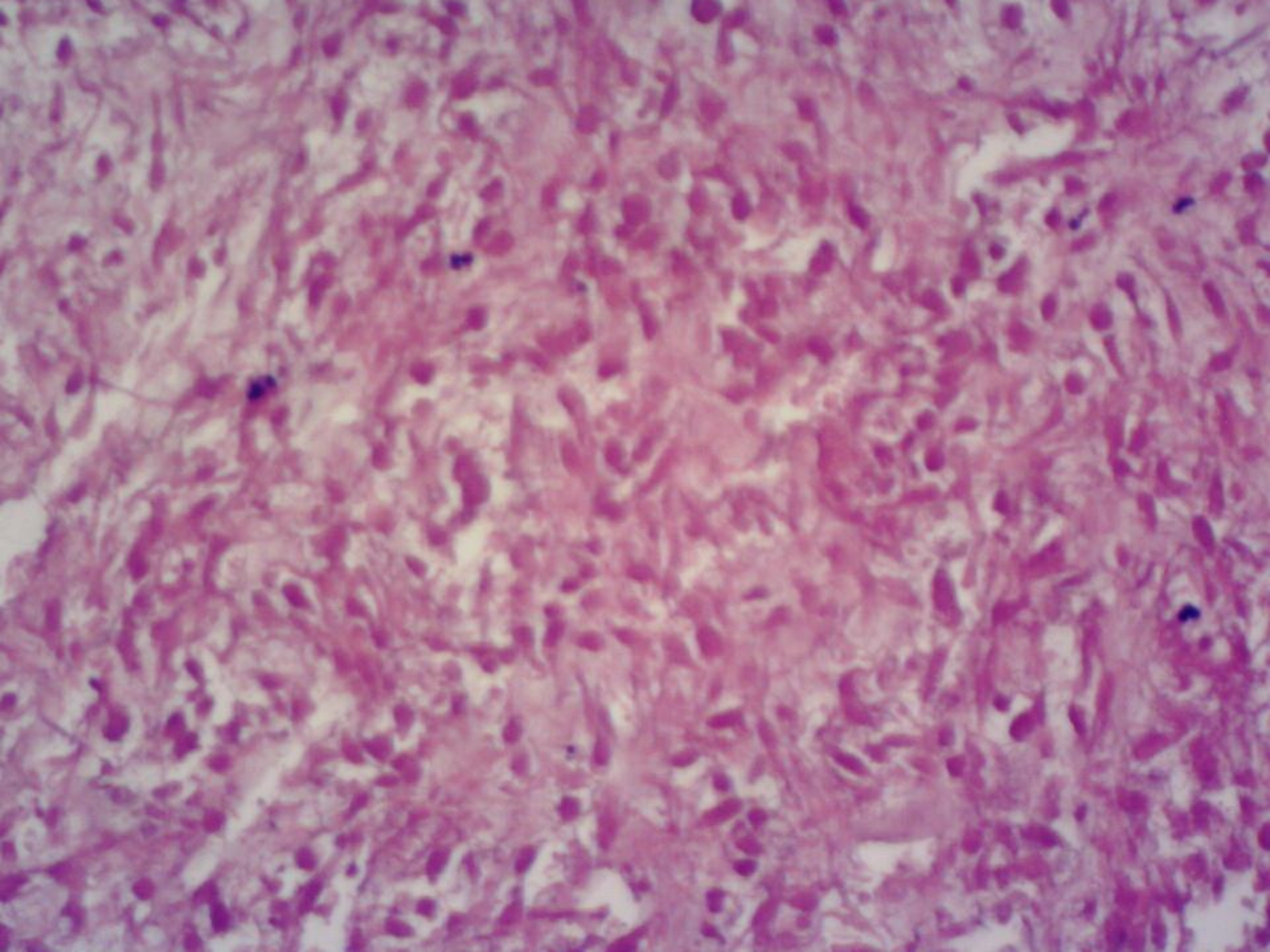
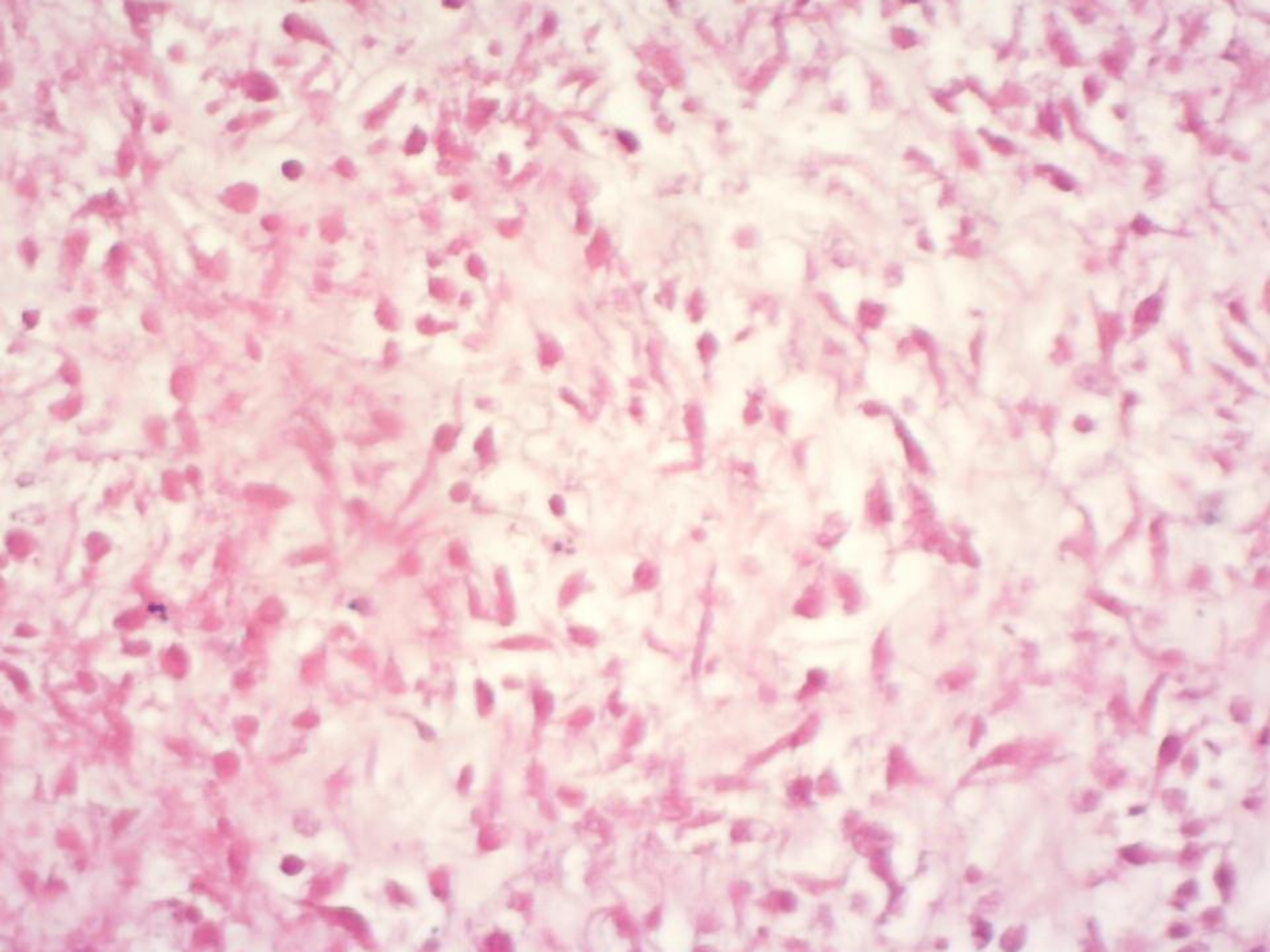
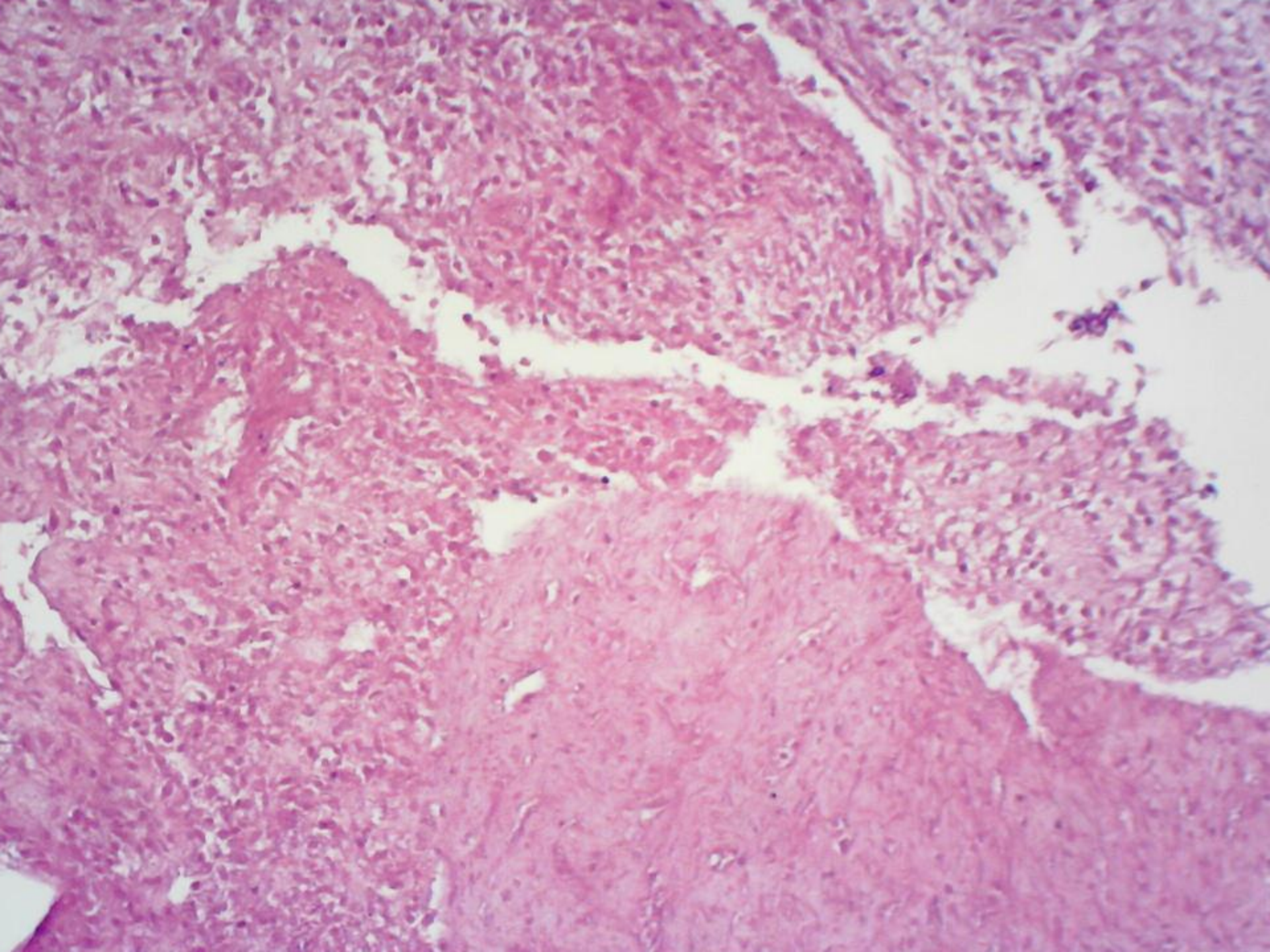






PATHOLOGICAL DIAGNOSIS:
Soft tissue, chest, left, fine needle biopsy, see descriptions.

GROSS:
Received in formalin consists of 2 cores of white soft tissue,measuring up to 2.6x0.2x0.1 cm in size fixed in formalin.
Entire specimen is embedded in one block.

MICRO:
Sections show a hypocellular and partially infarcted spindle-shaped cell tumor with relatively bland nuclei. The spindle cells are CK(-),Bcl-2(-),calretinin(-),S100(-),CD10(+),vimentin(+), Cd117(-) and CD34(-).As characterised by epithelial lined cystic spaces into which projects a hypercellular stroma, the presence of both epithelial and stromal elements are necessary to confirm the diagnosis of phyllodies tumor.Moreover,the stroma spindle cells are the neoplastic component and their anaplastic features determine the pathological behaviour of potential metastasis. Due to lacking of epithelial component and abscence of anaplastic features of the spindle cells,it is hard to labelled the biopsy as metastatic phyllodes tumor currently. However, metastatic phyllodes tumor is still compatilbe and more viable tissue is needed to confirmed the diagnosis.

KOO FOUNDATION SUN YAT-SEN CANCER CENTER
病理諮詢報告
SURGICAL PATHOLOGY CONSULTATION REPORT

姓　　名：黃瑞媛
出生日期：
身分證號：
病歷號碼：

檢體編號：R15-01223
申請科別：一般內科
申請醫師：

收件日期單號：R201508200007
申請日期：2015/08/18
採樣日期：2015/08/20

門/住床號：門診

SPECIMEN DESCRIPTION: Received are 8 H&E slides, labeled S2014-044274, with an accompanying pathology report dated 2014/07/04 from 林口長庚醫院. Additionnl 3 H&E and 7 IHC slides are received, labeled 104-10167 and 10338, with accompanying pathology reports dated 2015/08/07 and 08/11 from 振興醫院.

PATHOLOGIC DIAGNOSIS:
S2014-044274
Left breast, partial mastectomy: MALIGNANT PHYLLODES TUMOR (5.3x4.9x2.8 cm), with negative resection margins.

104-10167
Soft tissue, labeled as left chest, fine needle biopsy: NECROTIC SPINDLE CELL NEOPLASM. (see Micro)

104-10338
Left breast, 2 o'clock, sono-guided fine needle biopsy: benign breast tissue.

NOTE: The case has been presented in the Departmental Consensus Meeting on 2015-08-20 and 08-21. All the attending pathologists have agreed with the diagnosis.

MICROSCOPIC COMMENTS:
S2014-044274
The sections show a relative well-defined breast tumor composed of proliferating leaf-like ductal epithelium surrounded by cellular stroma with mild to moderate nuclear pleomorphism. There is no infiltrative growth noted. However, the tumor shows two unusual features suggesting malignancy including stromal overgrowth (>2x field devoid of glandular cells) and brisk mitotic figures (10/10 HPF, by olympus BX50). According to the reference, the tumor may be classified as a malignant tumor.

104-10167
The core biopsy shows a necrotic spindle cell tumor with the ghost shadow showing similar histology as to the stromal component of the phyllodes tumor. A recurrent or metastatic malignant phyllodes tumor should be considered. Please correlate with clinical findings and repeating biopsy is clinically indicated.

104-10338
The core biopsy shows benign breast tissue only.

Classification of Biphasic Lesions of the Breast

Fibroadenoma
Juvenile Fibroadenoma
Phyllodes Tumor
Adenomyoepithelioma
Gynecomastia
Hamartoma
Metaplastic Carcinoma
Pleomorphic Adenoma
Pubertal Macromastia

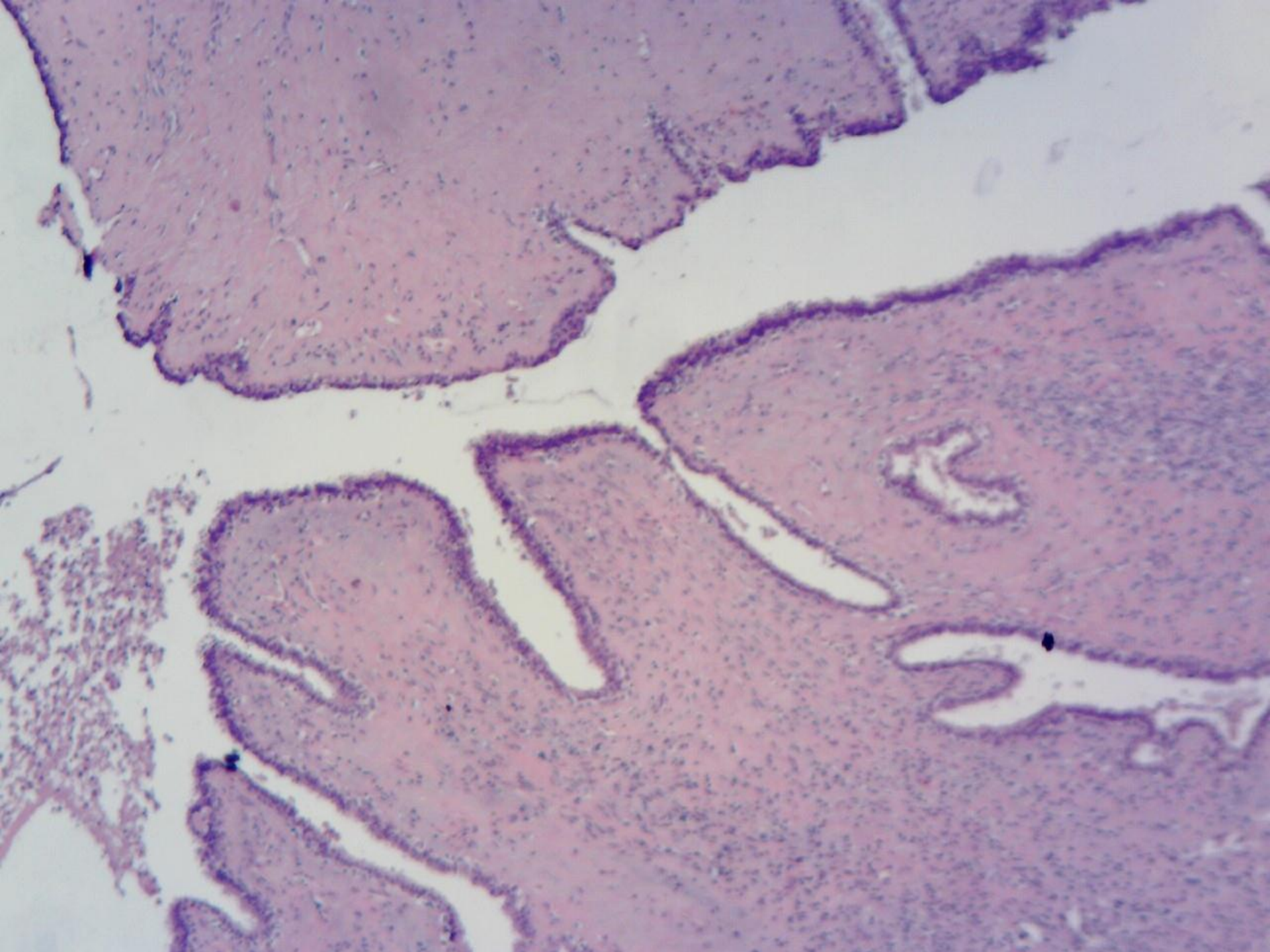
Phyllodes Tumor of the Breast

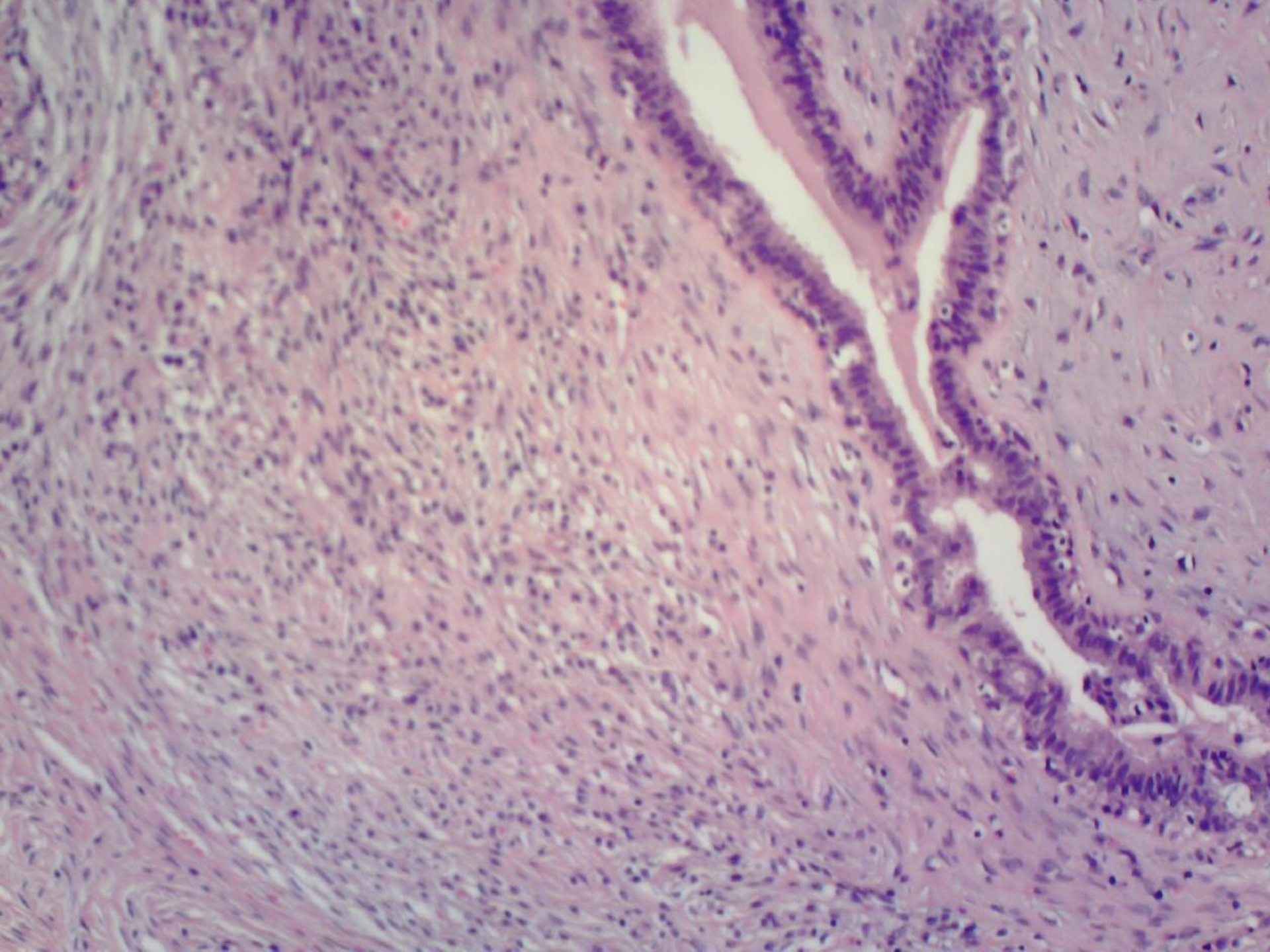
Phyllodes tumors are a fibroepithelial tumor composed of an epithelial and a **cellular stromal component** with **broad "leaf-like" papillae inserted into cleft-like spaces**

They may be considered benign, borderline, or malignant

depending on histologic features including stromal cellularity, infiltration at the tumor's edge, and mitotic activity.

All forms of phyllodes tumors are regarded as having malignant potential.





Phyllodes Tumor of the Breast

Clinical basics

Uncommon, generally well circumscribed lumps
Account for 2.5% of all fibroepithelial lesions of the breast
Patient usually older than 40 years
In Asian countries occur at an earlier age (average 25-30 yrs)
Lesion usually larger than 4 cm
May be a history of recent growth
Principal clinical concern is the risk of local recurrence after excision, also....
....very rarely, malignant transformation with metastatic potential
Malignant lesions more common in Latino whites, particularly those born in Central & South America

http://www.breastpathology.info/phyllodes.html

Phyllodes Tumor of the Breast

Diagnostic Criteria:

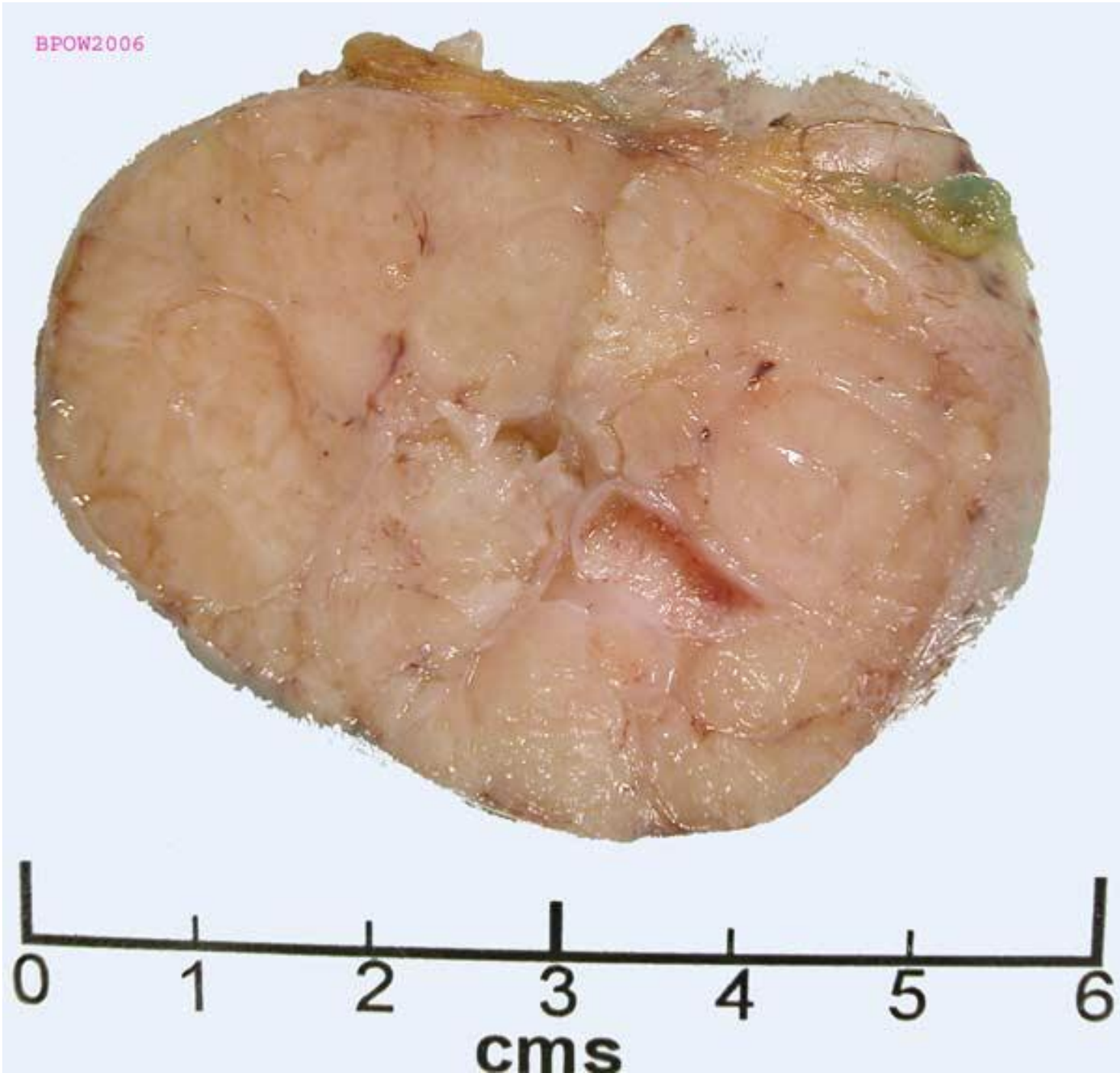
Usually large and grossly circumscribed

Fibroepithelial proliferation with broad "leaf-like" papillae inserting into slit-lilke or cleft-like spaces

Exaggerated intracanalicular pattern

Cellular stroma

Periductal stromal condensation may be seen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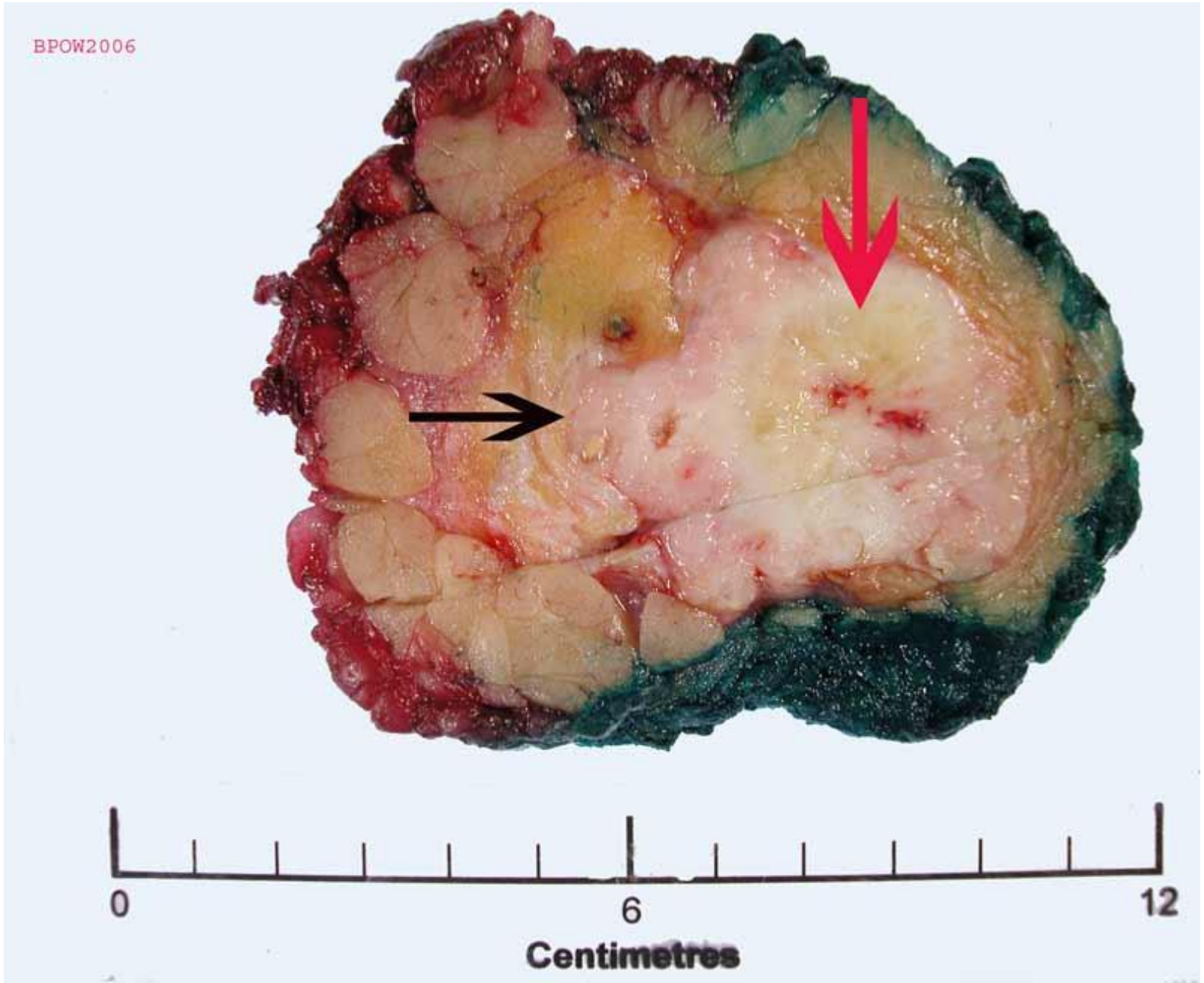
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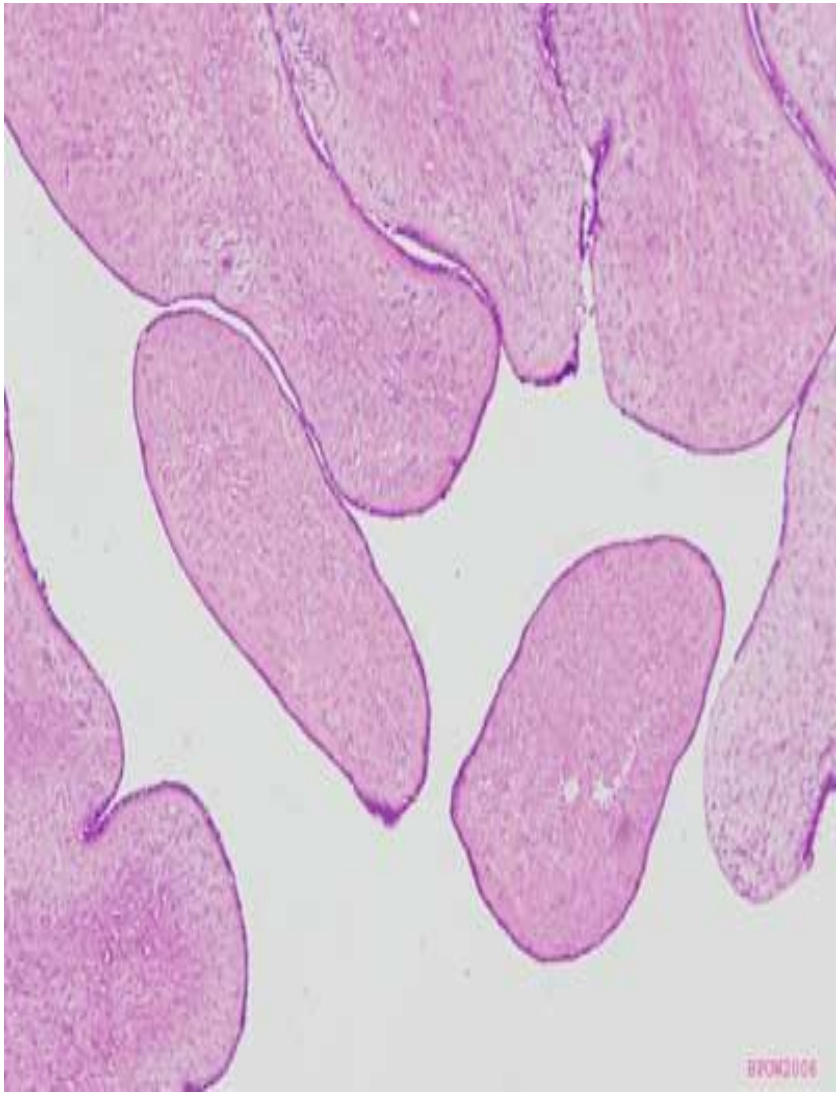
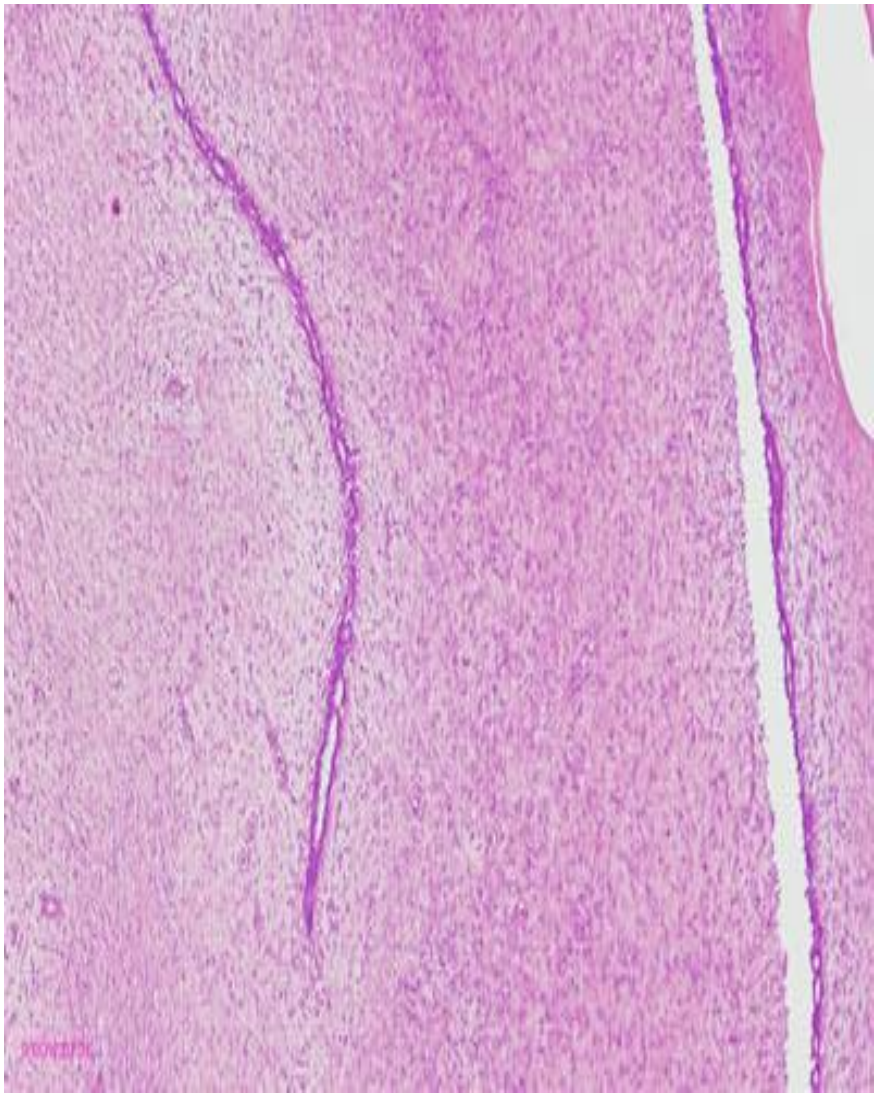
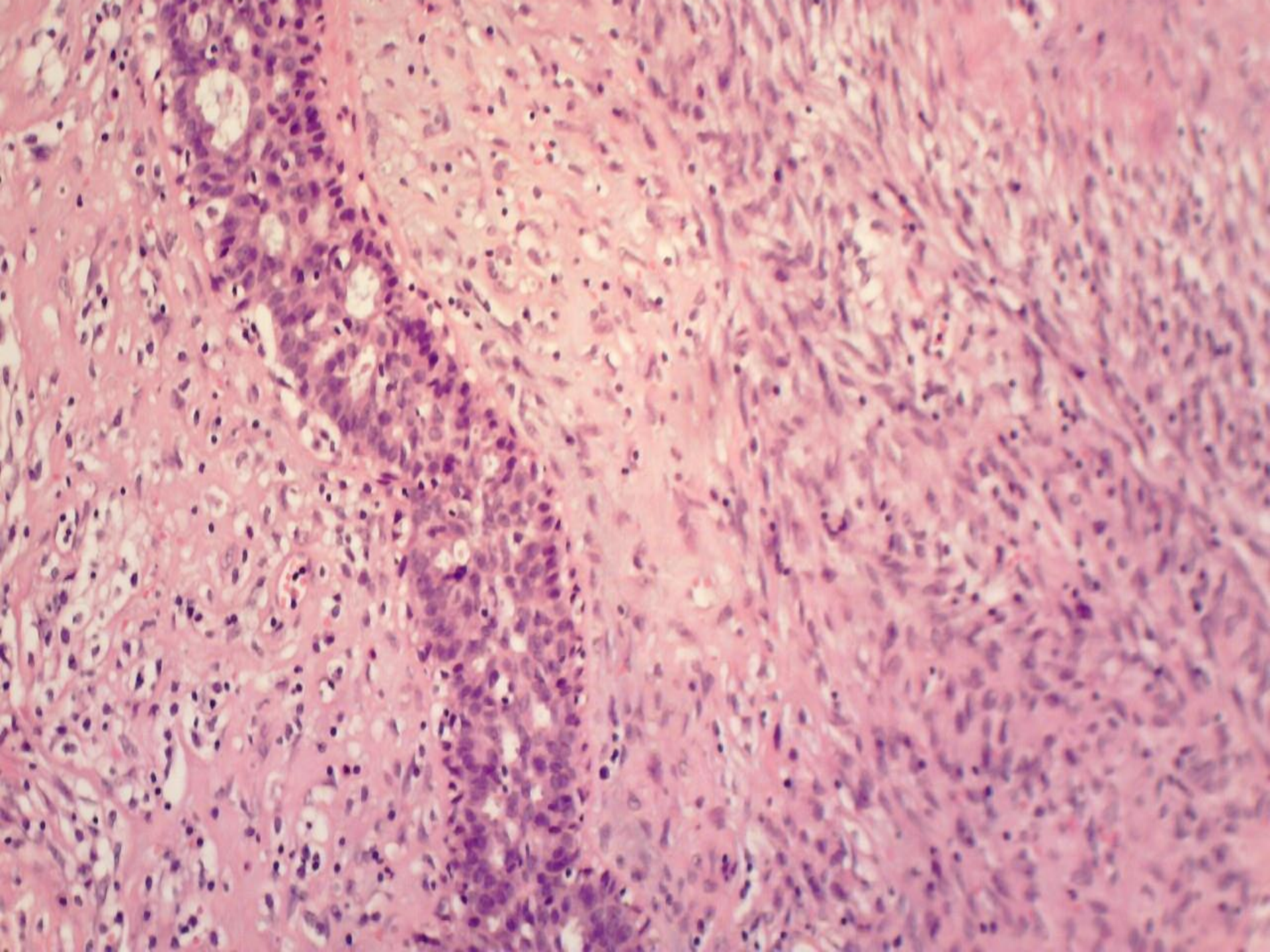
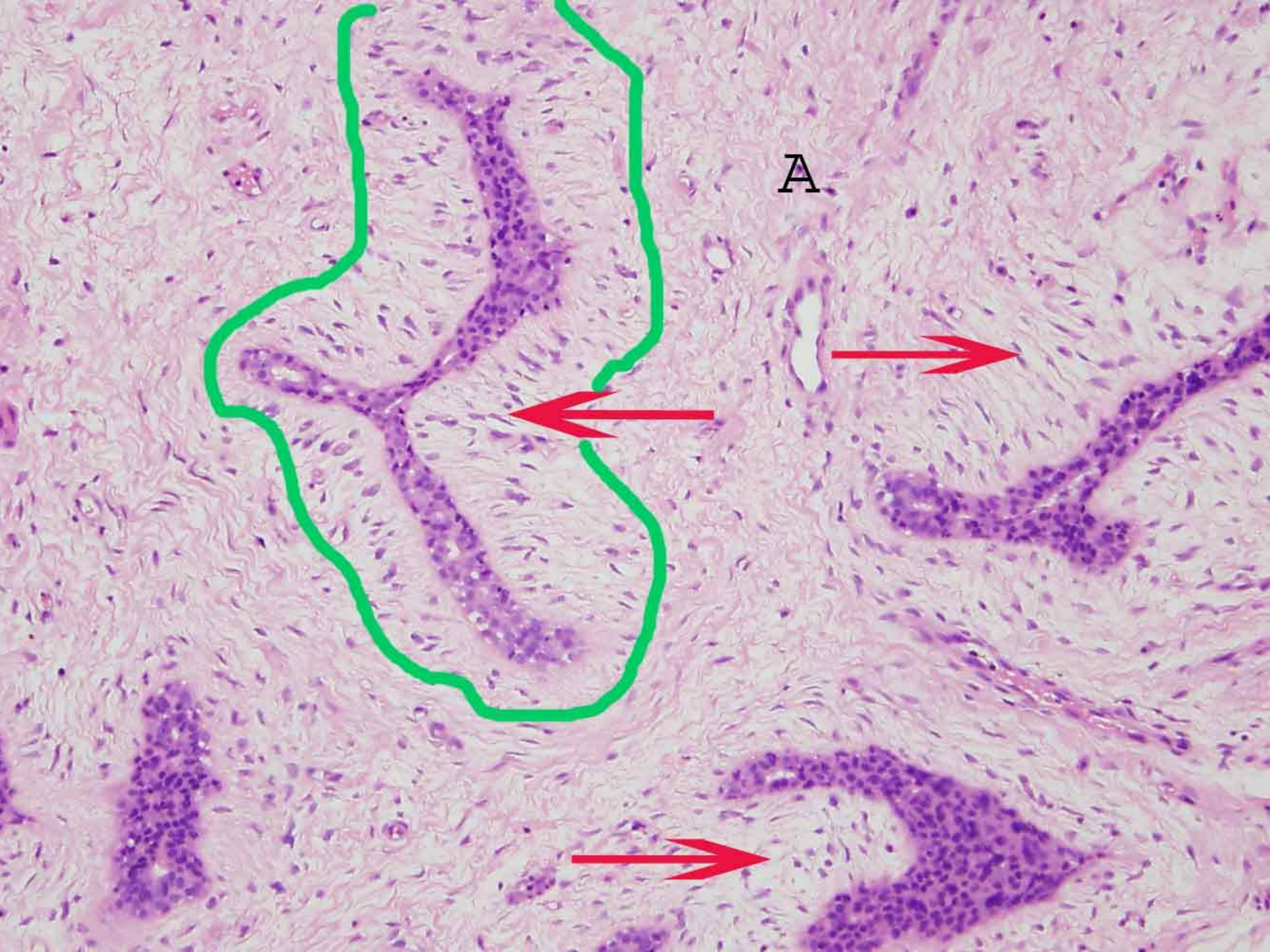







A

Phyllodes Tumor of the Breast

Fibroadenoma	Low Grade Phyllodes Tumor
Lacks significant stromal hypercellularity	Hypercellular stroma is prominent
No stromal overgrowth	May have stromal overgrowth
No leaf-like architecture	Prominent leaf-like architecture
No condensation around ducts	Stromal condensation around ducts
Does not infiltrate	May infiltrate surrounding breast

The histologic border between these two is not always sharp

Phyllodes Tumor of the Breast

Juvenile Fibroadenoma	Low Grade Phyllodes Tumor
No leaf-like architecture	Prominent leaf-like architecture
No condensation around ducts	Stromal condensation around ducts
Does not infiltrate	May infiltrate surrounding breast

The histologic border between these two is not always sharp

Phyllodes Tumor of the Breast

Phyllodes tumors are a fibroepithelial tumor composed of an epithelial and a cellular stromal component with broad "leaf-like" papillae inserted into cleft-like spaces

They may be considered benign, borderline, or malignant

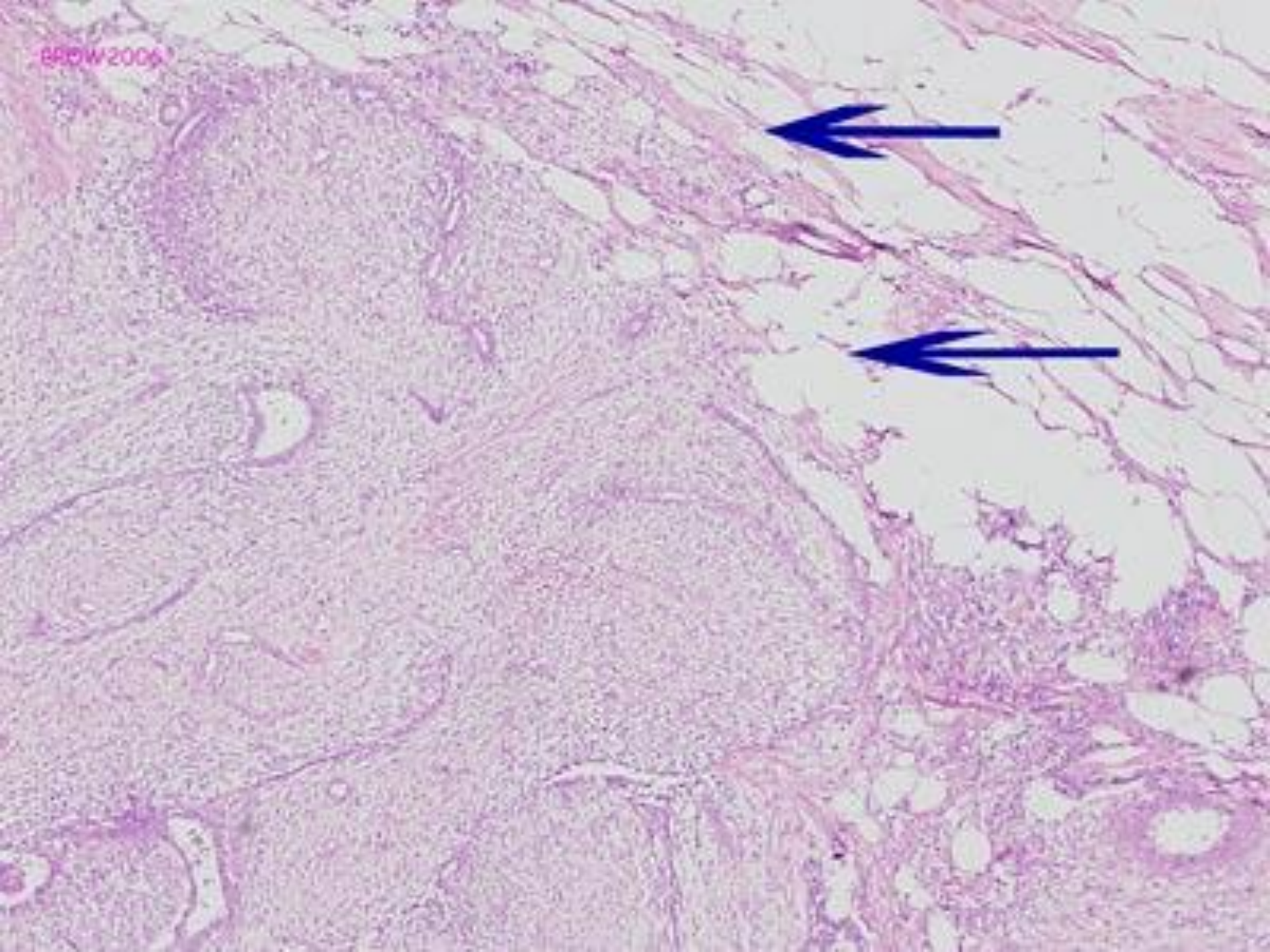
depending on histologic features including **stromal cellularity, infiltration at the tumor's edge, and mitotic activity.**

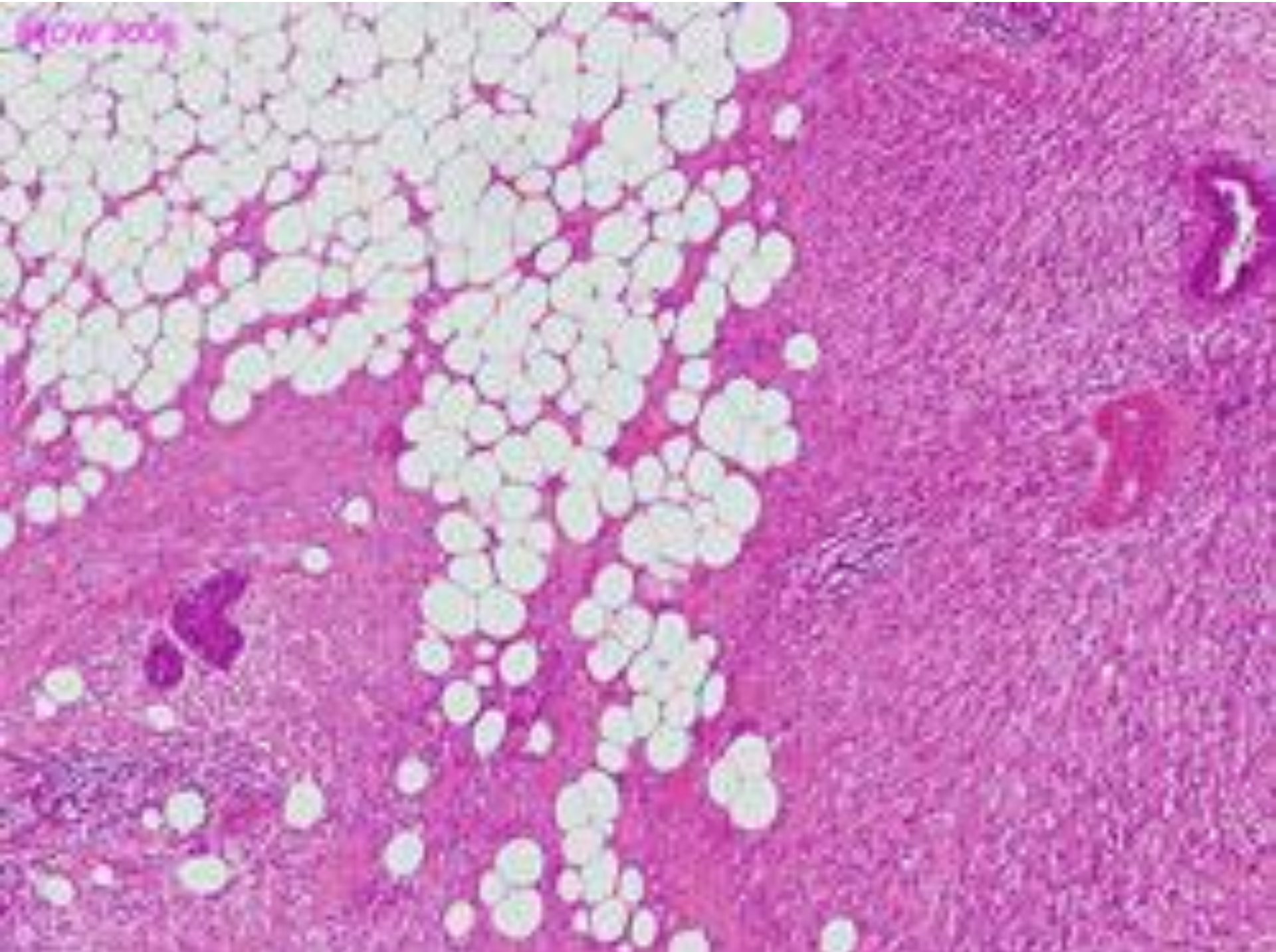
All forms of phyllodes tumors are regarded as having malignant potential.

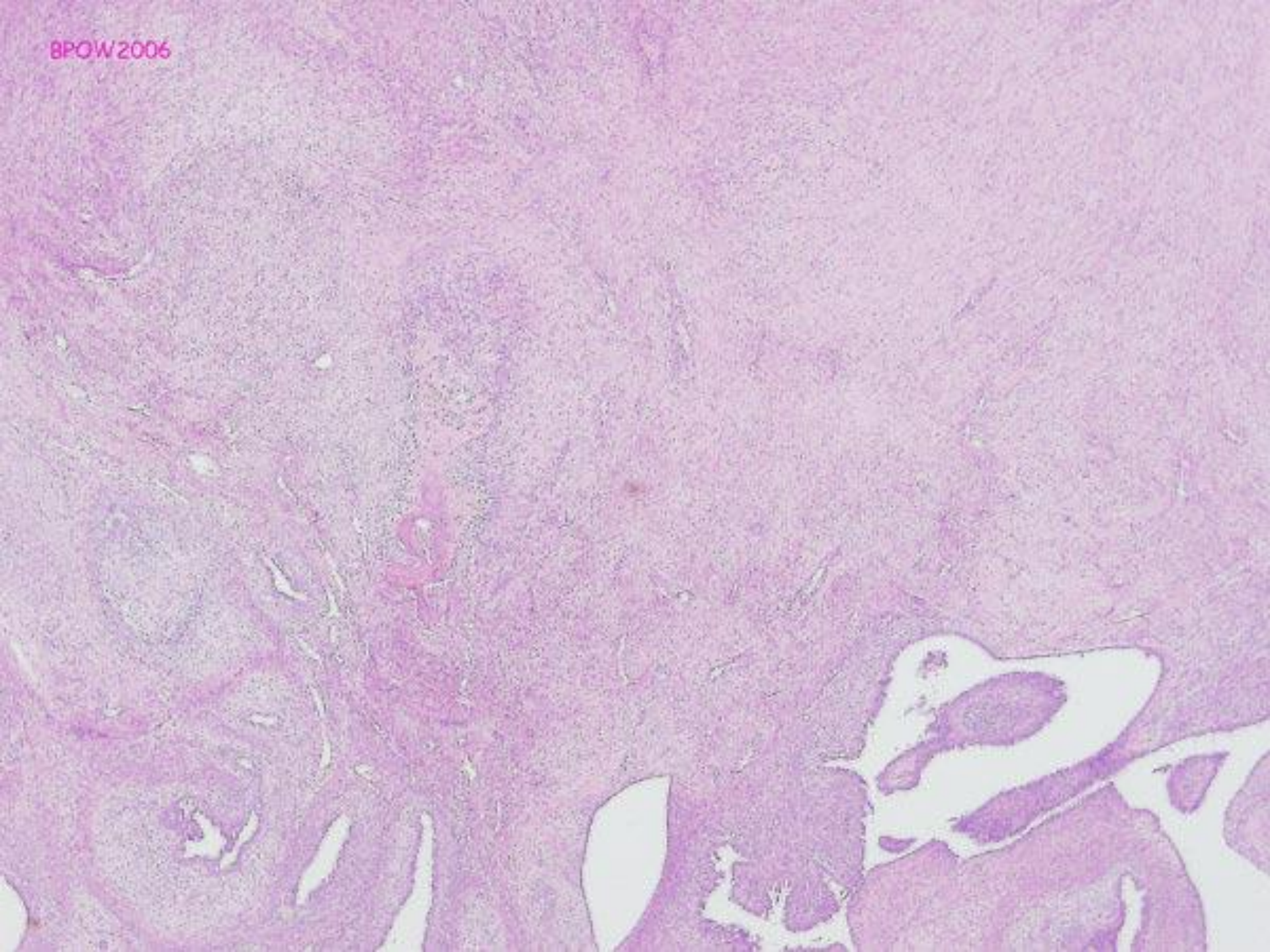
Phyllodes Tumor of the Breast

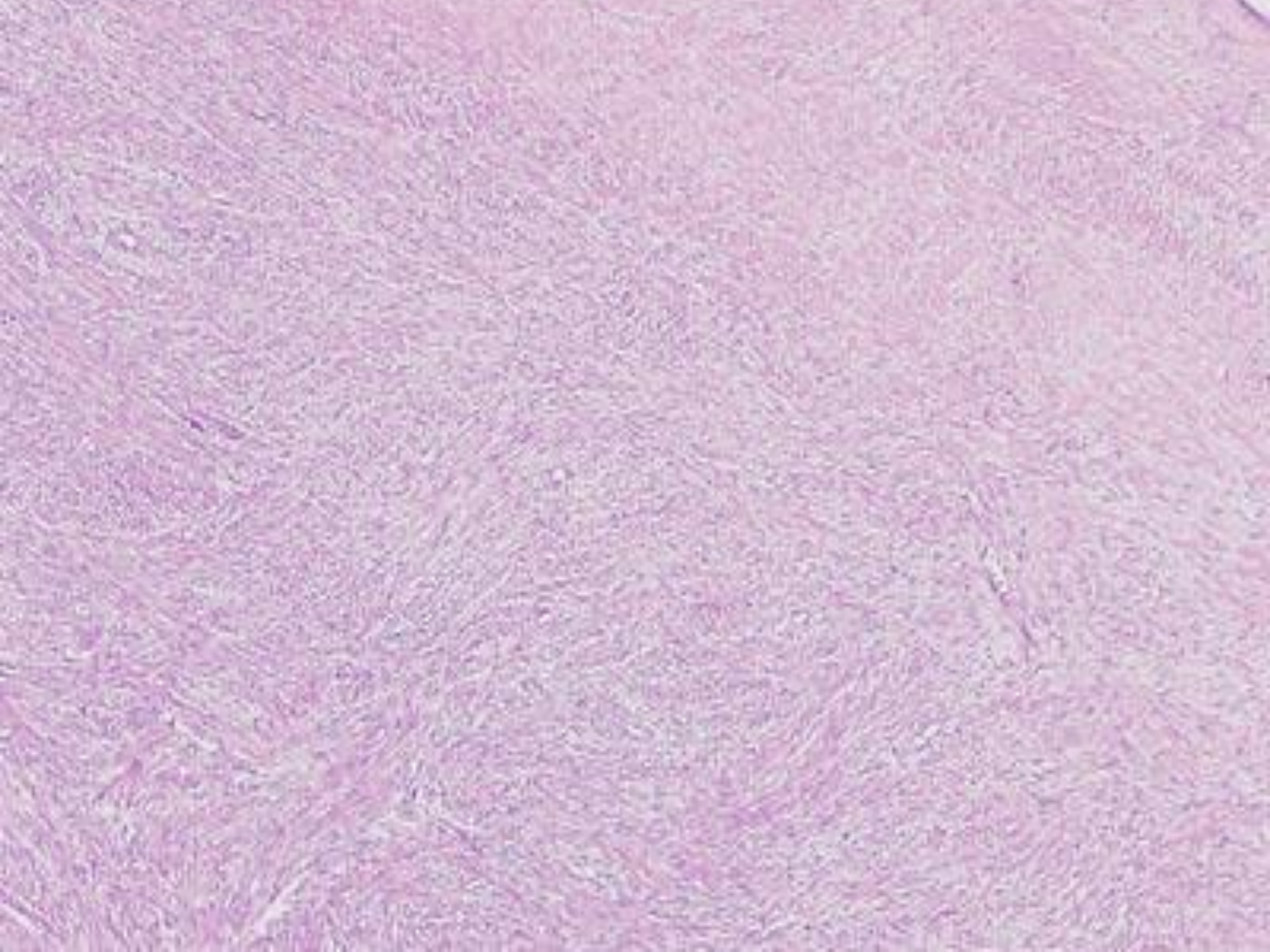
Adverse features

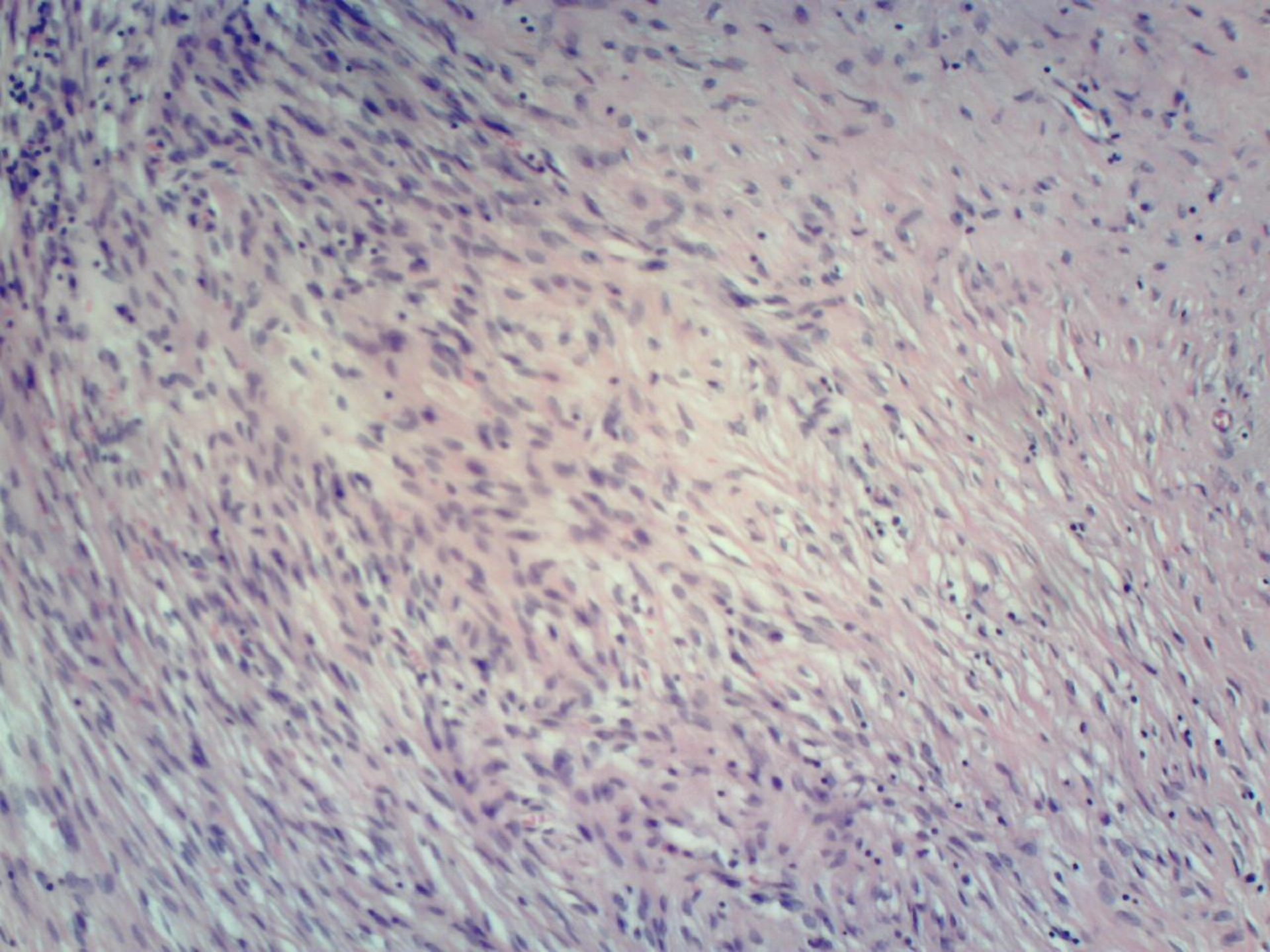
- Infiltrative margin
- Stromal overgrowth (> one 40x field without epithelium)
- High mitotic index (>10 /10 hpf)
- Sarcomatous stroma (nuclear pleomorphism and atypia)

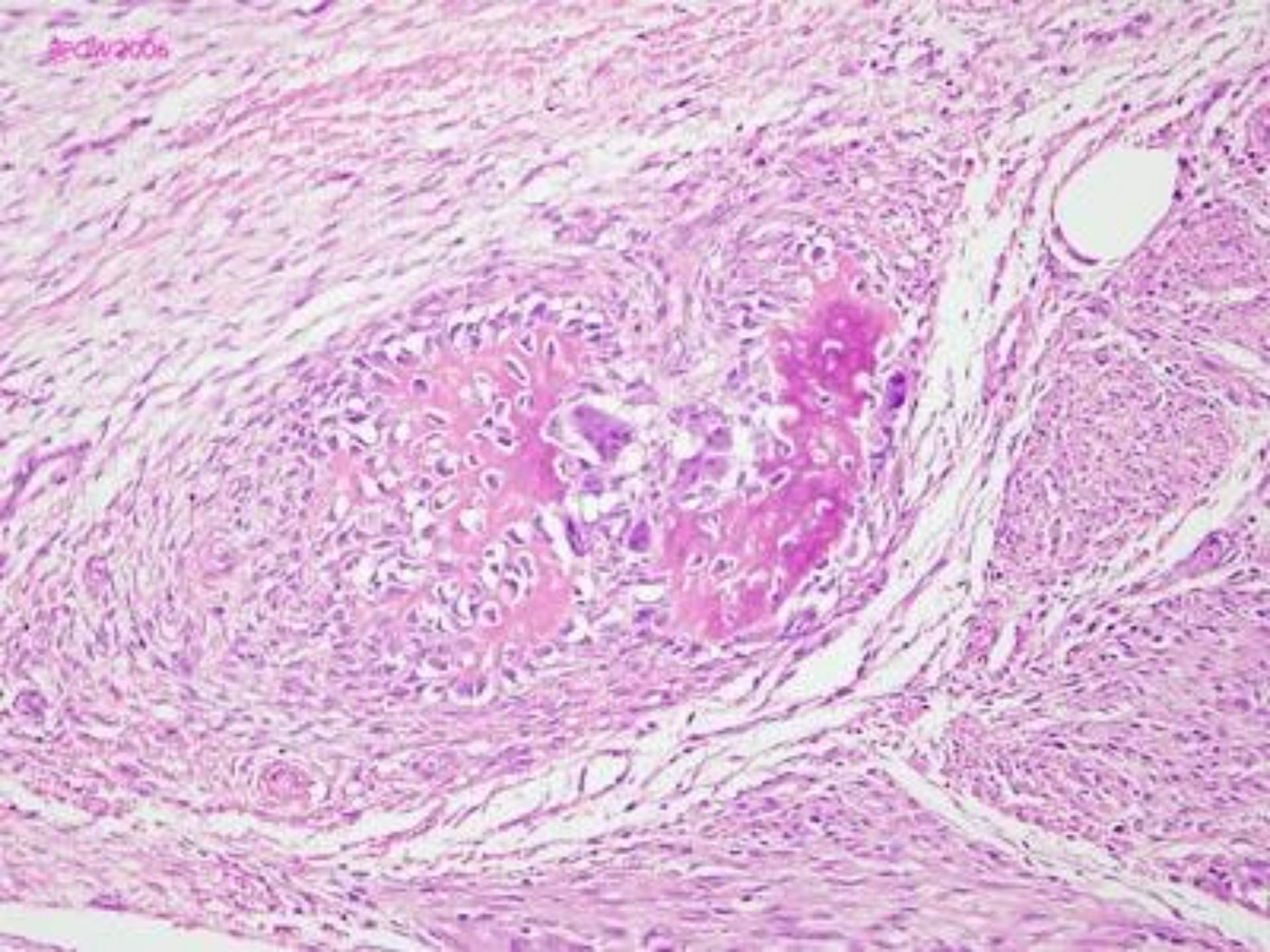












WHO Classification[63]	*Benign PT*	*Borderline PT*	*Malignant PT*
Stromal cellularity	Modest	Modest	Marked
Cellular pleomorphism	Little	Moderate	Marked
Mitoses	Few, if any	Intermediate	Numerous (>10/ HPF)
Margins	Well circumscribed (Pushing)	Intermediate	Invasive
Stromal pattern	Uniform stromal distribution	Heterogenous stromal distribution	Marked stromal overgrowth
Heterologous stromal distribution	Rare	Rare	Not uncommon
Overall average distribution (%)	60	20	20

	Benign	Borderline	Malignant
Pushing boundary	Yes	Usually	Not usually
Stromal/epithelial balance	Even	Even	Uneven
Stromal cellularity	High	High	High
Variability of stromal cellularity	Yes	Yes	Yes ++
Stromal mitoses /10 hpf	< 5	5 - 10	>10

http://www.breastpathology.info/phyllodes.html

Phyllodes Tumor of the Breast

Benign

- No adverse features
- 20% recurrence rate after local excision
- 10% recurrence rate after wide excision (at least 1 cm margin)
- No reported metastases

In: Tavassoli FA, Devilee P, editors. Pathology and genetics: tumours of the breast and female genital organs. Lyon, France: IARC Press, 2003, pp. 99-103.

Phyllodes Tumor of the Breast

Borderline

- One or more adverse features but short of definition for malignant (see below)
- 45% recurrence rate after local excision
- 30% recurrence rate after wide excision (at least 1 cm margin)
- No reported metastases

In: Tavassoli FA, Devilee P, editors. Pathology and genetics: tumours of the breast and female genital organs. Lyon, France: IARC Press, 2003, pp. 99-103.

Phyllodes Tumor of the Breast

Malignant

- High mitotic index and sarcomatous stroma
- Stroma overgrowth and high mitotic index or sarcomatous stroma
- 65% recurrence rate after local excision
- 35% recurrence rate after wide excision (at least 1 cm margin)
- 30% metastatic rate

In: Tavassoli FA, Devilee P, editors. Pathology and genetics: tumours of the breast and female genital organs. Lyon, France: IARC Press, 2003, pp. 99-103.

	Benign	Borderline	Malignant
Local Recurrence (%)	15	25	30
Distant Metastases (%)	0	5	20

http://www.breastpathology.info/phyllodes.html

Phyllodes Tumor of the Breast

Juvenile Fibroadenoma	High Grade Phyllodes Tumor
No stromal atypia	Atypical stroma
Stromal mitotic rate < 3/10 hpf	Elevated stromal mitotic rate
No stromal overgrowth	Stromal overgrowth
Does not infiltrate	May infiltrate surrounding breast

Stromal overgrowth defined as at least one low power field (40x total magnification) composed entirely of stroma

Phyllodes Tumor of the Breast

Metaplastic Carcinoma	Phyllodes Tumor
Spindled component may be positive for high molecular weight keratin or p63	Stromal component negative for high molecular weight keratin and p63
Epithelial component is malignant	Epithelial component is benign
Squamous differentiation may be present	No squamous differentiation

Pure Sarcoma of the Breast

Phyllodes Tumors of the Breast
The Role of Pathologic Parameters

Abstract

We aimed to establish whether morphologic parameters were prognostically important in a large series of breast phyllodes tumors in Asian women. Of 335 phyllodes tumors diagnosed at the Department of Pathology, Singapore General Hospital, Singapore, between January 1992 and December 2002, 250 (74.6%) were benign, 54 (16.1%) borderline, and 31 (9.3%) malignant, based on histologic review of archival slides. Of the women, 43 (12.8%) experienced recurrences during the follow-up period. Recurrent disease was correlated with grade or classification (P = .028), stromal atypia (P = .016), stromal hypercellularity (P = .046), and permeative microscopic borders (P = .021). Multivariate analysis revealed that independent predictors of recurrence were pseudoangiomatous stromal hyperplasia (PASH) and margin status, whereby the presence of PASH and complete or negative margins reduced recurrence hazards by 51.3% and 51.7%, respectively. The 7 women who died of disease during follow-up had malignant phyllodes tumor at the outset and experienced recurrences, and death was preceded by distant metastases.

Am J Clin Pathol 2005;123:529-540

Malignant phyllodes tumors: a review of 752 cases.

Abstract

Because of the scarcity of the disease, there are no evidence-based treatment or follow-up guidelines established. We identified 752 cases of malignant phyllodes tumors in the California Cancer Registry from the years 1988 to 2003. Relative survival was determined using Berkson-Gage life table analysis which was then compared with the nonphyllodes breast cancer patients.

For MPT patients, the relative annual survival at 1 year was 94 per cent and at 10 years was 99.6 per cent. Thus, after 10 years, these patients are no more likely to die than the general population. At 10 years, the relative cumulative survival of the MPT patients was 87.4 per cent, whereas the nonphyllodes breast cancer patients had only a 57.2 per cent relative cumulative survival. MPT patients with localized disease had a higher 10-year relative cumulative survival than those with regional disease (90.9% vs. 61.5%, $P < 0.001$). MPT has a good prognosis, particularly in patients with localized disease. After 10 years, MPT patients have no increased mortality relative to the general population.

Am Surg. 2007 Oct;73(10):967-9.

Clinicopathologic Details for Nine Women With PT Who Died*

Case No./Race/ Age (y)†	Tumor Size (mm)	Mitoses (/10 hpf)	Stromal Cyto-logic Atypia	Stromal Overgrowth	PASH	Surgical Procedure	Margin Status	Local Recur-rence (No.)	Distant Recurrence	Cause of Death (Survival, mo)
1/C/34	60	5	Marked	Absent	Absent	Excisional biopsy	Involved	Yes (2)	CT, metastasis to lung, ilium; histology, metastasis to spine	PT (40)
2/C/43	250	20	Moderate	Present	Present	Mastectomy	<0.5 mm away	Yes (1)	CT, metastasis to bone, liver, lung	PT (112)
3/C/42	35	40	Marked	Present	Absent	Wide excision	<1 mm away	Yes (1)	CT, metastasis to lung	PT (14)
4/C/52	150	39	Moderate	Present	Absent	Chest wall resection‡	Complete	Yes (3)	CT, metastasis to bone, lung	PT (17)
5/C/54	250	8	Marked	Present	Present	Mastectomy	Complete	Yes (1)	Histology, metastasis to lung	PT (25)
6/C/40	220	23	Marked	Present	Present	Mastectomy	1 mm away	Yes (1)	CT, metastasis to lung	PT (4)
7/C/45	120	7	Marked	Absent	Present	Mastectomy	Complete	None	None	AMI (112)
8/C/58	90	30	Marked	Present	Absent	Mastectomy	Involved	Yes (1)	CT, metastasis to lung, liver	PT (9)
9/M/43	170	1	Minimal	Absent	Present	Mastectomy	Complete	None	None	Cancer, unknown origin (92)

AMI, acute myocardial infarction; C, Chinese; CT, computed tomographic scan; hpf, high-power fields; M, Malay; PT, phyllodes tumor.

* All tumors were malignant with permeative borders and marked stromal hypercellularity except in case 9, which involved a benign tumor with pushing borders and mild stromal hypercellularity.

† Age at diagnosis.

‡ Clinicoradiologic evidence of skeletal muscle and rib involvement before surgery.

Am Surg. 2007 Oct;73(10):967-9.

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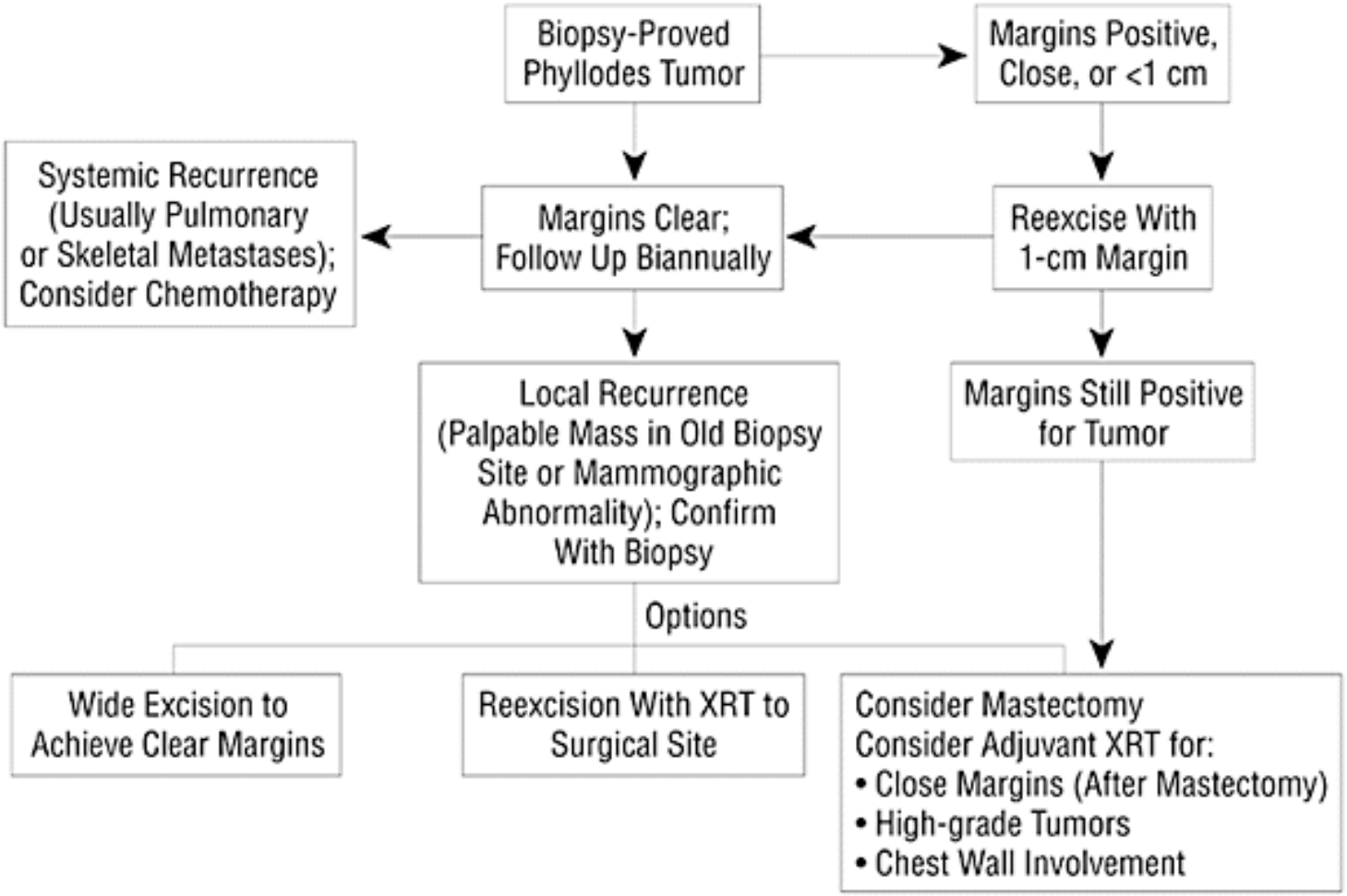
depending on histologic features including stromal cellularity, infiltration at the tumor's edge, and mitotic activity.

All forms of phyllodes tumors are regarded as having **malignant potential.**



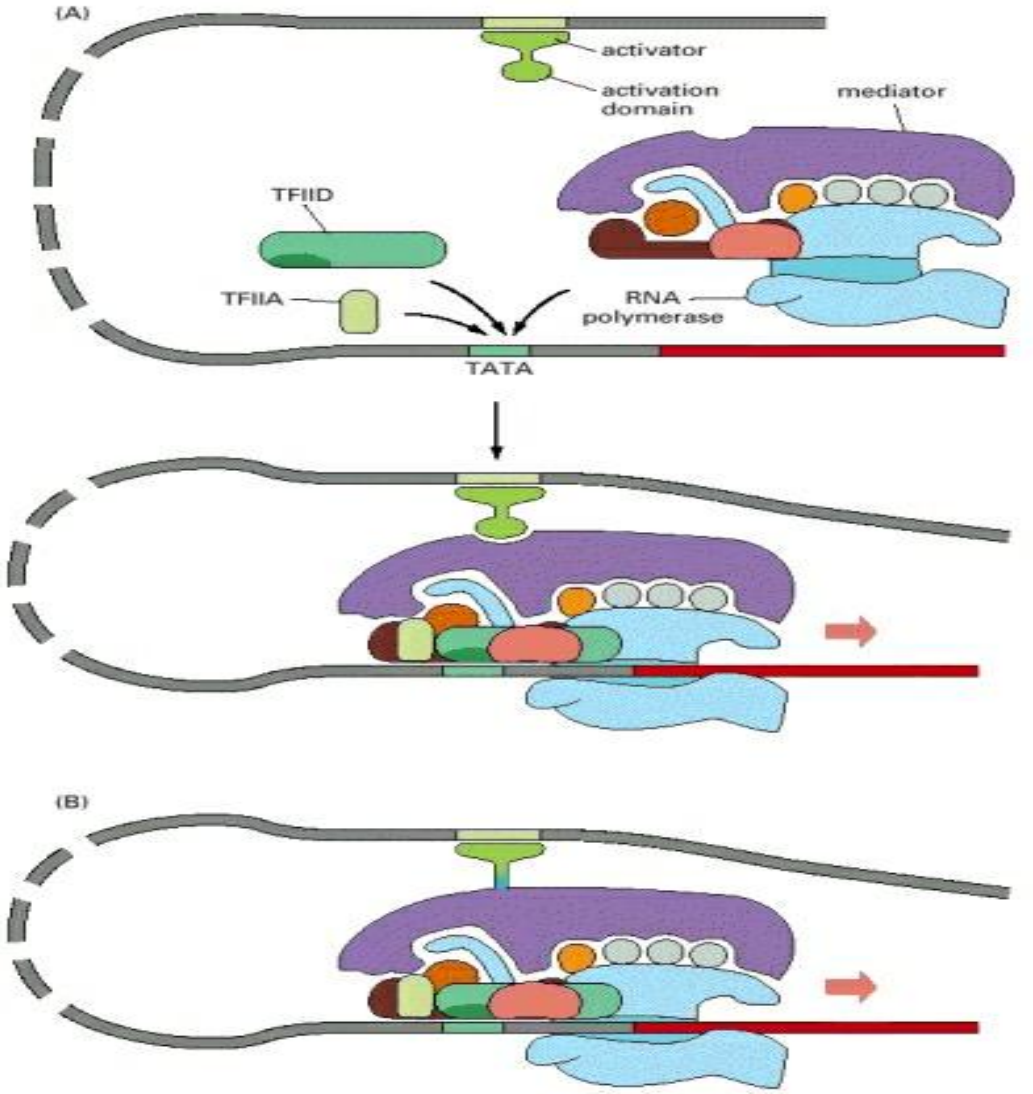
Arch Surg. 1999;134(5):487-493. doi:10.1001/archsurg.134.5.487

Next-Gen Sequencing Exposes Frequent MED12 Mutations and Actionable Therapeutic Targets in Phyllodes Tumors

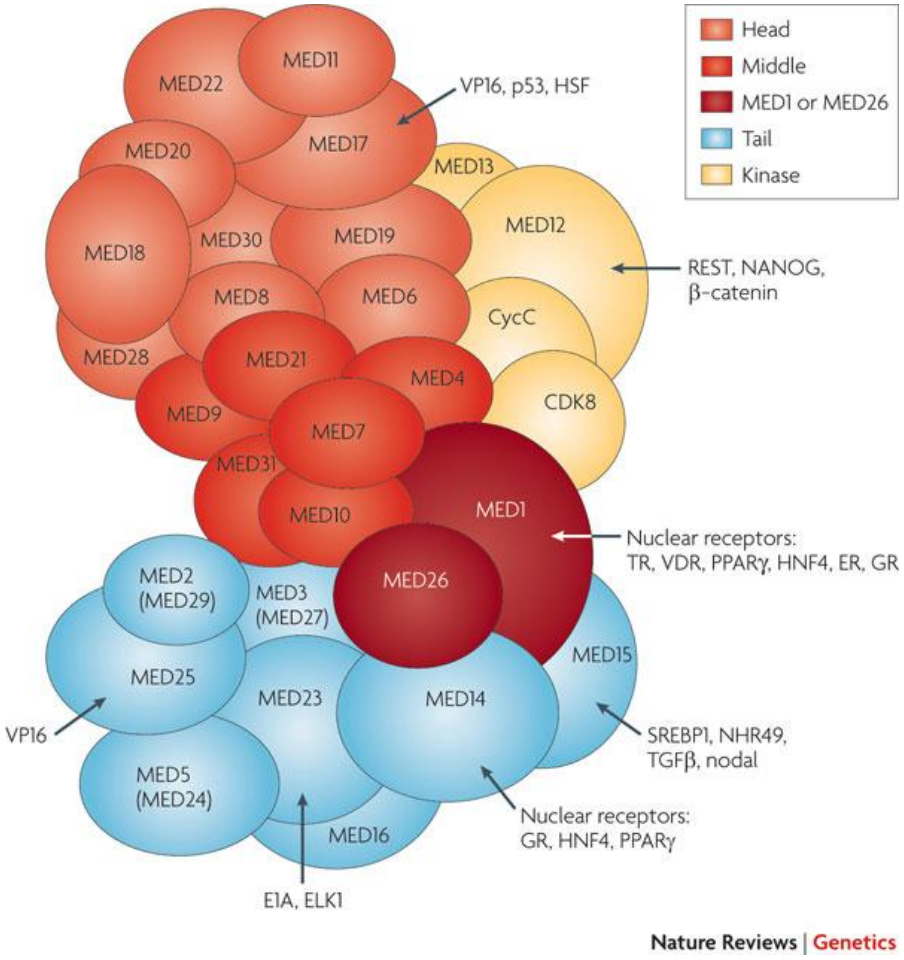
Abstract

Little is known about the genetic alterations that drive phyllodes tumor initiation and/or progression. Here targeted next generation sequencing (NGS) was used to identify somatic alterations in formalin fixed paraffin embedded (FFPE) patient specimens from malignant, borderline and benign cases. NGS revealed mutations in mediator complex subunit 12 (MED12) affecting the G44 hotspot residue in the majority (67%) of cases spanning all three histological grades. In addition, loss-of-function mutations in p53 (TP53) as well as deleterious mutations in the tumor suppressors retinoblastoma (RB1) and neurofibromin 1 (NF1) were identified exclusively in malignant tumors. High-level copy number alterations (CNAs) were nearly exclusively confined to malignant tumors, including potentially clinically actionable gene amplifications in IGF1R and EGFR. Taken together, this study defines the genomic landscape underlying phyllodes tumor development, suggests potential molecular correlates to histologic grade, expands the spectrum of human tumors with frequent recurrent MED12 mutations, and identifies IGF1R and EGFR as potential therapeutic targets in malignant cases. Implications: Integrated genomic sequencing and mutational profiling provides insight into the molecular origin of phyllodes tumors and indicates potential druggable targets in malignant disease

January 15, 2015; doi:10.1158/1541-7786.MCR-14-0578



Mediator as a bridge binds to the RNA polymerase II holoenzyme and transcription factors.



The Mediator complex is composed of up to at least 31 subunits in all eukaryotes

Selected Tumor Suppressor Genes Involved in Human Neoplasms

Subcellular Locations	Gene	Function	Tumors Associated with Somatic Mutations	Tumors Assocated with Inherited Mutations
Cell surface	TGF-β receptor	Growth inhibition	Carcinomas of colon	Unknown
	E-cadherin	Cell adhesion	Carcinoma of stomach	Familial gastric cancer
Inner aspect of plasma membrane	*NF1*	Inhibition of RAS signal transduction and of p21 cell cycle inhibitor	Neuroblastomas	Neurofibromatosis type 1 and sarcomas
Cytoskeleton	*NF2*	Cytoskeletal stability	Schwannomas and meningiomas	Neurofibromastosis type 2, acoustic schwannomas, and meningiomas
Cytosol	*APC*/β-catenin	Inhibition of signal transduction	Carcinomas of stomach, colon, pancreas; melanoma	Familial adenomatous polyposis coli/colon cancer
	PTEN	PI3 kinase signal transduction	Endometrial and prostate cancers	Cowden syndrome
	SMAD2 and *SMAD4*	TGF-β signal transduction	Colon, pancreas tumors	Unknown
Nucleus	*RB1*	Regulation of cell cycle	Retinoblastoma; osteosarcoma carcinomas of breast, colon, lung	Retinoblastomas, osteosarcoma
	p53	Cell cycle arrest and apoptosis in response to DNA damage	Most human cancers	Li-Fraumeni syndrome; multiple carcinomas and sarcomas
	WT1	Nuclear transcription	Wilms' tumor	Wilms' tumor
	P16/INK4a	Regulation of cell cycle by inhibition of cyclindependent kinases	Pancreatic, breast, and esophageal cancers	Malignant melanoma
	BRCA1 and *BRCA2*	DNA repair	Unknown	Carcinomas of female breast and ovary; carcinomas of male breast

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They may be considered benign, borderline, or malignant

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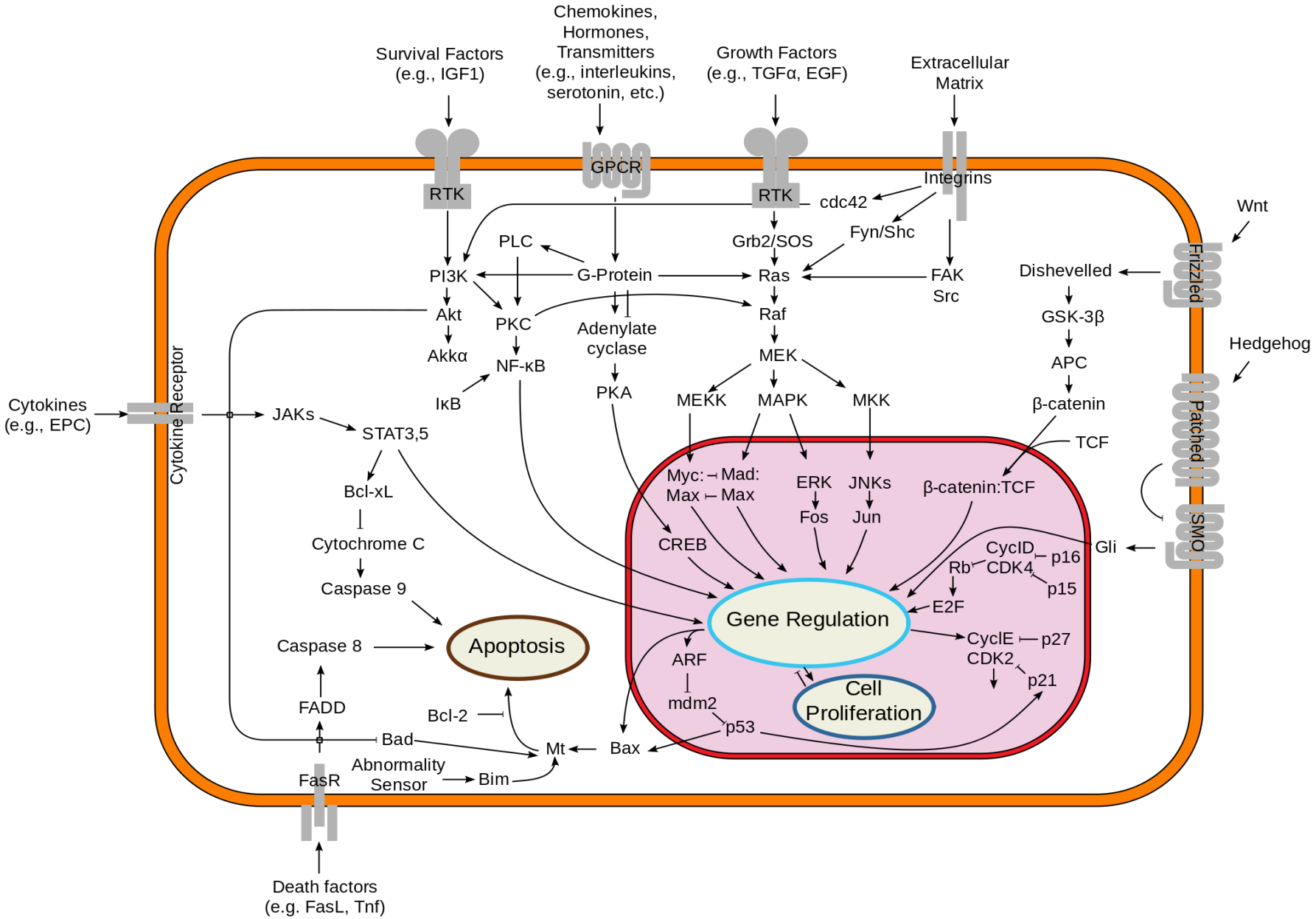
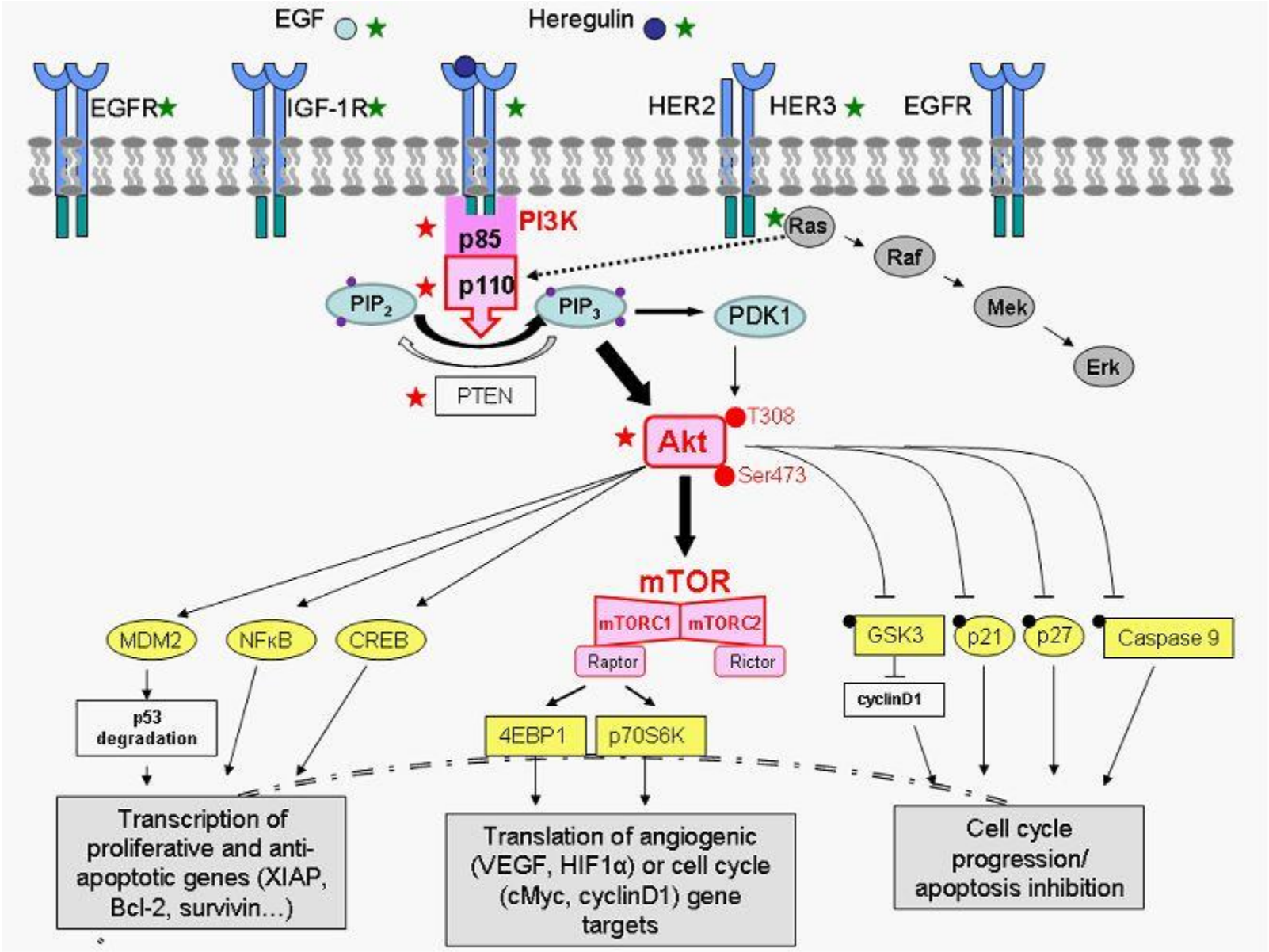
All forms of phyllodes tumors are regarded as having **malignant potential.**

SOME PROTO-ONCOGENES AND THEIR FUNCTIONS, MUTATIONS, AND ASSOCIATED CANCERS

PROTO-ONCOGENE	FUNCTION	MUTATION	CANCER
ABL	Nonreceptor tyrosine kinase activity	Translocation t(9:22)	**Chronic myelogenous leukemia** (chromosome 22 is Philadelphia chr.)
HER (ERBB2)	Receptor synthesis	Amplification	Breast carcinoma (marker of aggressiveness)
MYC	Nuclear transcription	Translocation t(8:14)	Burkitt's lymphoma
N-MYC	Nuclear transcription	Amplification	Neuroblastoma
RAS	Guanosine triphosphate signal transduction	Point mutation	Leukemia; lung, colon, pancreatic carcinomas
RET	Receptor synthesis	Point mulation	Multiple endocrine neoplasia IIa/IIb syndromes
SIS'	Growth factor synthesis	Overexpression	Osteogenic sarcoma, astrocytoma

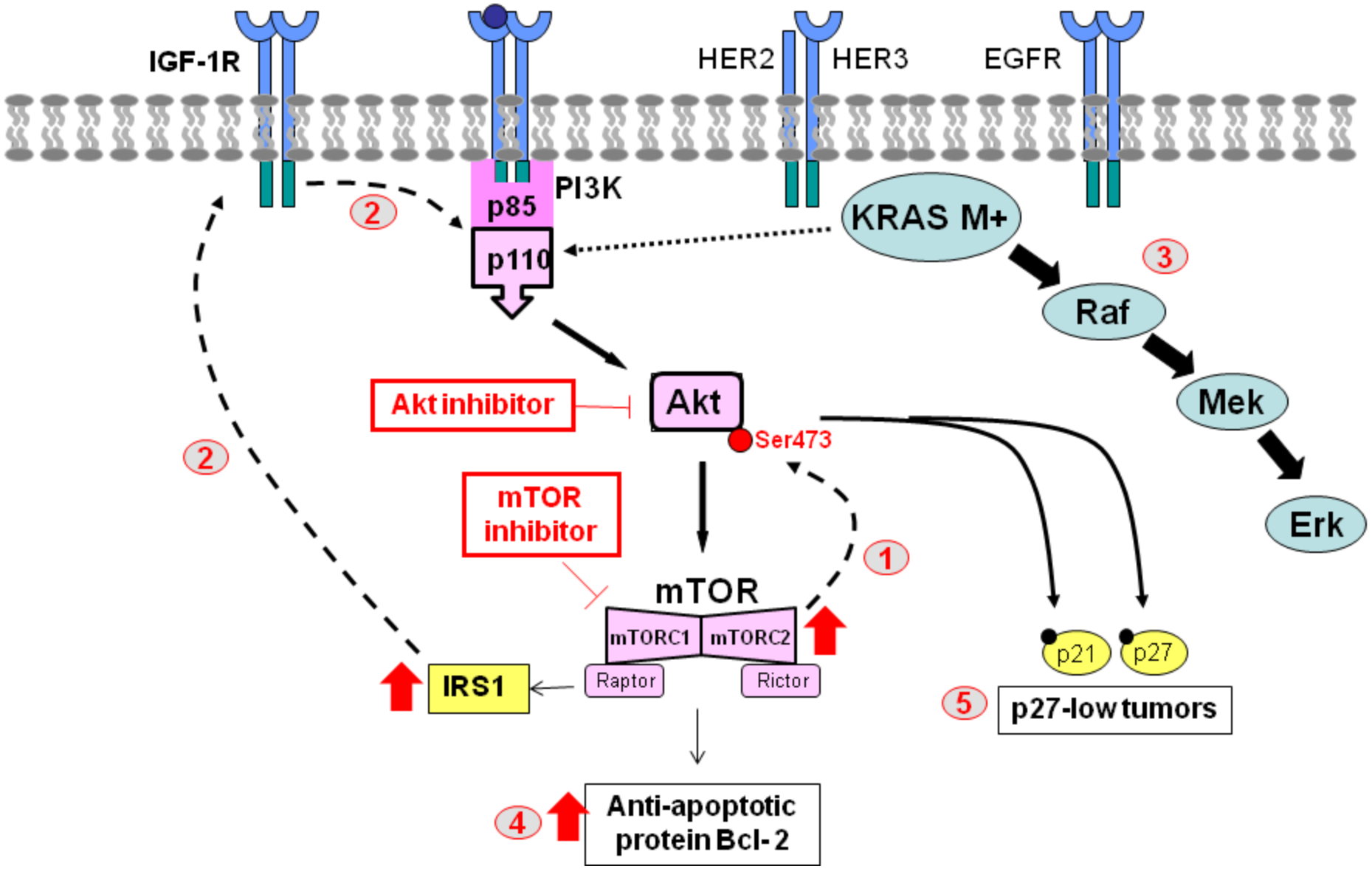

Survival Factors
(e.g., IGF1)
Chemokines,
Hormones,
Transmitters
(e.g., interleukins,
serotonin, etc.)
Growth Factors
(e.g., TGFα, EGF)
Extracellular
Matrix
RTK
GPCR
RTK
Integrins
cdc42
Fyn/Shc
Grb2/SOS
PLC
PI3K
G-Protein
Ras
FAK
Src
Wnt
Frizzled
Dishevelled
GSK-3β
APC
β-catenin
Hedgehog
Patched
SMO
Akt
PKC
Adenylate
cyclase
Raf
Akkα
NF-κB
IκB
PKA
MEK
MEKK
MAPK
MKK
Cytokines
(e.g., EPC)
Cytokine Receptor
JAKs
STAT3,5
TCF
Bcl-xL
Myc:
Max
Mad:
Max
ERK
JNKs
Fos
Jun
β-catenin:TCF
Cytochrome C
CREB
Gli
CyclD
CDK4
p16
p15
Rb
E2F
Caspase 9
Gene Regulation
Caspase 8
Apoptosis
CyclE
CDK2
p27
p21
ARF
mdm2
p53
Cell
Proliferation
FADD
Bcl-2
Bad
Mt
Bax
FasR
Abnormality
Sensor
Bim
Death factors
(e.g. FasL, Tnf)

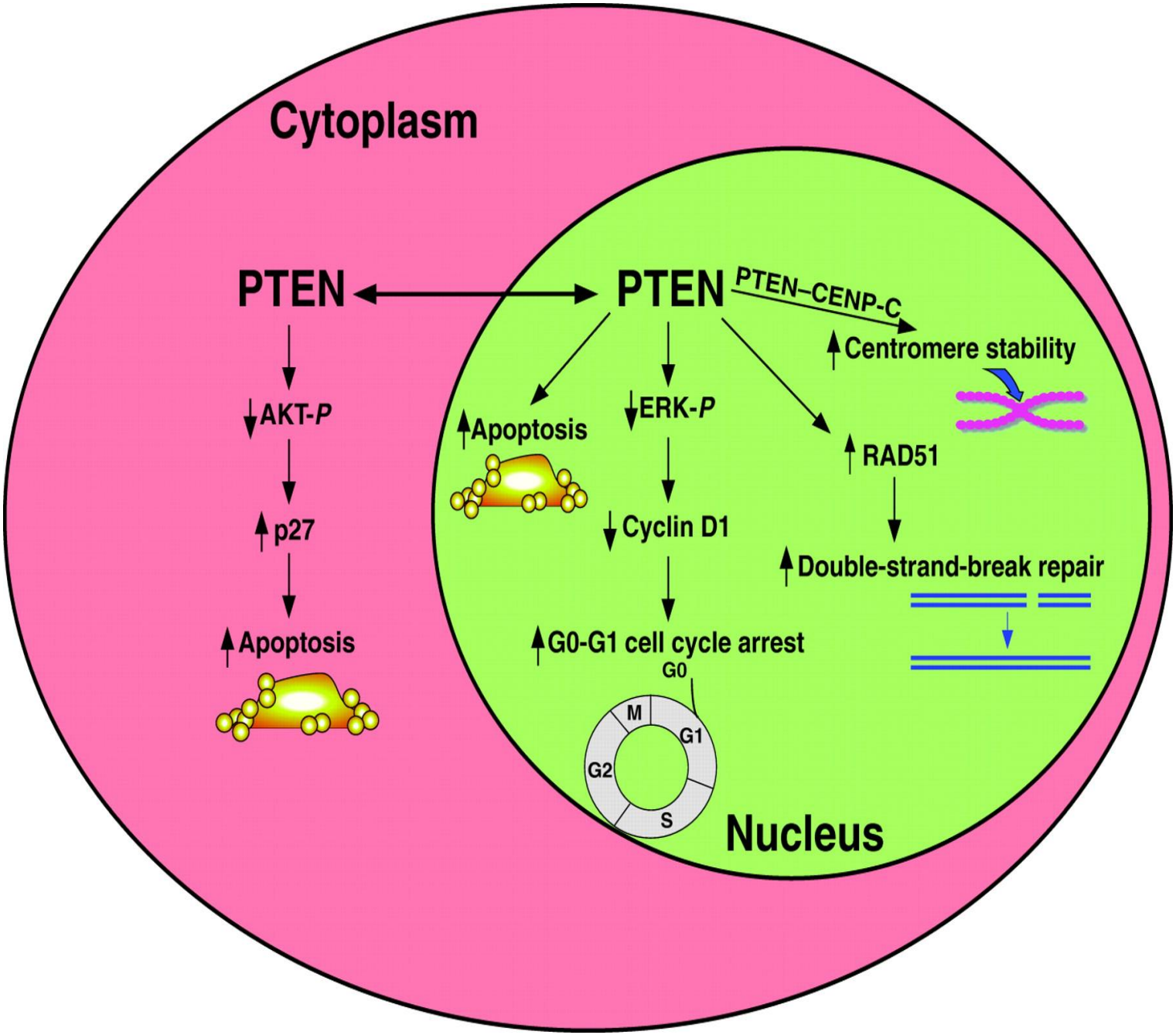


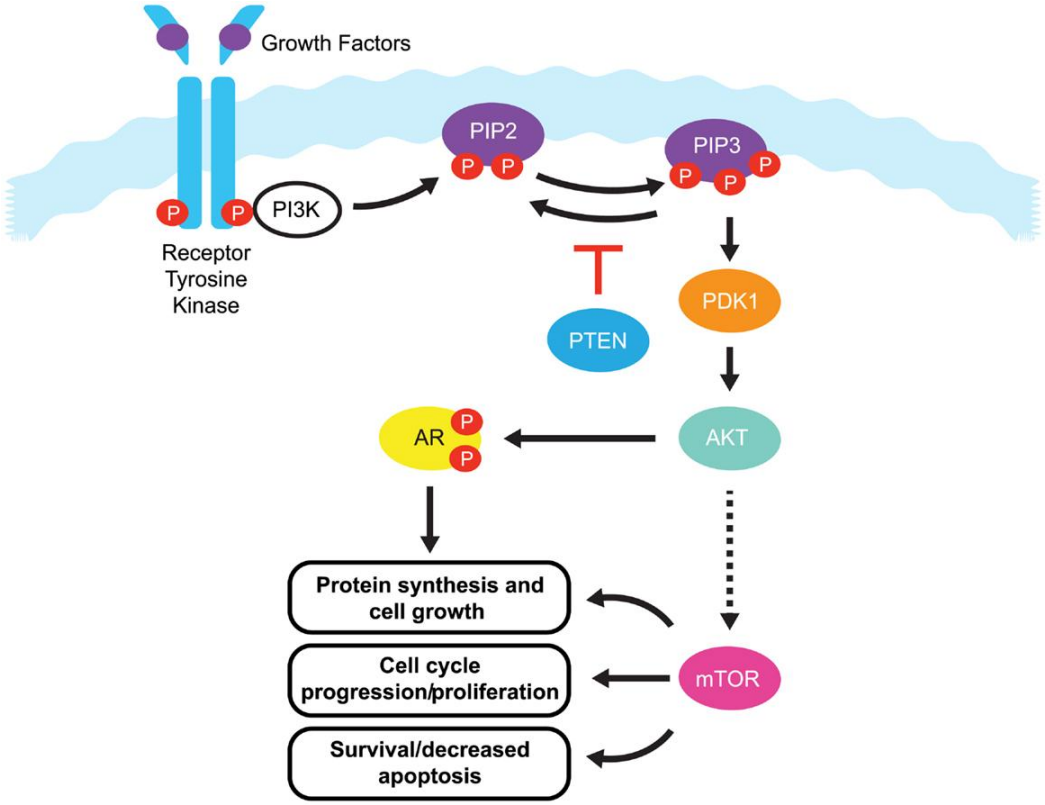
* Upstream activation of PI3K pathway: directly via membrane RTKs or their ligands, or indirectly via Ras

* Intrinsic activation of PI3K pathway via mutations in the p110 (*PIK3CA*) or p85 (*PIK3R*) subunits of PI3K, Akt mutations/amplifications, or PTEN loss.

····► Cross-talk


IGF-1R
HER2
HER3
EGFR
PI3K
p85
p110
KRAS M+
Raf
Mek
Erk
Akt inhibitor
Akt
Ser473
mTOR inhibitor
mTOR
mTORC1
mTORC2
Raptor
Rictor
IRS1
p21
p27
p27-low tumors
Anti-apoptotic protein Bcl-2
1
2
2
3
4
5


Cytoplasm
PTEN
PTEN
PTEN–CENP-C
Centromere stability
AKT-P
p27
Apoptosis
Apoptosis
ERK-P
Cyclin D1
G0-G1 cell cycle arrest
RAD51
Double-strand-break repair
G0
G1
S
G2
M
Nucleus


Growth Factors
PIP2
PIP3
P
PI3K
Receptor
Tyrosine
Kinase
PTEN
PDK1
AR
AKT
Protein synthesis and
cell growth
Cell cycle
progression/proliferation
Survival/decreased
apoptosis
mTOR

Phyllodes Tumor of the Breast

Phyllodes tumors are a fibroepithelial tumor composed of an epithelial and a cellular stromal component with **broad "leaf-like" papillae inserted into cleft-like spaces**

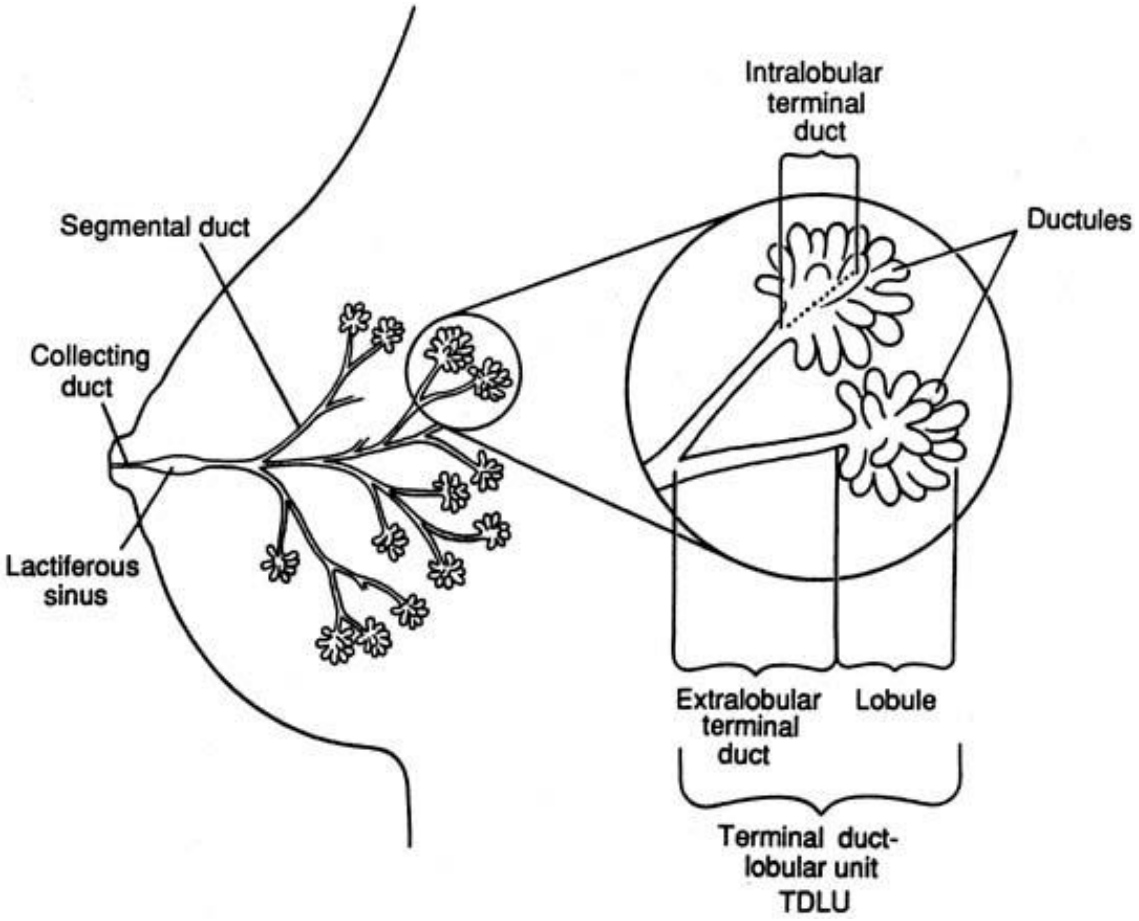
They may be considered benign, borderline, or malignant

depending on histologic features including stromal cellularity, infiltration at the tumor's edge, and mitotic activity.

All forms of phyllodes tumors are regarded as having malignant potential.

Phyllodes Tumor of the Breast

- **Report**
- Grade
- Size
- Margin status
- Presence and type of heterologous differentiation


Intralobular terminal duct
Ductules
Segmental duct
Collecting duct
Lactiferous sinus
Extralobular terminal duct
Lobule
Terminal duct-lobular unit
TDLU

	FA	Benign PT	Borderline PT	Malignant PT	Total
n	117	45	17	14	193
Age (years)					
Mean±SD	28.5±11.8	41.7±12.9	48.6±10.4	42.1±12.3	
(Range)	(10-59)	(19-74)	(30-78)	(25-67)	
Size tumor (cm)					
Mean±SD	3.4±2.0	6.5±4.4	12.6±8.0	11.0±8.4	
(Range)	(0.4-11.5)	(2.3-23.0)	(1.5-32.0)	(2.5-27.0)	
<3 cm	53 (45.3%)	5 (11.1%)	1 (5.9%)	2 (14.3%)	61
3-5 cm	50 (42.7%)	18 (40.0%)	2 (11.8%)	3 (21.4%)	73
>5 cm	14 (12.0%)	22 (48.9%)	14 (82.4%)	9 (64.3%)	59

Abbreviations: FA: Fibroadenoma; PT: Phyllodes tumor

Phyllodes Tumor of the Breast

- Differential Diagnosis
- Juvenile (cellular) fibroadenoma vs low grade phyllodes tumor
- Juvenile (cellular) fibroadenoma vs high grade phyllodes tumor
- (Usual adult type) fibroadenoma vs low grade phyllodes tumor
- Metaplastic carcinoma
- Pure sarcoma of the breast
- Fibromatosis
- Myofibroblastoma