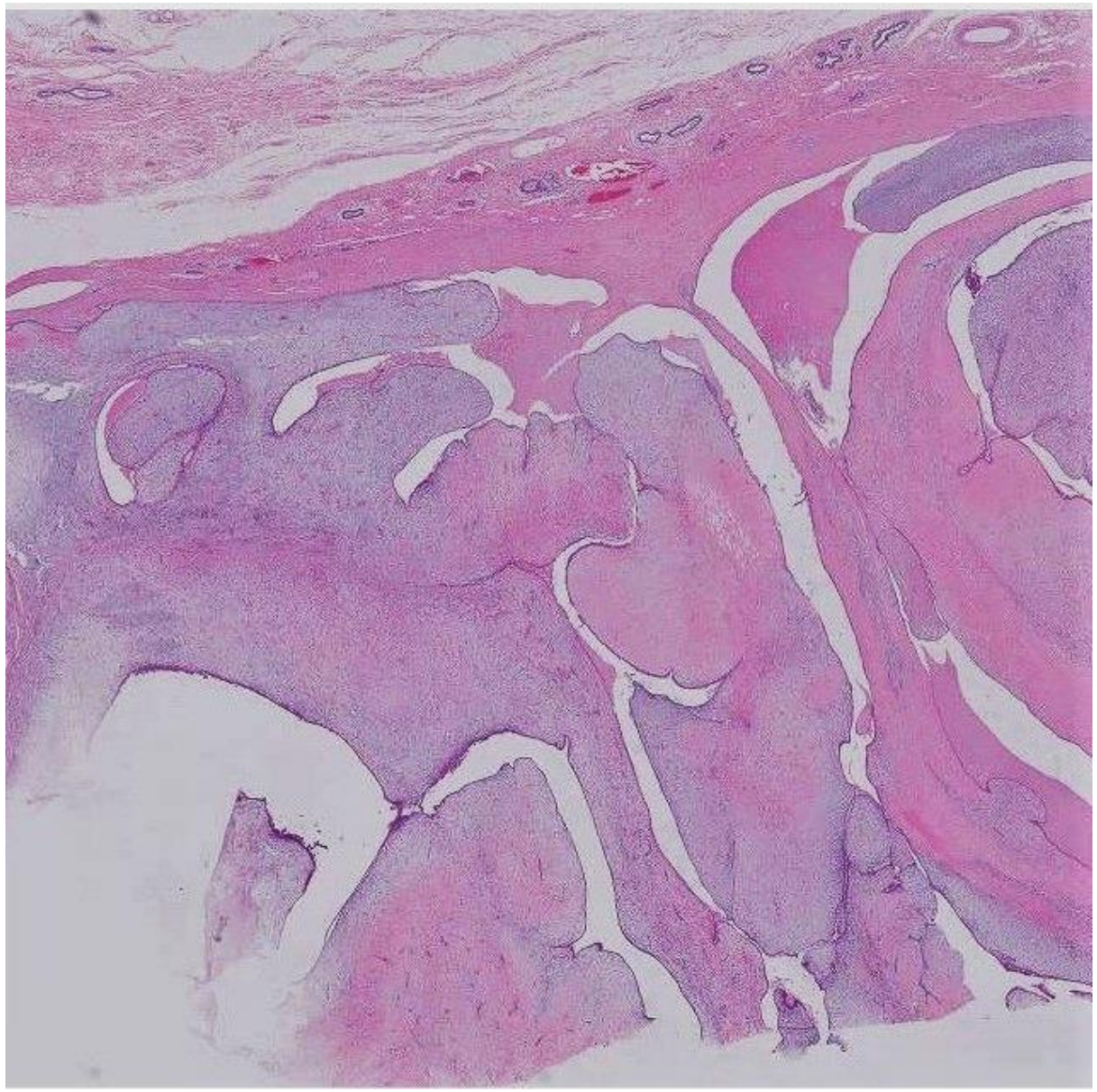
A. Core Biopsy Left Breast Mass, Lateral:
Chondromyxoid stromal lesion. (B3)
The differential diagnoses include:
1. Phyllodes tumour
2. Metaplastic carcinoma
3. Chondromyxoid mesenchymal tumour.

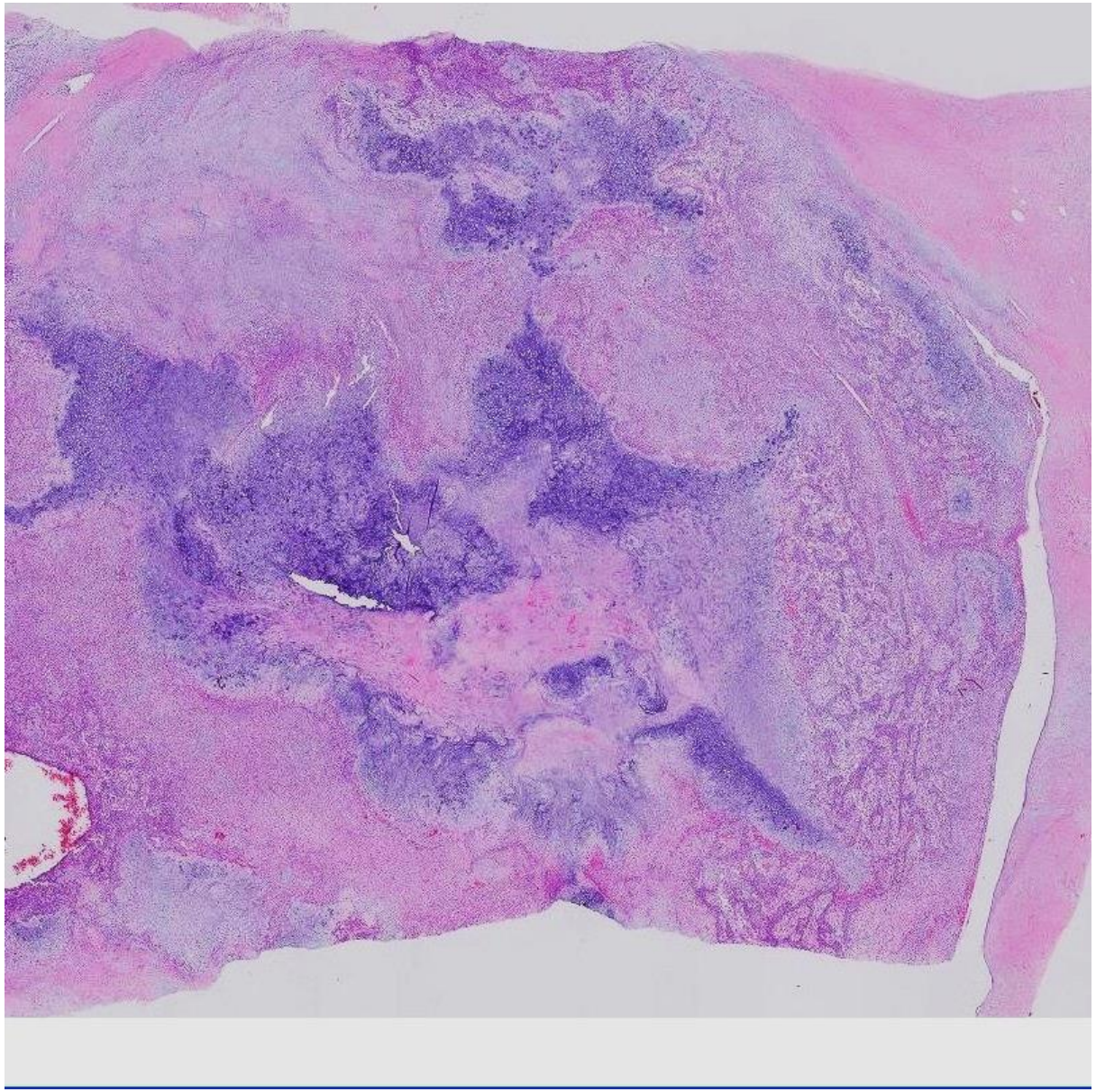

50 mm

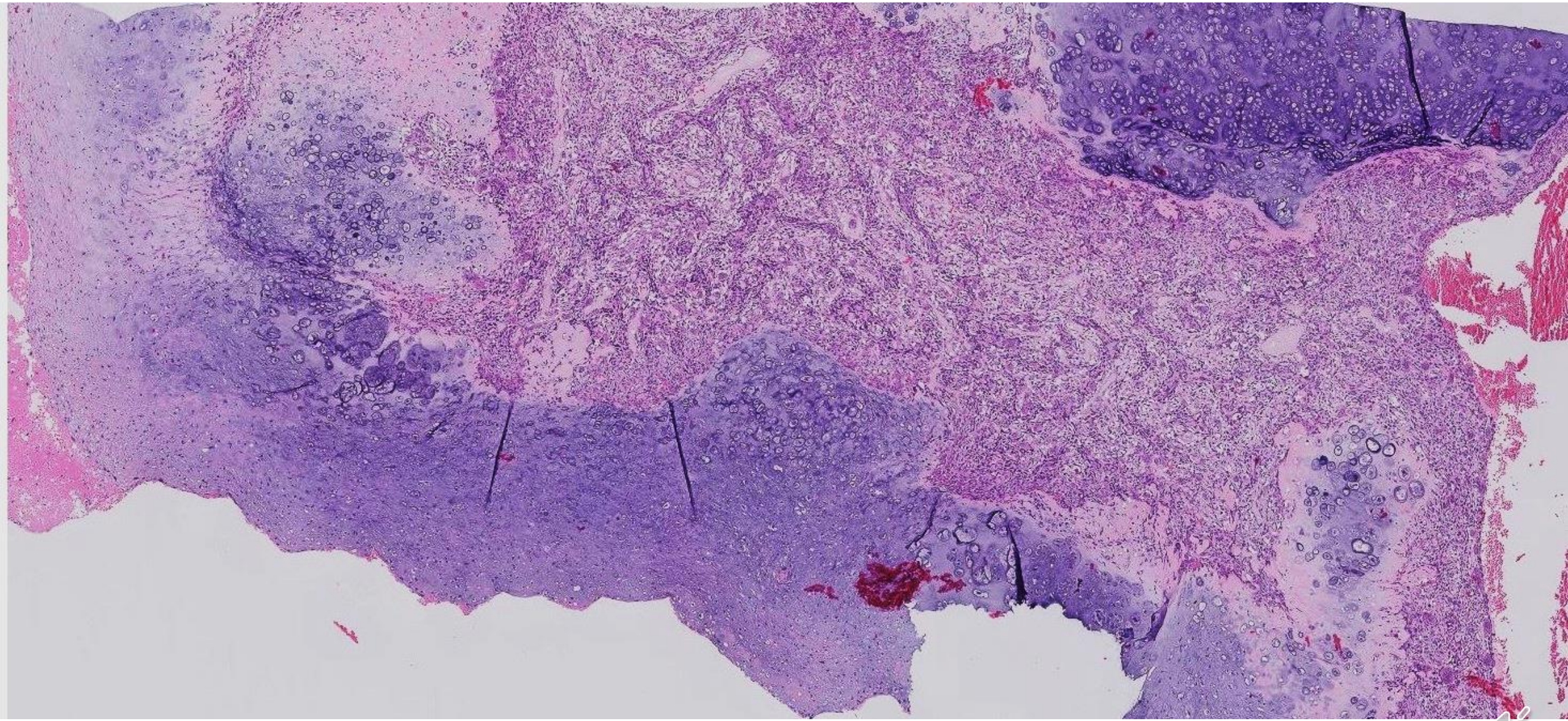


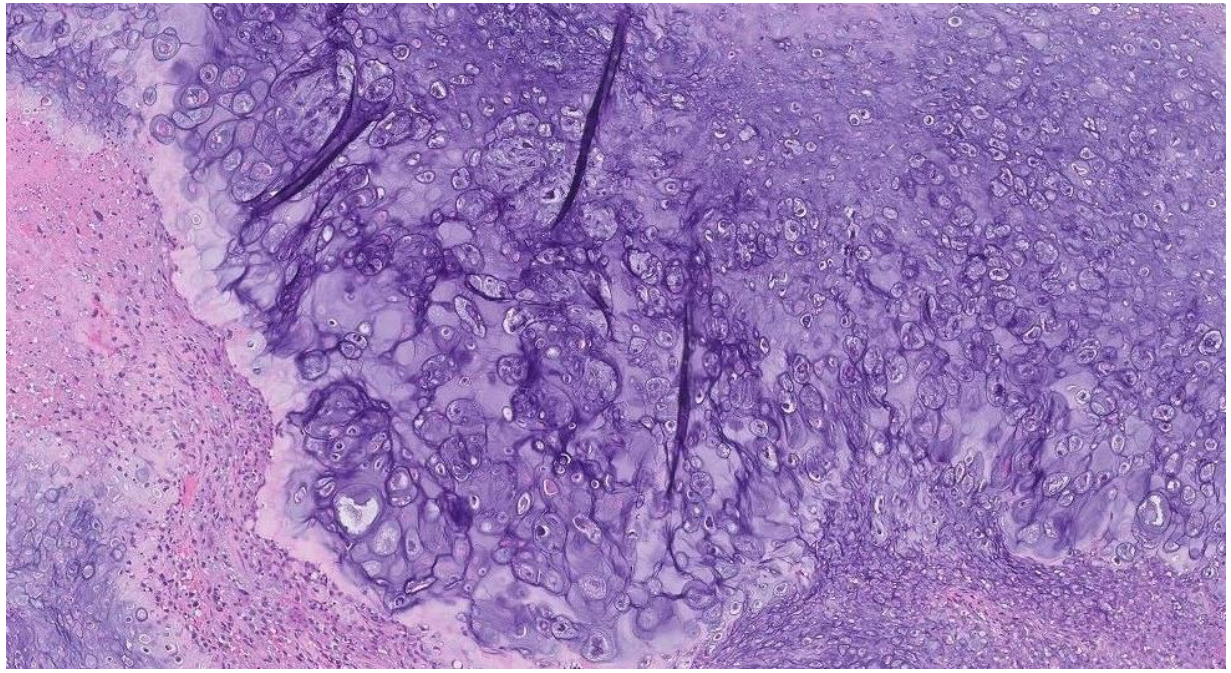


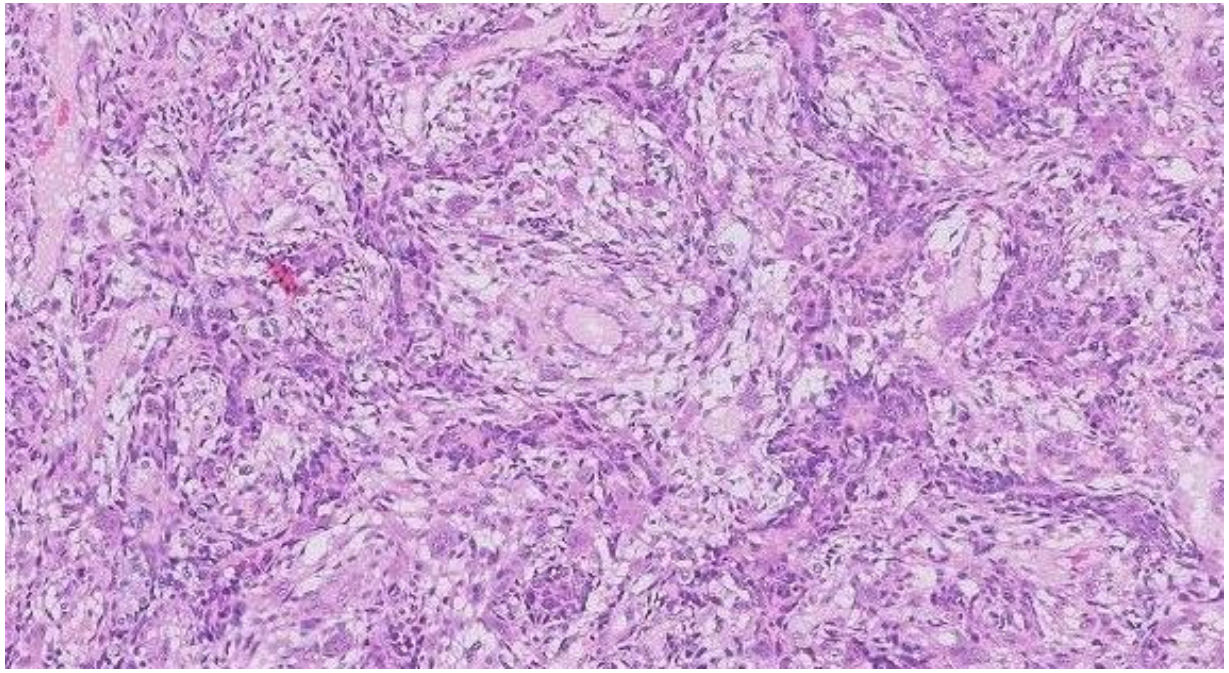


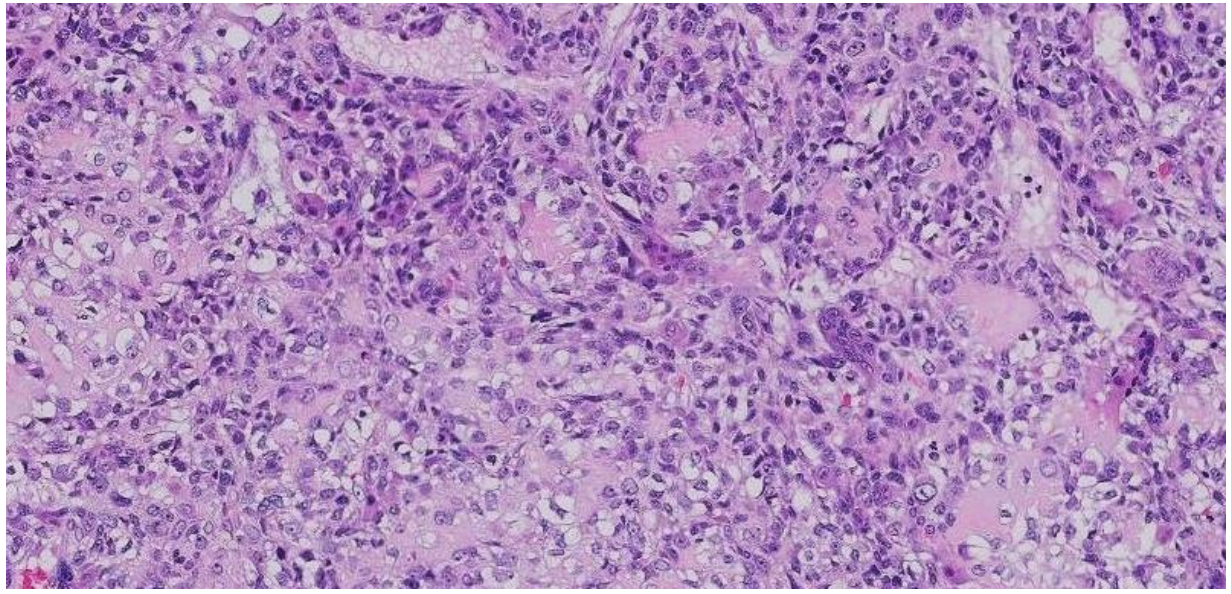


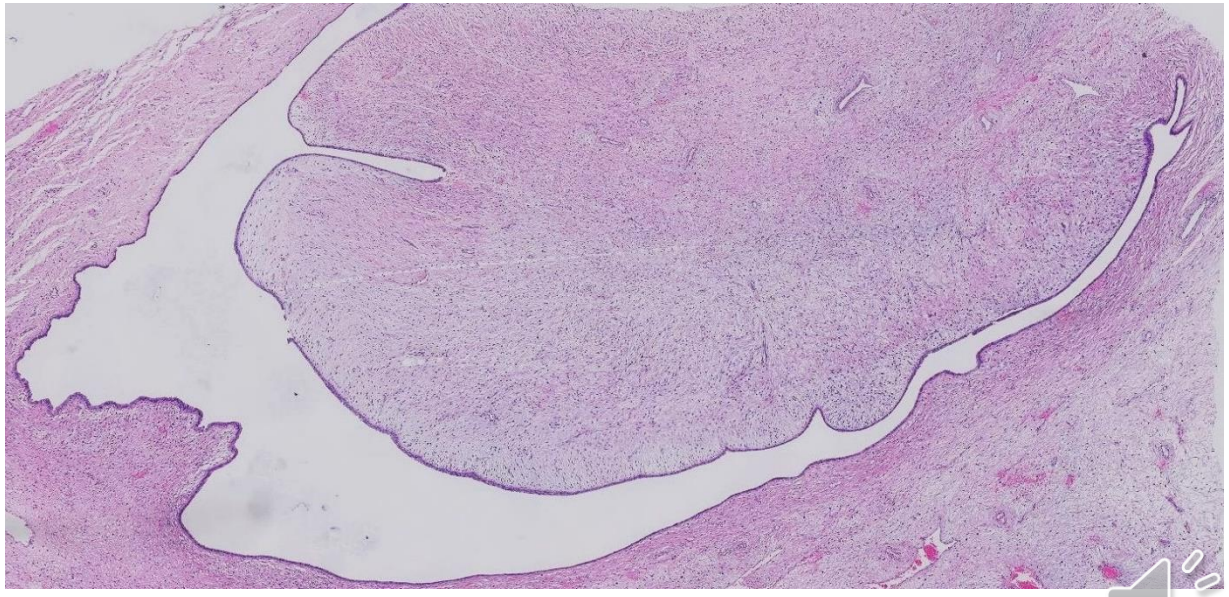


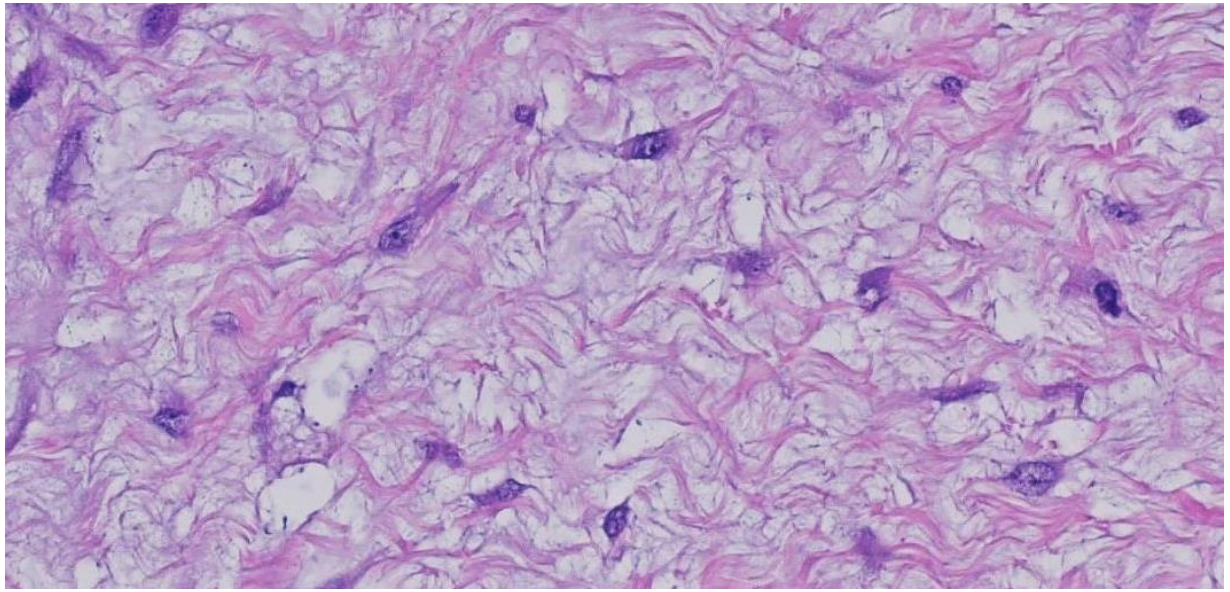


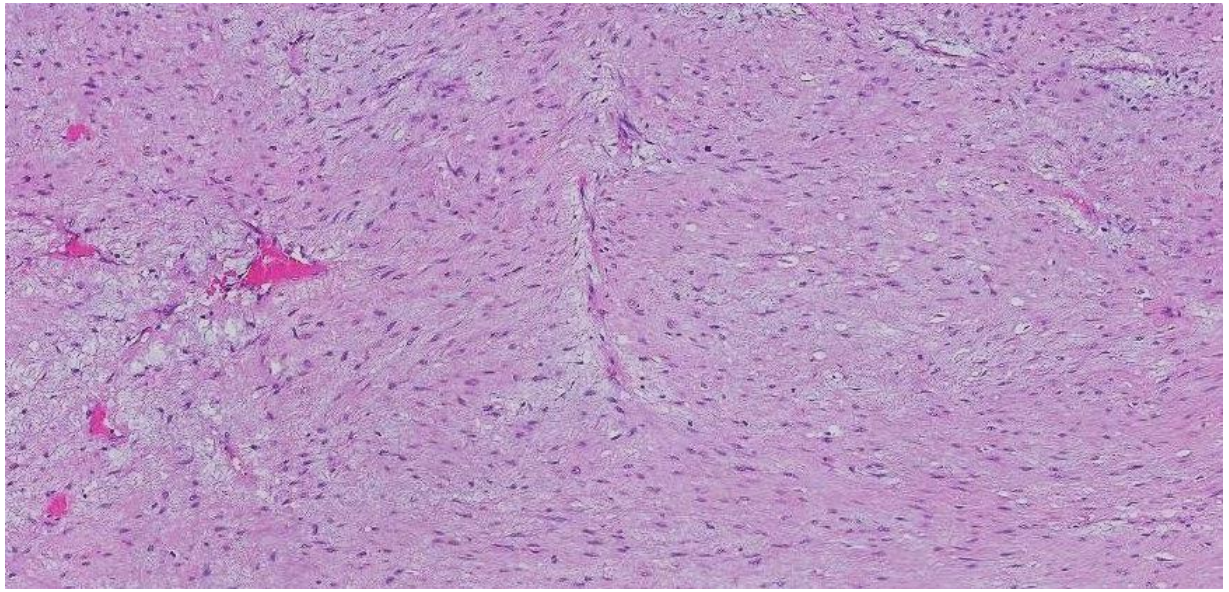


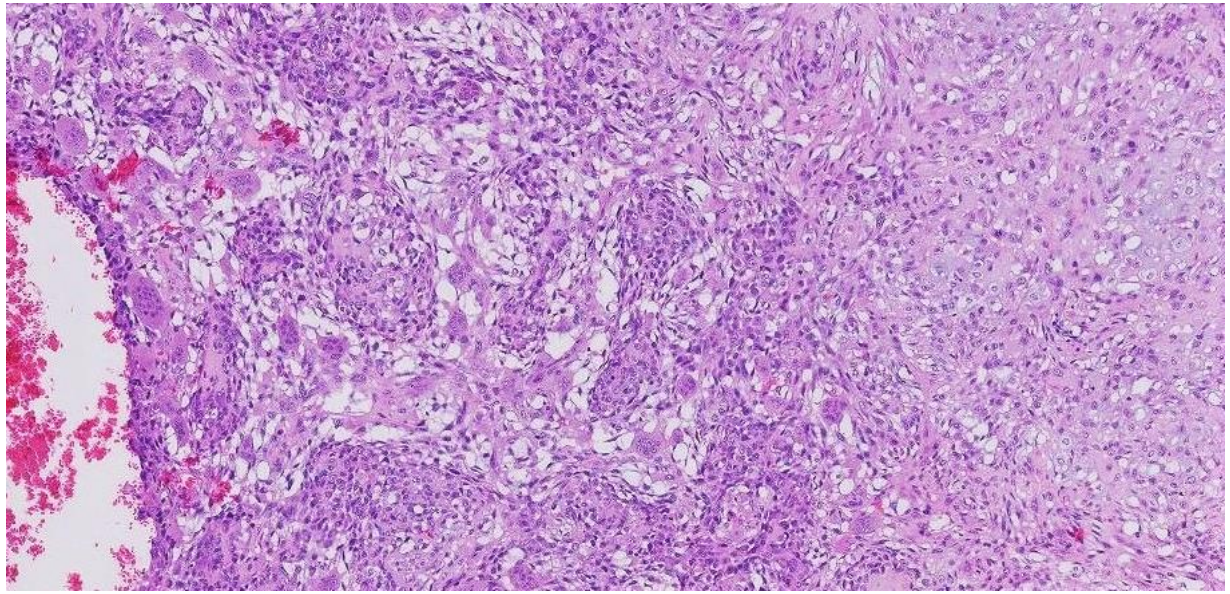


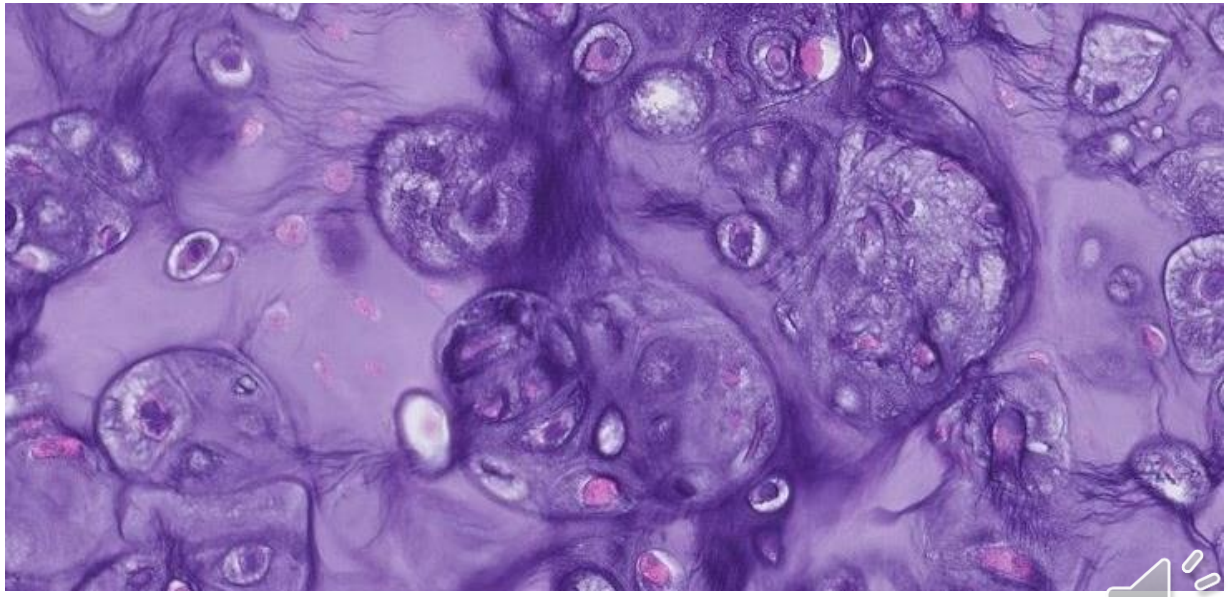


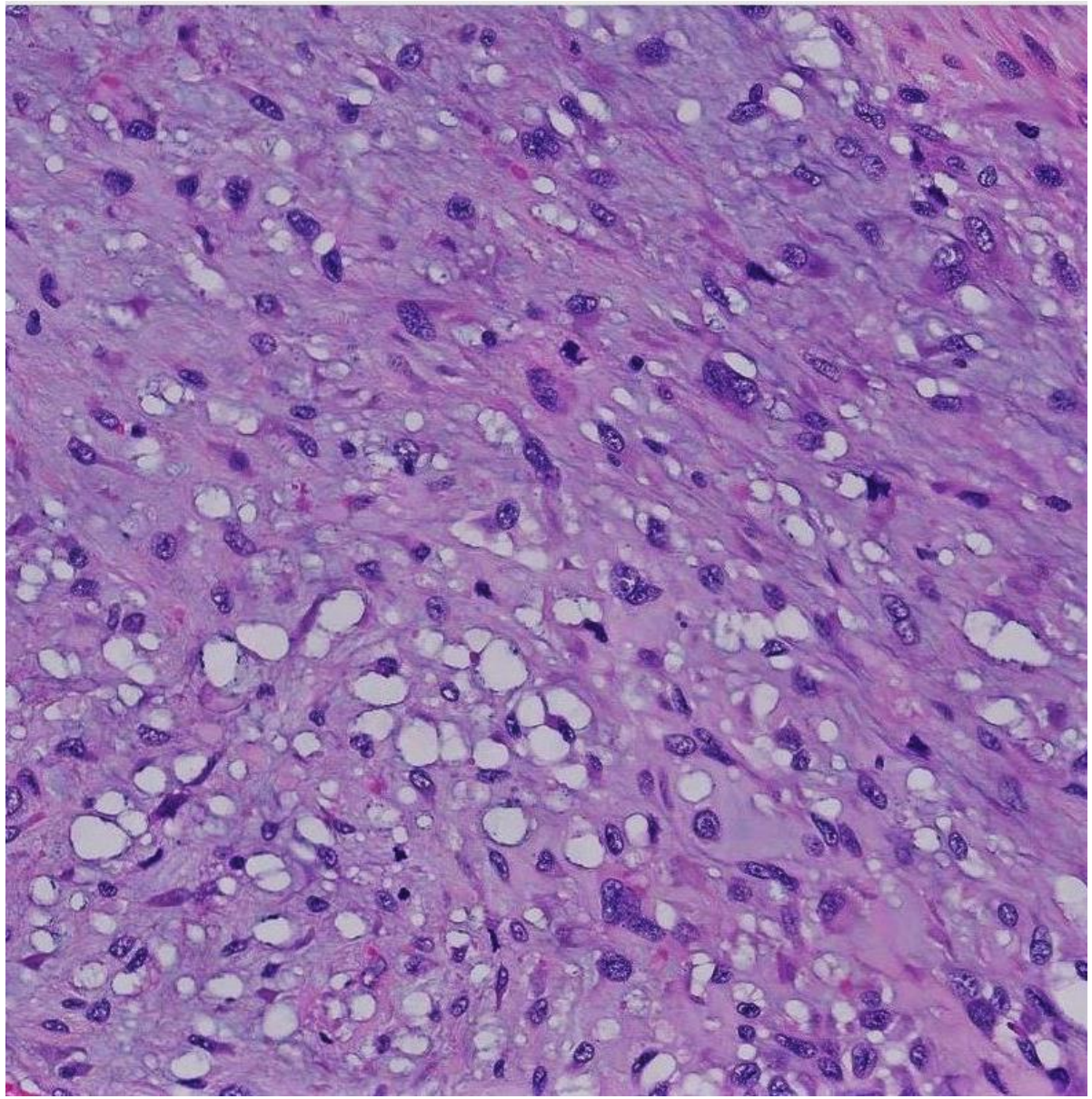


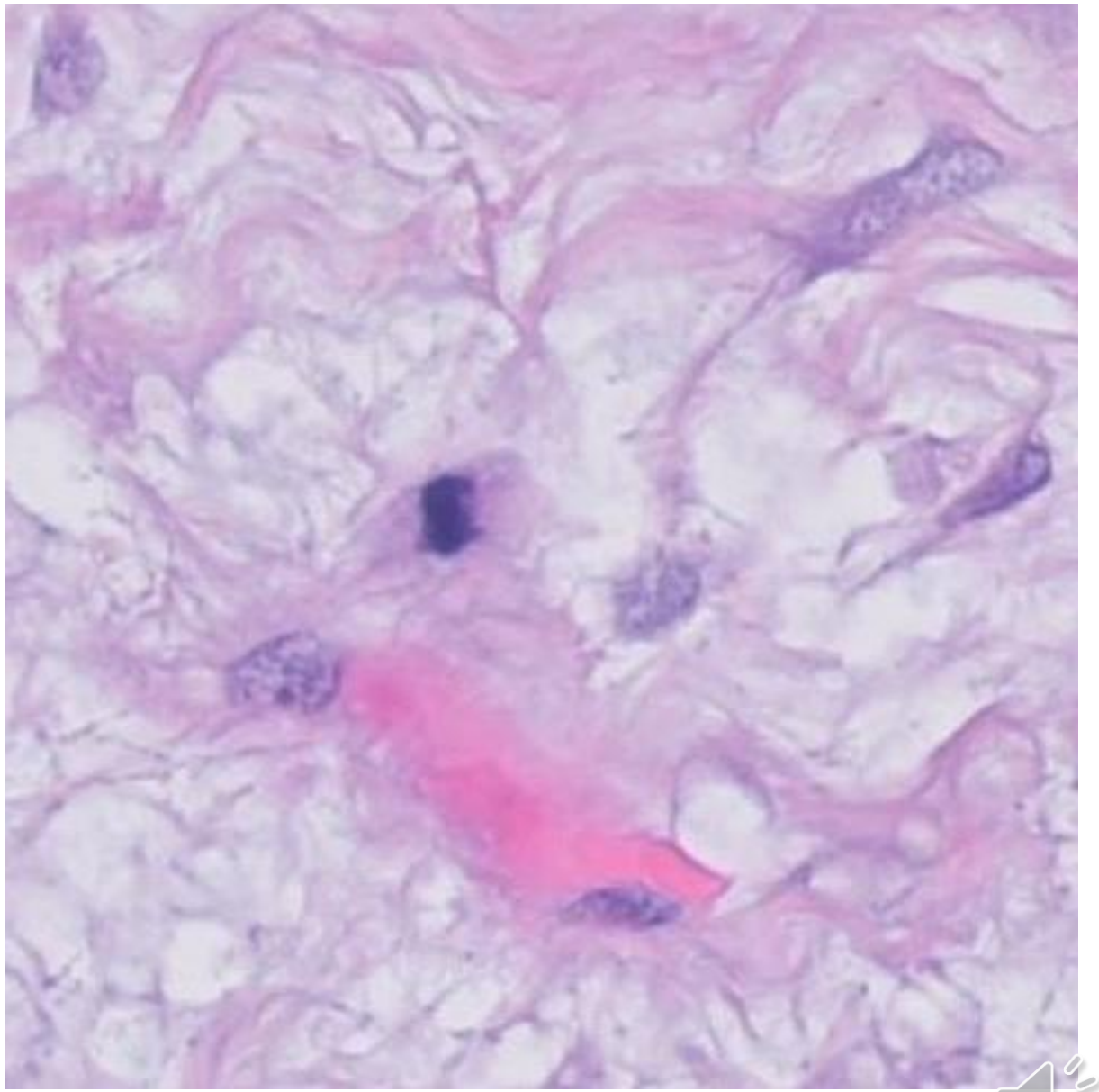












Malignant Phyllodes with Heterologous elements

Malignant Phyllodes tumours

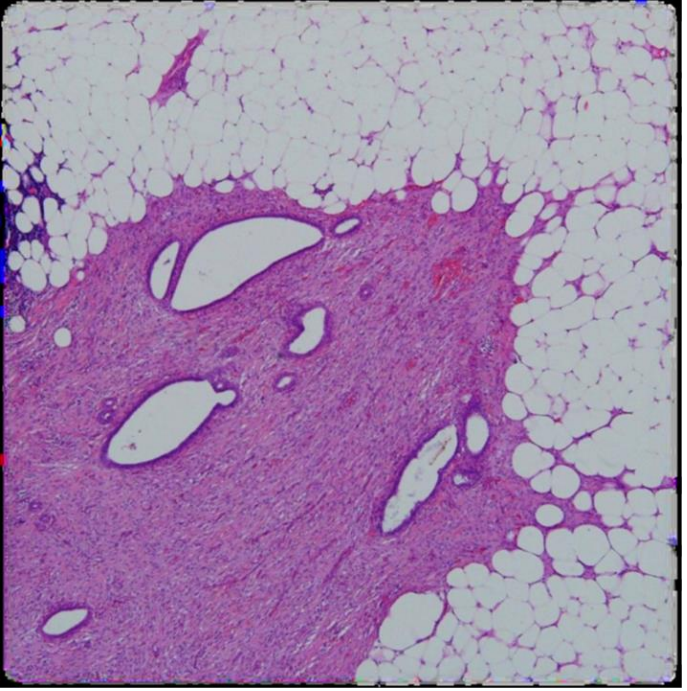
- PT's usually unilateral, firm masses.
- No specific clinical feature distinguishes between FA, benign PT and Malignant PT
- Large, may distort breast and ulcerate the skin but size does not confer higher grade.
- Reactive axillary lymphadenopathy due to tumour necrosis or infection is common but infrequent lymph node metastases.
- Malignant phyllodes develop on an average 2-5 years later than benign tumours.
- More frequent among Hispanics and Asians.
- Women with p53 germline mutation (Li- Fraumeni syndrome) increased risk of Malignant PT.

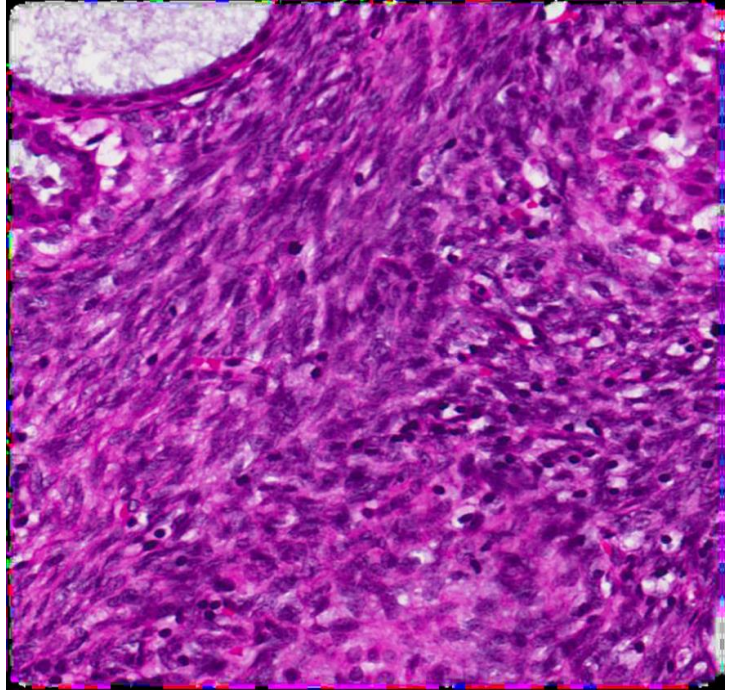
Table 3.01 Histological features of fibroadenoma and benign, borderline, and malignant phyllodes tumours

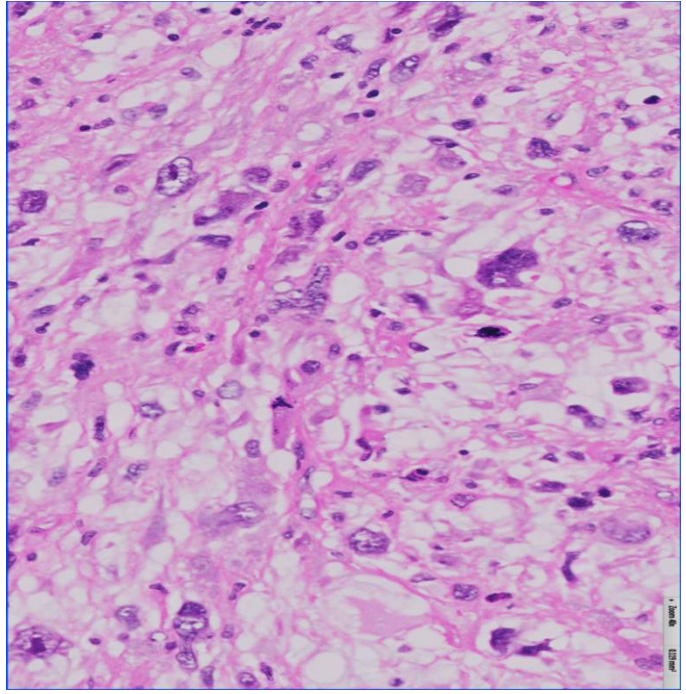
Histological feature	Fibroadenoma	Phyllodes tumours		
		Benign	Borderline	Malignant[a]
Tumour border	Well defined	Well defined	Well defined, may be focally permeative	Permeative
Stromal cellularity	Variable, scant to uncommonly cellular, usually uniform	Cellular, usually mild, may be non-uniform or diffuse	Cellular, usually moderate, may be non-uniform or diffuse	Cellular, usually marked and diffuse
Stromal atypia	None	Mild or none	Mild or moderate	Marked
Mitotic activity	Usually none, rarely low	Usually low: < 2.5 mitoses/mm^2 (< 5 per 10 HPFs)	Usually frequent: 2.5 to < 5 mitoses/mm^2 (5–9 per 10 HPFs)	Usually abundant: ≥ 5 mitoses/mm^2 (≥ 10 per 10 HPFs)
Stromal overgrowth	Absent	Absent	Absent (or very focal)	Often present
Malignant heterologous elements	Absent	Absent	Absent	May be present
Distribution relative to all breast tumours	Common	Uncommon	Rare	Rare
Relative proportion of all phyllodes tumours	n/a	60–75%	15–26%	8–20%

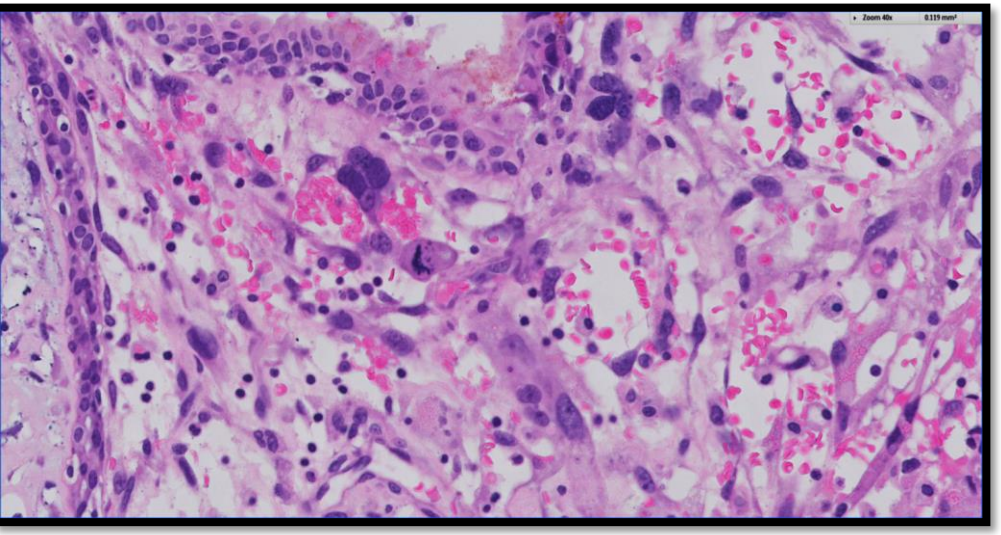
HPF, high-power field; n/a, not applicable.

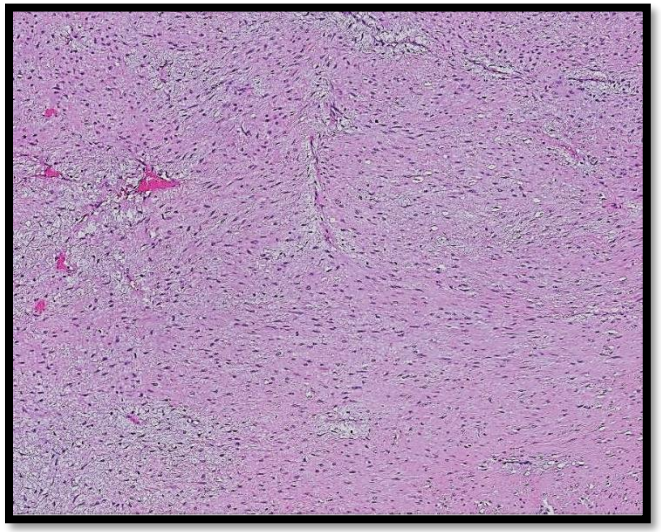
[a]Although these features are often observed in combination, they may not always be present simultaneously. The presence of a malignant heterologous element (apart from liposarcoma) qualifies designation as a malignant phyllodes tumour, without requirement for other histological criteria.

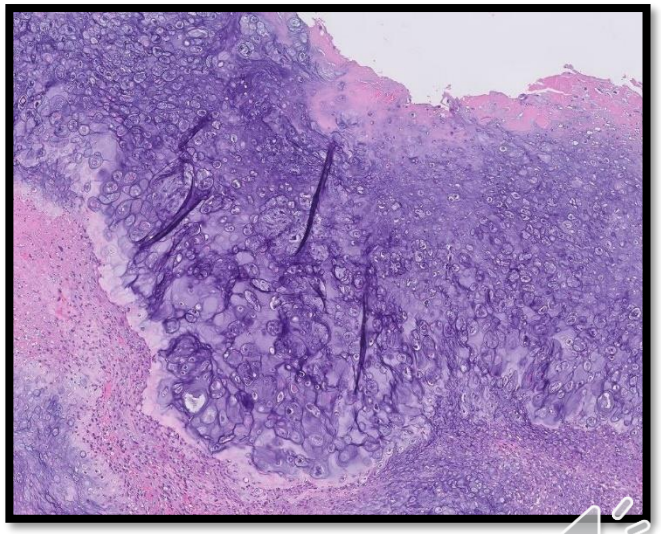








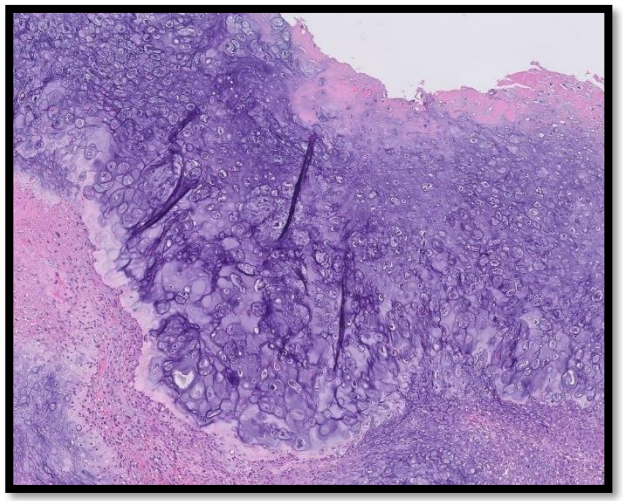


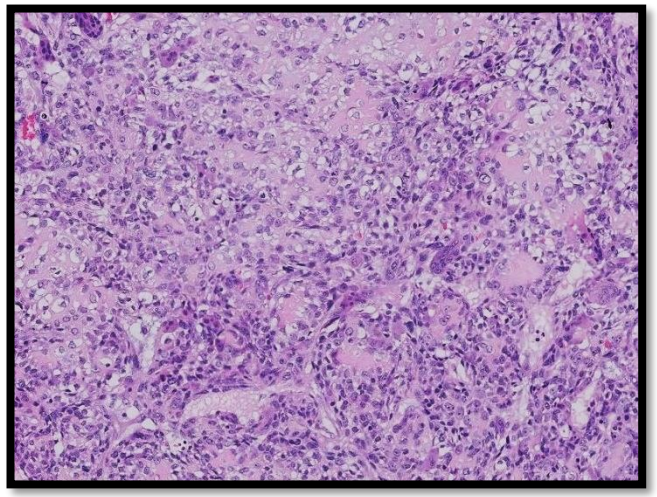


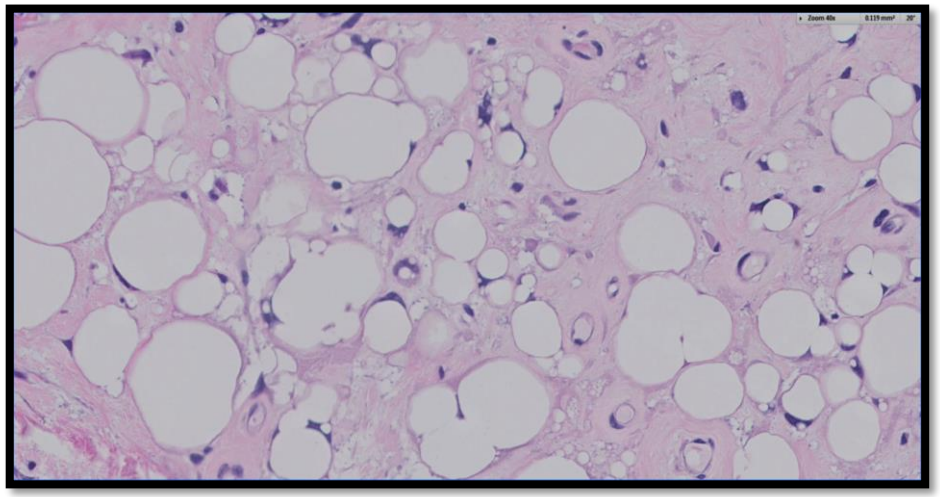
Criteria for diagnosing malignant phyllodes

Grading

- Benign: local recurrence; Borderline: local recurrence but very low risk of metastases and Malignant: highest risk of metastases.
- Tumour heterogeneity.
- Use all criteria to diagnose malignant subtype.
- Malignant Heterologous element trumps other criteria except liposarcomatous component.







Distinguishing histological features of malignant spindle cell breast lesions

Tumour	Malignant phyllodes tumour	Spindle cell metaplastic breast carcinoma	Breast sarcoma
Epithelial component	Benign; distinct leaf-like pattern	Malignant	Absent
Ductal carcinoma in situ	Usually absent	May be present	Usually absent
Squamous differentiation	Usually absent	May be present	Absent
Heterologous differentiation	May be present	May be present	Tumour-specific differentiation
Broad-spectrum cytokeratins	Usually negative (−/+) in spindle cells	Invariably positive (+/−) in spindle cells	Usually negative (−/+) in spindle cells
p63	Usually negative (−/+) in spindle cells	Usually positive (+/−) in spindle cells	Usually negative (−/+) in spindle cells

Tan BY, Tan PH et all. Phyllodes tumours of the breast: a consensus review. Histopathology. 2016 Jan;68(1):5-21.

Practical hints

- Probably the most important thing is adequate sampling to look for the phyllodial growth pattern to establish a diagnosis of Phyllodes.
- Can be challenging in Core biopsies.
- Ancillary tests like HMWCK, p40, CD34 and CD117 may help but beware of pitfalls.

Phyllodes tumours: prediction of biological behaviour

- Grade correlates with behaviour.
- •Grade assignment is imperfect:
- -Stromal hypercellularity, atypia, mitoses, overgrowth, borders.
- •Questions:
- -Does each histological parameter have equal importance?
- *-Can we determine if some parameters have a greater weightage in predicting behaviour?*
- *-Is there an objective scoring system that can define behaviour?*

Table 9 Multivariate analysis of recurrence-free survival without interaction

Factor	No. of patients	No. of events	Median survival (months)	HR (95% CI)	p Value
Mitoses per 10 hpf	552	82	NR	1.03 (1.00 to 1.06)	**0.0580**
Surgical margin					
Negative					
Positive					**<0.0001**
Atypia					
Mild					
Moderate					**0.0446**
Marked					**0.0033**
Overgrowth					
Absent					
Present					**0.0126**
Hypercellularity					
Mild	302	31	NR	Reference	
Moderate	208	41	NR	1.21 (0.71 to 2.06)	0.4786
Marked	42	10	NR	0.47 (0.17 to 1.31)	0.1496

HR (hazard ratio) refers to recurrence risk relative to reference. It should be noted that the nomogram has a score range between 0 and 100, but the total histological score has a more limited range between 5 and 13, accounting for the apparently higher HR.
hpf, high-power fields; NR, not reached.

A : Atypia
M: Mitoses
O: Overgrowth
S : Surgical margin

Courtesy Prof Tan PH

Singapore General Hospital
SingHealth

Phyllodes Tumour Recurrence Risk Assessment

Welcome to the Singapore General Hospital's Department of Pathology risk assessment tool for estimating a person's recurrence free likelihood following a histologic diagnosis of breast phyllodes tumour.

This tool is based on a study undertaken at the Singapore General Hospital (Tan PH et al. J Clin Pathol. 2012 Jan;65(1):69-76.)

This tool was designed for use by healthcare professionals. If you are not a healthcare professional, you are encouraged to discuss the results with your doctor. Please read the SGH Nomogram Terms of Use before proceeding with this tool.

Detailed information on this risk assessment tool is available [Definitions for nomogram].

Risk assessment tool

Does the tumor show stromal cytologic atypia	○ None or mild ⓘ	○ Moderate ⓘ	○ Marked ⓘ
How many mitoses are visible per 10 high powered fields? ⓘ	Mitoses per 10 hpf 0		
Is there stromal overgrowth seen? ⓘ	○ Absent	○ Present	
Are the margins histologically involved (positive)?	○ Negative ⓘ	○ Positive ⓘ	

https://mobile.sgh.com.sg/ptrra/

SGH Nomogram Terms of Use | Privacy Policy

Courtesy Prof Tan PH

Risk assessment tool

Does the tumor show stromal cytologic atypia	○ None or mild	◉ Moderate	○ Marked
How many mitoses are visible per 10 high powered fields?	Mitoses per 10 hpf 6		
Is there stromal overgrowth seen?	○ Absent	◉ Present	
Are the margins histologically involved (positive)?	○ Negative	◉ Positive	

Nomogram Score : 67

Based on the data you have provided above, the following estimates of outcomes can be inferred

At 1 year, the recurrence free probability is estimated as 82%, with a 95% confidence interval between 65% to 91%.

At 3 years, the recurrence free probability is estimated as 50%, with a 95% confidence interval between 23% to 72%.

At 5 years, the recurrence free probability is estimated as 35%, with a 95% confidence interval between 11% to 61%.

At 10 years, the recurrence free probability is estimated as 25%, with a 95% confidence interval between 5% to 52%.

These results are based on a large study undertaken at the Singapore General Hospital, and are subject to inherent limitations of a single-institution retrospective series

Courtesy Prof Tan PH

Utility of the Singapore nomogram for predicting recurrence-free survival in Japanese women with breast phyllodes tumours

Rieko Nishimura,[1] Puay Hoon Tan,[2] Aye Aye Thike,[2] Min-Han Tan,[3] Naruto Taira,[4] Hui Hua Li,[5] Shozo Ohsumi[6]

Concordance index 0.904

J Clin Pathol. 2014 Aug;67(8):748-50.

Validation of the Singapore nomogram for outcome prediction in breast phyllodes tumours: an Australian cohort

Concordance index 0.933

Tze Wei Chng,[1] Jonathan Y H Lee,[2] C Soon Lee,[3] HuiHua Li,[4] Min-Han Tan,[5] Puay Hoon Tan[6]

J Clin Pathol. 2016 Dec;69(12):1124-1126.

Validation of the Singapore nomogram for outcome prediction in breast phyllodes tumours in a large patient cohort

Concordance index 0.863

259

Tze Wei Chng,[1] Mihir Gudi,[2] Swee Ho Lim,[3] HuiHua Li,[4] Puay Hoon Tan[5]

J Clin Pathol 2018;**71**:125–128.

Courtesy Prof Tan PH

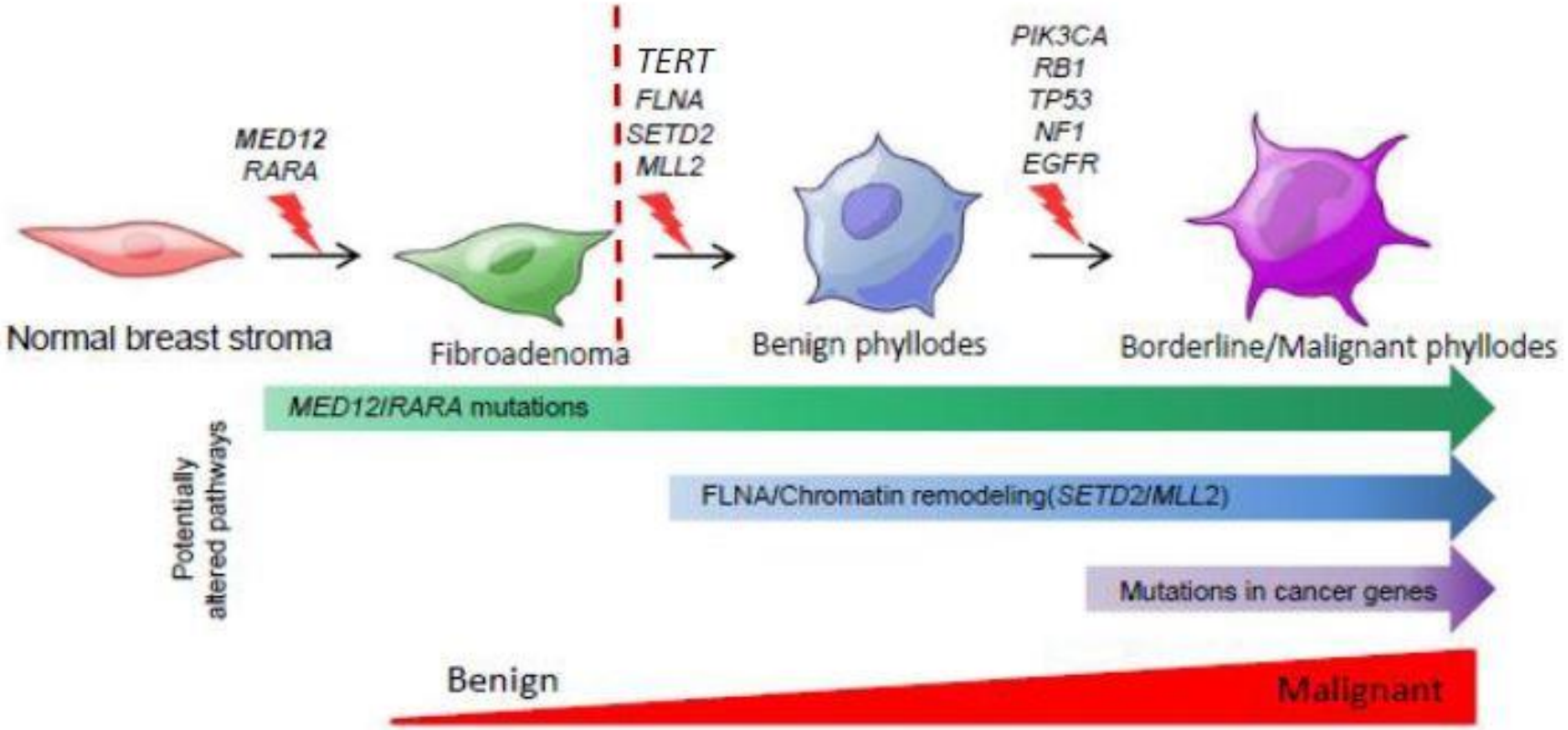
Recurrence rates and metastatic potential of Malignant Phyllodes Tumours

- Highest rates of recurrence in malignant phyllodes (23-30%).
- Metastases invariably indicate a poor prognosis. Large tumour size and malignant heterologous elements are associated with metastases.
- Sites of metastases lung, heart and skeleton and invariably involves the malignant stromal component.
- Rate of metastases 22%.

Treatment Malignant phyllodes

- Surgical excision with clear margins.
- 10 mm but no consensus.
- Axillary lymph node dissection not recommended.
- Adjuvant Radiotherapy for better local control rates.
- Adjuvant Chemotherapy merits considered on a case to case basis.

A proposed model of the genomic progression of breast fibroepithelial tumours



Tan J et al. Nat Genet. 2015 Nov;47(11):1341-5.

Multiple papers on the genomics of fibroepithelial tumours have been published

Courtesy Prof Tan PH

ARTICLE OPEN

Phyllodes tumors with and without fibroadenoma-like areas display distinct genomic features and may evolve through distinct pathways

Fresia Pareja[1], Felipe C. Geyer[1], Rahul Kumar[1], Pier Selenica[1], Salvatore Piscuoglio[1,2], Charlotte K. Y. Ng[1,2,3], Kathleen A. Burke[1], Marcia Edelweiss[1], Melissa P. Murray[1], Edi Brogi[1], Britta Weigelt[1] and Jorge S. Reis-Filho[1]

npj Breast Cancer (2017)3:40

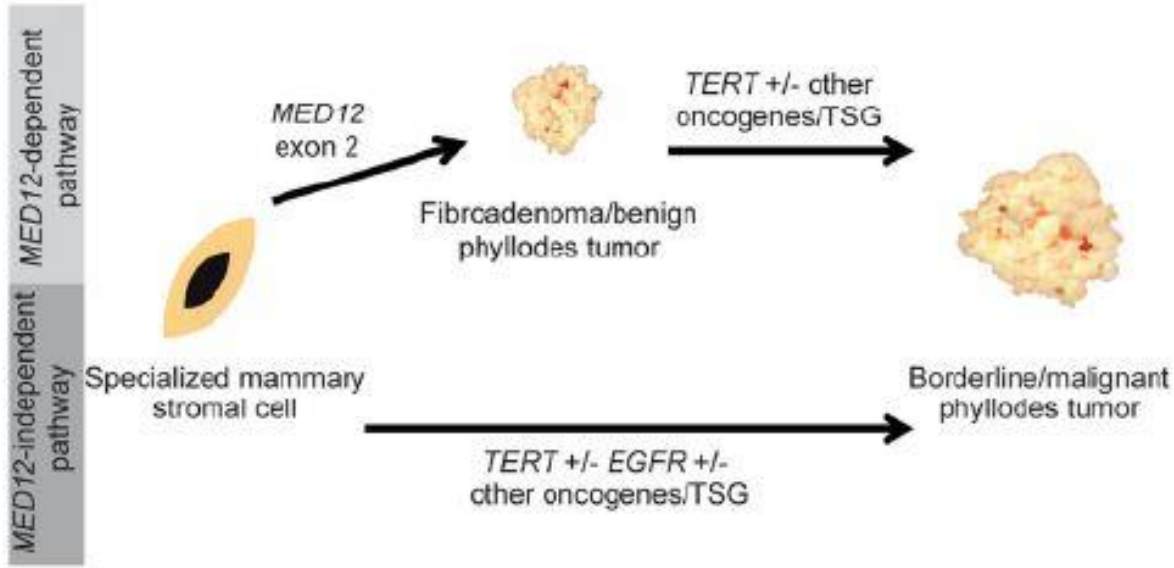


Fig. 4 Proposed model of the evolutionary origin of borderline and malignant phyllodes tumors. Phyllodes tumors might follow two different evolutionary pathways. (i) In the *MED12*-mutant pathway, *MED12* exon 2 mutations are posited to lead to the development of a benign fibroepithelial lesion, which upon the occurrence of additional genetic alterations affecting *TERT* and/ or other cancer genes may progress to a borderline or malignant phyllodes tumor. (ii) In the *MED12*-independent pathway, borderline or malignant phyllodes tumors might arise *de novo*, through the acquisition of genetic alterations targeting cancer genes, such as *TERT* and/ or *EGFR*. TSG tumor suppresor genes

Courtesy Prof Tan PH

What's the clinical relevance?

- **Genomics based classification of breast fibroepithelial lesions, enhancing diagnostic accuracy ~**
  - **Differentiating FA from PT *(J Pathol 2016;238:508-518)***
  - **Differentiating PT from other spindle cell tumours *(APMIS 2016;124:356-364)***
  - **Differentiating malignant PT from metaplastic carcinoma *(Pathology 2017;49:786-789)***
- Discovery of candidate therapeutic targets in borderline/malignant PT ~
  - PIK3CA activating mutations
  - EGFR amplifications
- *MED12 mutations correlated with improved disease free survival (J Clin Pathol 2015;68:685-91; Genes,Chromosomes&Cancer 2016;55:495–504)*
- *MED12* and *RARA* mutations linked to hormone receptor signaling

Case Reports > Pathology. 2019 Aug;51(5):531-534. doi: 10.1016/j.pathol.2019.04.005. Epub 2019 Jul 2.

The utility of a targeted gene mutation panel in refining the diagnosis of breast phyllodes tumours

Valerie Cui Yun Koh [1], Cedric Chuan Young Ng [2], Boon Huat Bay [3], Bin Tean Teh [4], Puay Hoon Tan [5]

BMC Med Genomics. 2019; 12: 142.
Published online 2019 Oct 23. doi: 10.1186/s12920-019-0588-2
PMCID: PMC6813086
PMID: 31647027

A novel genomic panel as an adjunctive diagnostic tool for the characterization and profiling of breast Fibroepithelial lesions

Yirong Sim,[✉1,2] Gwendolene Xin Pei Ng,[1,3,4] Cedric Chuan Young Ng,[3,4] Vikneswari Rajasegaran,[3,4] Suet Far Wong,[3,4] Wei Liu,[3,4] Peiyong Guan,[5] Sanjanaa Nagarajan,[3,4] Wai Yee Ng,[1] Aye Aye Thike,[7] Jeffrey Chun Tatt Lim,[7] Nur Diyana Binte Md Nasir,[7] Veronique Kiak Mien Tan,[1,2] Preetha Madhukumar,[1,2] Wei Sean Yong,[1,2] Chow Yin Wong,[2] Benita Kiat Tee Tan,[1,2] Kong Wee Ong,[1,2] Bin Tean Teh,[4,6] and Puay Hoon Tan[7,8]

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- Tan PH, Ellis I, Allison K, et al. The 2019 World Health Organization classification of tumors of the breast. Histopathology. 2020 Aug;77(2):181-185