



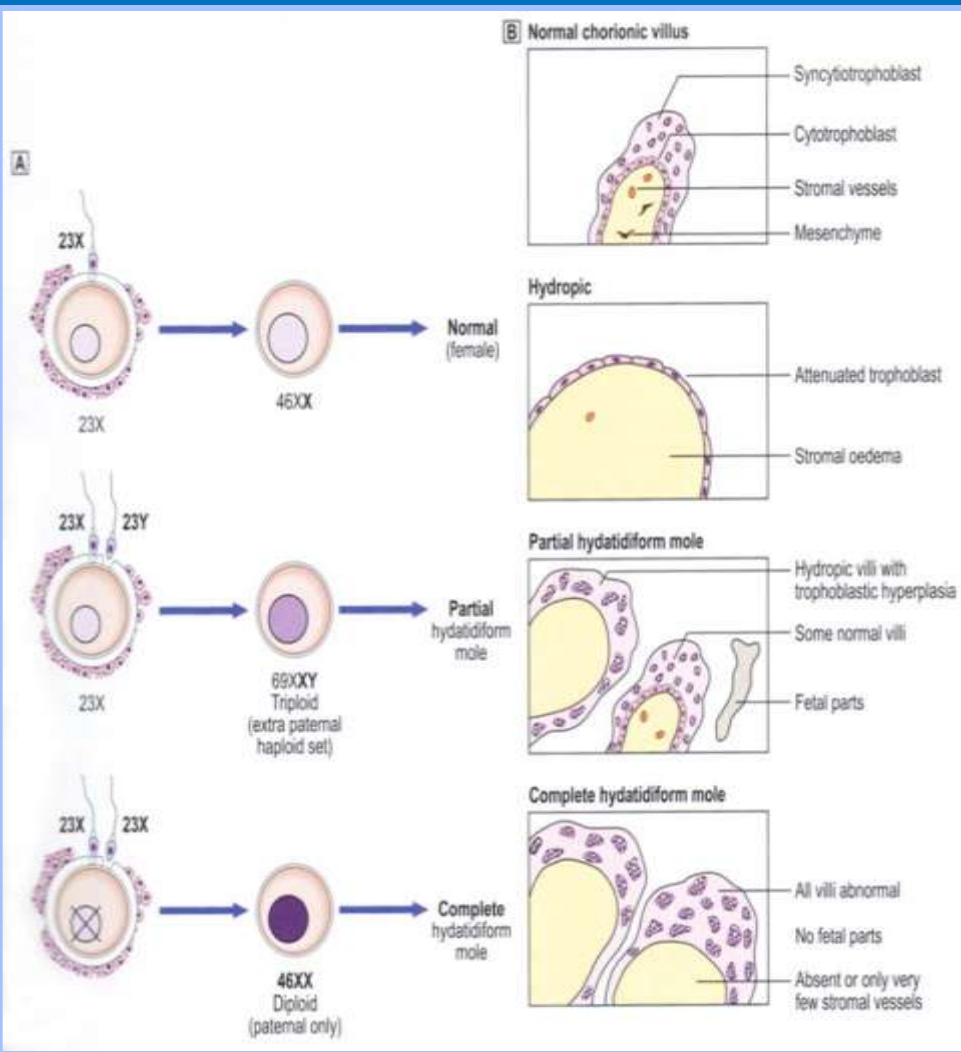
# The Pathology of Gestational Trophoblastic Neoplasia

Professor Mike Wells  
University of Sheffield

# Histopathological classification of Gestational Trophoblastic Disease

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- Hydatidiform mole - complete
  - partial
- Invasive hydatidiform mole
- Choriocarcinoma
- Placental site trophoblastic tumour
- Epithelioid trophoblastic tumour



# Hydatidiform mole

gestational age at evacuation

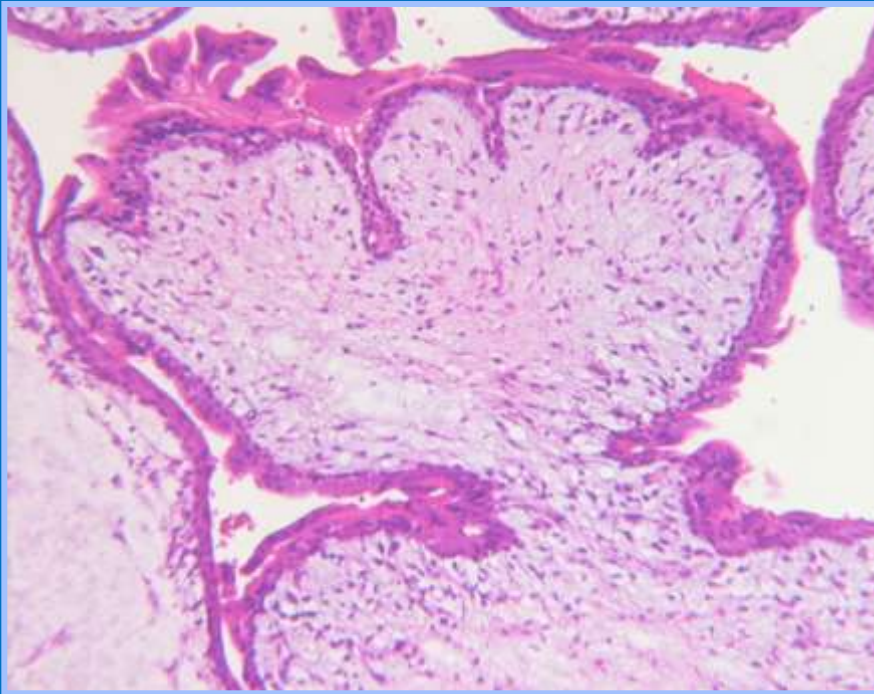
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- **1960s:** 17 weeks

- **2000s:** 9.4 weeks

# Early complete mole

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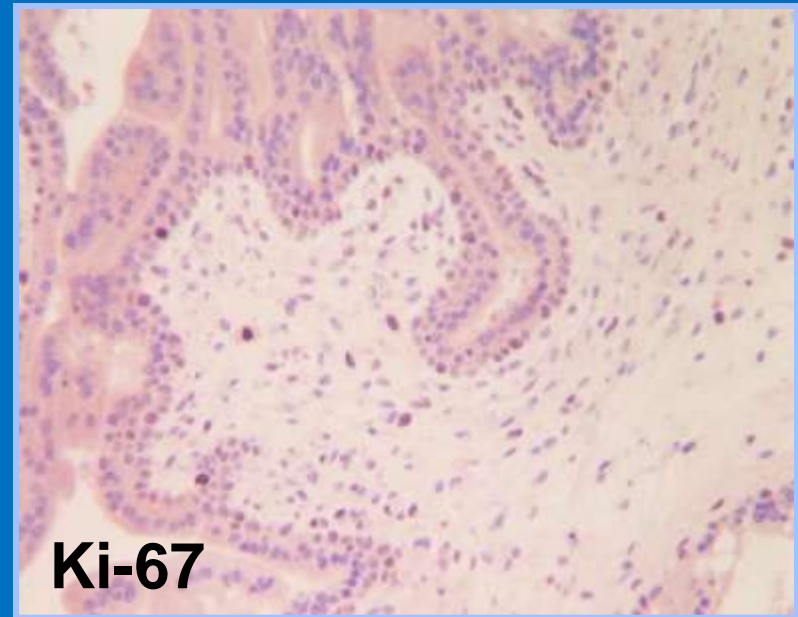
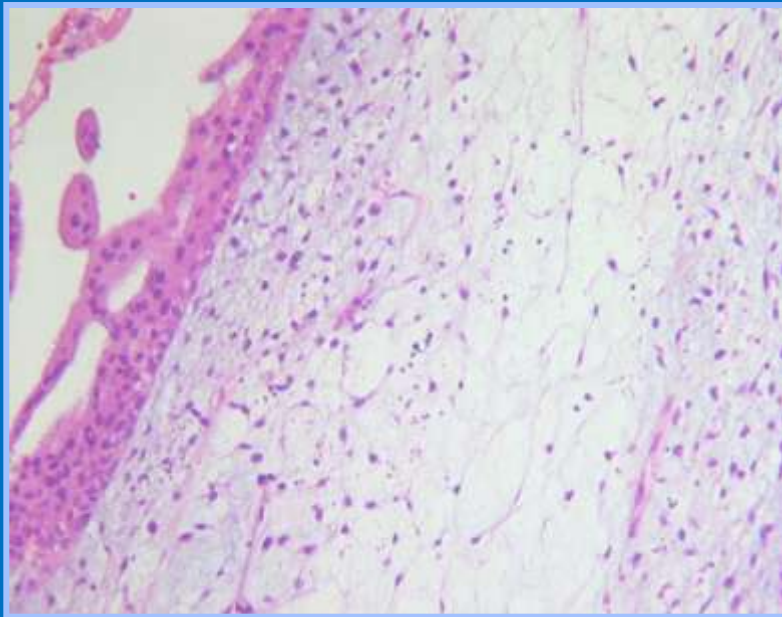


- **abnormally shaped villi**  
- branching or polypoid
- **stromal mucin**
- **stromal vessels may be present**
- **STROMAL NUCLEAR DEBRIS**

# Early complete mole

## Stromal nuclear debris

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**cases of partial mole and hydropic miscarriage exhibit no or inconspicuous karyorrhetic debris**

# Partial mole

- fetal parts may be present
- focal hydropic change
- cistern formation
- irregular profile of villi
- round trophoblastic pseudoinclusions
- excess trophoblast may be subtle
- abnormal (angiomatoid) vasculature in second trimester

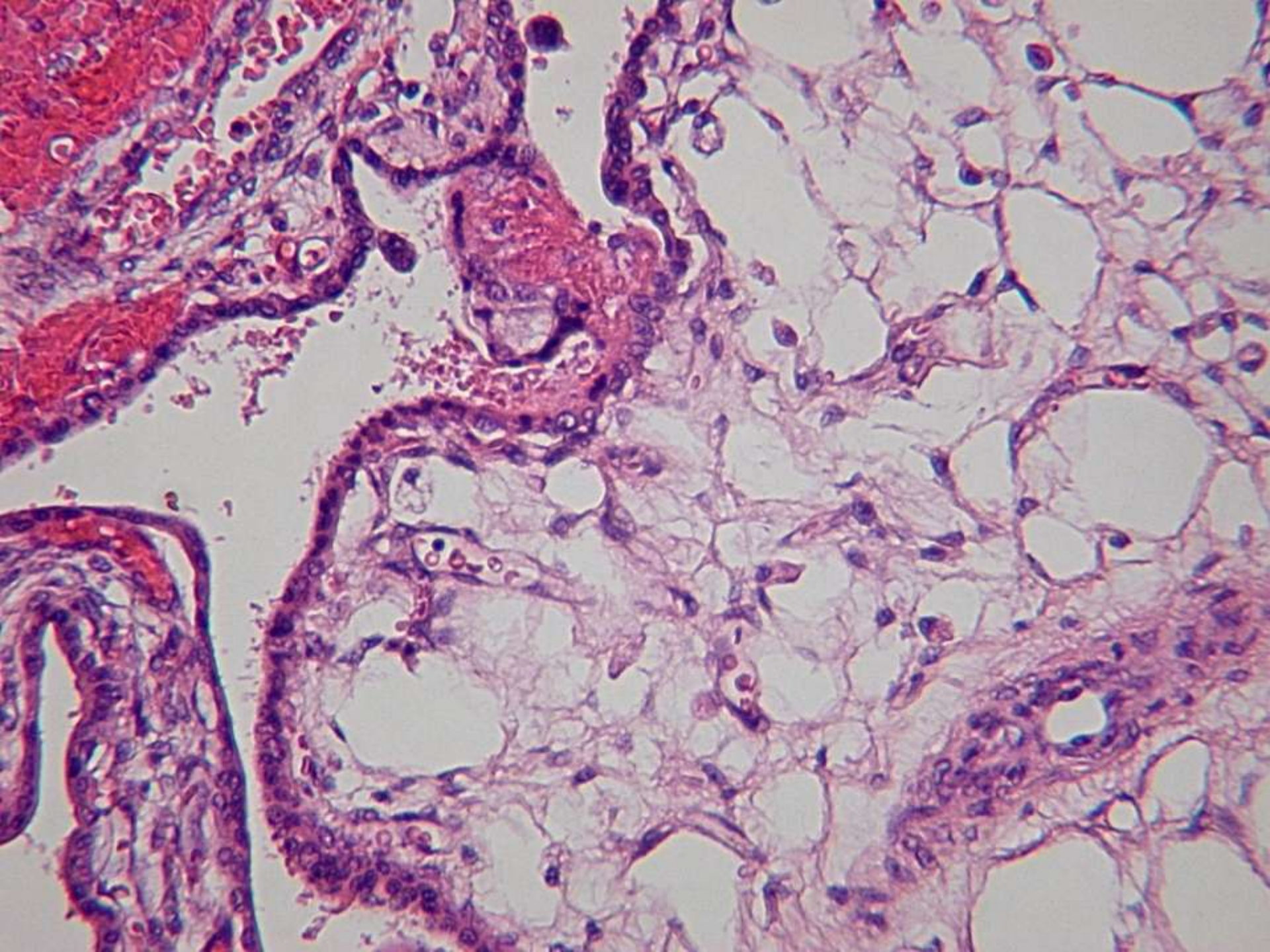


Partial mole



Partial mole



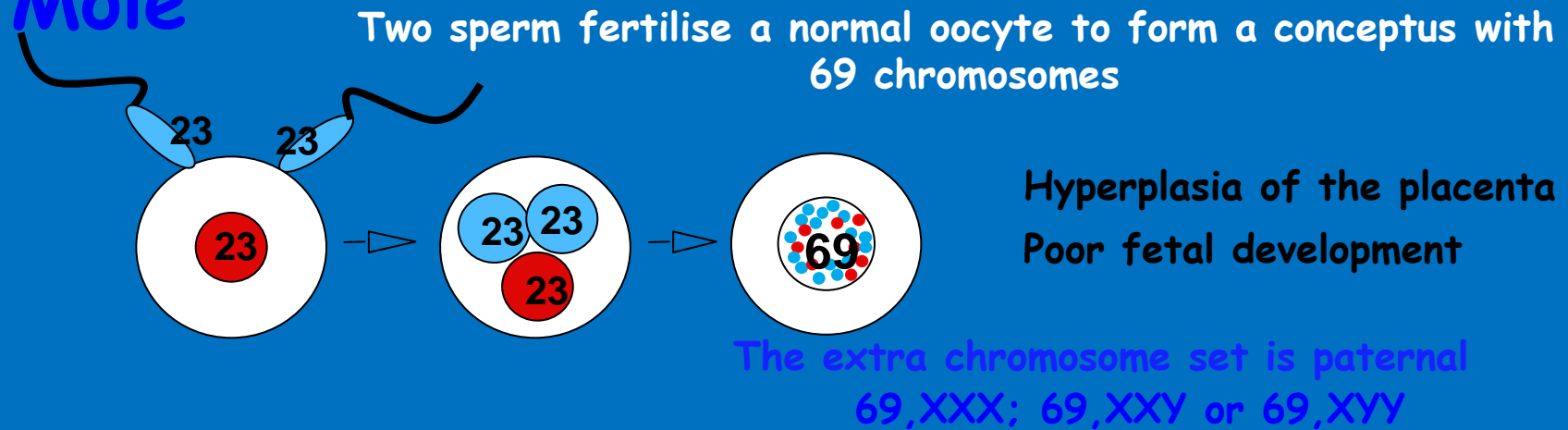


Partial mole  $\nu$  non-molar triploidy –  
pragmatic approach to diagnosis  
(4-14% of hydropic miscarriages - non-molar  
triploid)

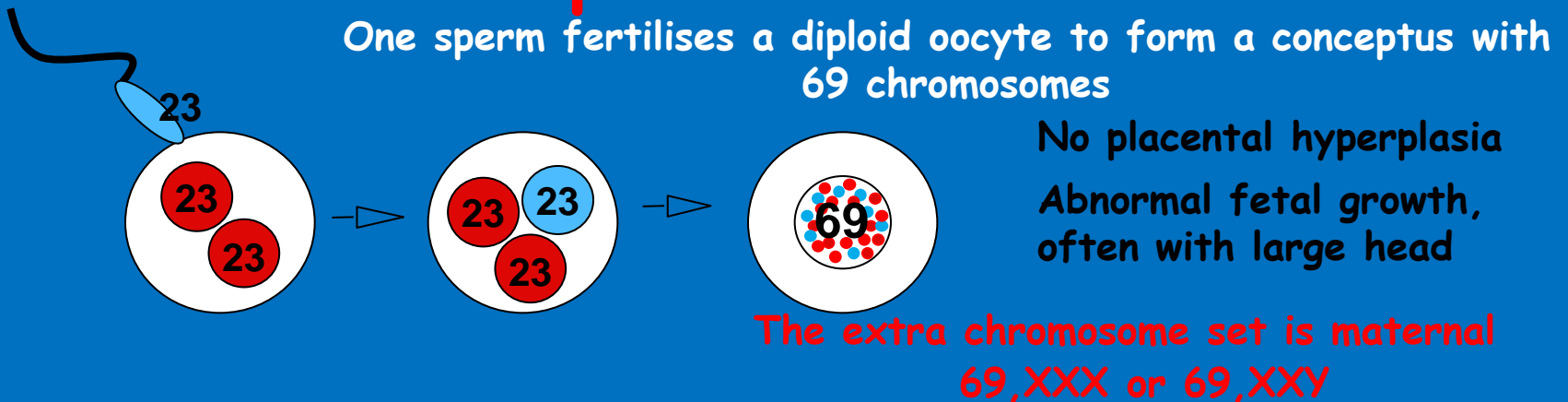
- **partial mole**
- **favour partial mole**
- **possible partial mole/partial mole cannot be excluded**
- **non-molar**

# Genetic Origin of Triploid Conceptions

## Partial Mole



## Non-Molar Triploid



Histogram Draftsman  
 File Options Graph Plot Stats Windows About  
 File State Graph Misc.

**View** Cell Display

Select Gallery

- Gallery 1 001
- Gallery 2 14
- Gallery 3 0
- Gallery 4 5
- Gallery 5 0
- Gallery 6 0
- Selection Gallery

Gallery Page Navigation

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Analysis

View Mask Line Sort Nuclei

Cell Deletion

Delete Cells Clear Selection

Move Marked Cells to Gallery

View Histogram Exit

Ploidy Distribution (IOD)

**Diploid complete mole**

IOD Class	Number of Nuclei
1020	360
4050	60
8090	0
160	0
320	0

User Name: Fairfield No. of Cells Not Shown 0 0 0 0 0 0

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Histogram Draftsman

File Options Graph Plot Stats Windows About

File State Graph Msc.

View Cell Display

Select Gallery

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- Gallery 2 16
- Gallery 3 0
- Gallery 4 0
- Gallery 5 0
- Gallery 6 0
- Selection Gallery

Gallery Page Navigation

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Analysis

View Mask Line Sort Nuclei

Cell Deletion

Delete Cells Clear Selection

Move Marked Cells to Gallery

View Histogram Exit

Ploidy Distribution (IOD)

**Triploid partial mole**

IOD Class	Number of Nuclei
10-20	~65
20-30	~165
30-40	~170
40-50	~170
50-60	~5
60-70	~5
70-80	~5
80-90	~5
90-100	~5
100-110	~5
110-120	~5
120-130	~5
130-140	~5
140-150	~5
150-160	~5

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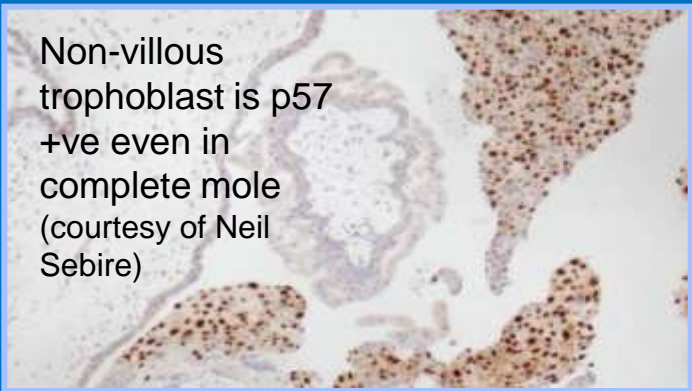
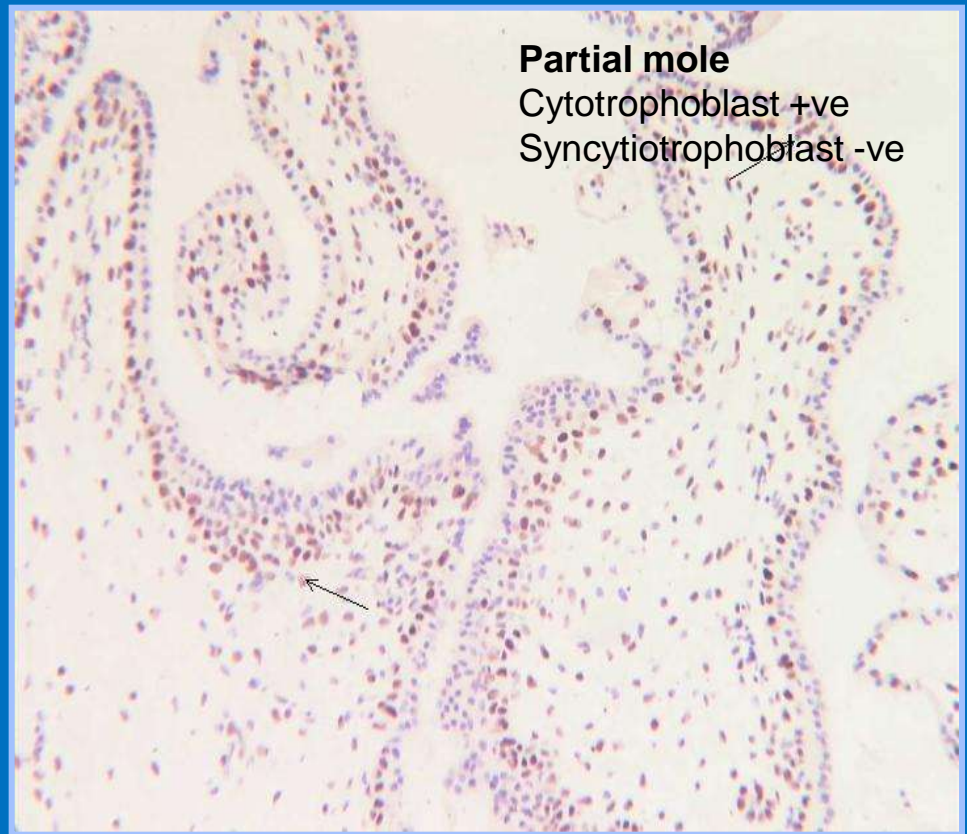
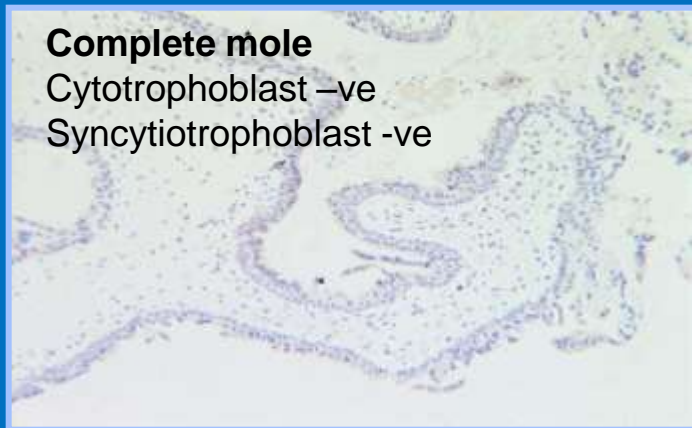
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# P57<sup>kip2</sup>

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- paternally imprinted gene
- maternally expressed
- villous cytotrophoblast p57<sup>kip2</sup> -ve in CM
- villous cytotrophoblast p57<sup>kip2</sup> +ve in PM
- syncytiotrophoblast always p57<sup>kip2</sup> -ve

# P57<sup>kip2</sup> in hydatidiform mole





## Refining the diagnosis of hydatidiform mole: image ploidy analysis and p57<sup>KIP2</sup> immunohistochemistry

H Crisp, J L Burton, R Stewart & M Wells

*Academic Unit of Pathology, Division of Genomic Medicine, University of Sheffield Medical School, Sheffield, UK*

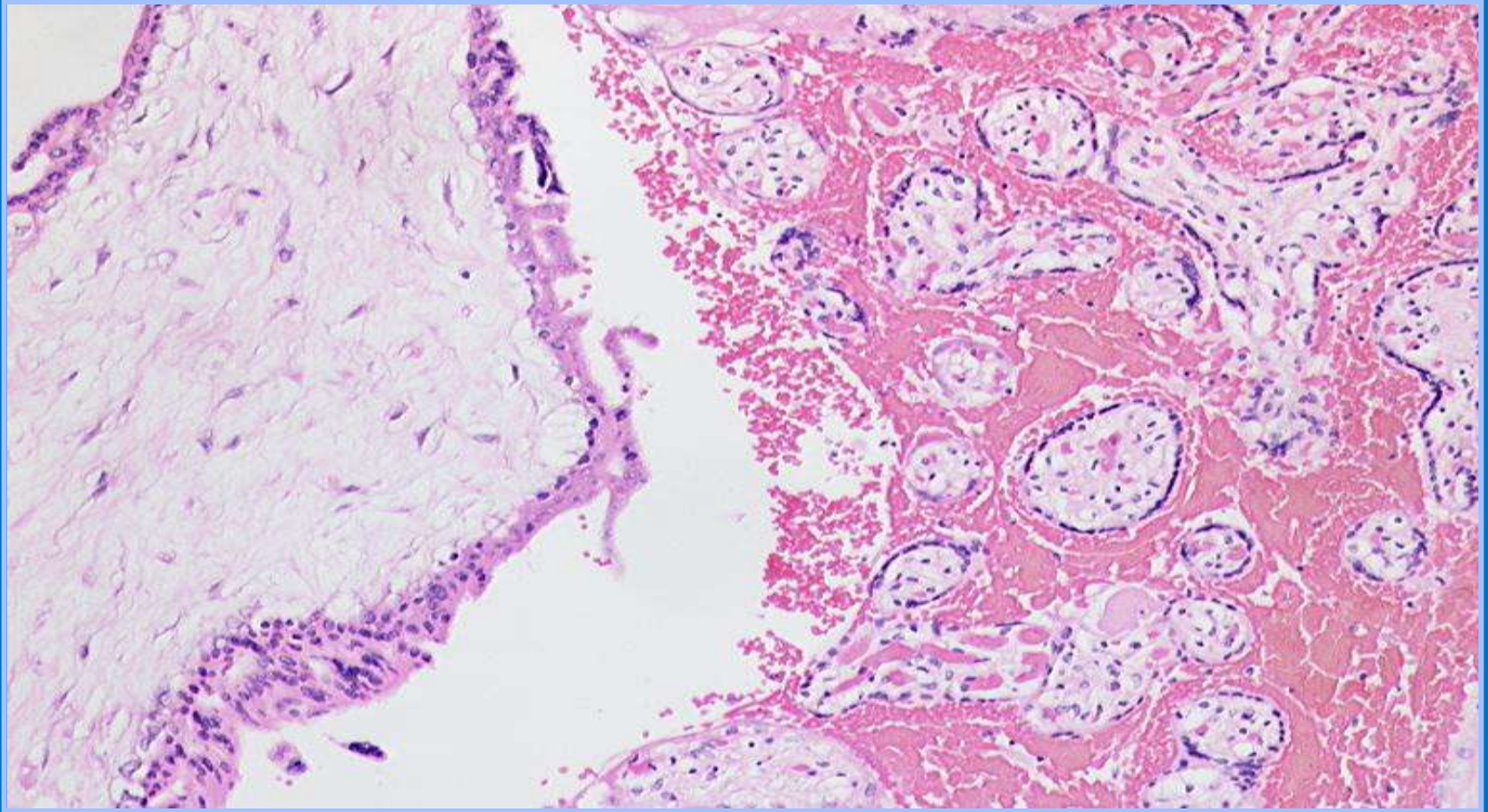
Date of submission 13 February 2003  
Accepted for publication 28 May 2003

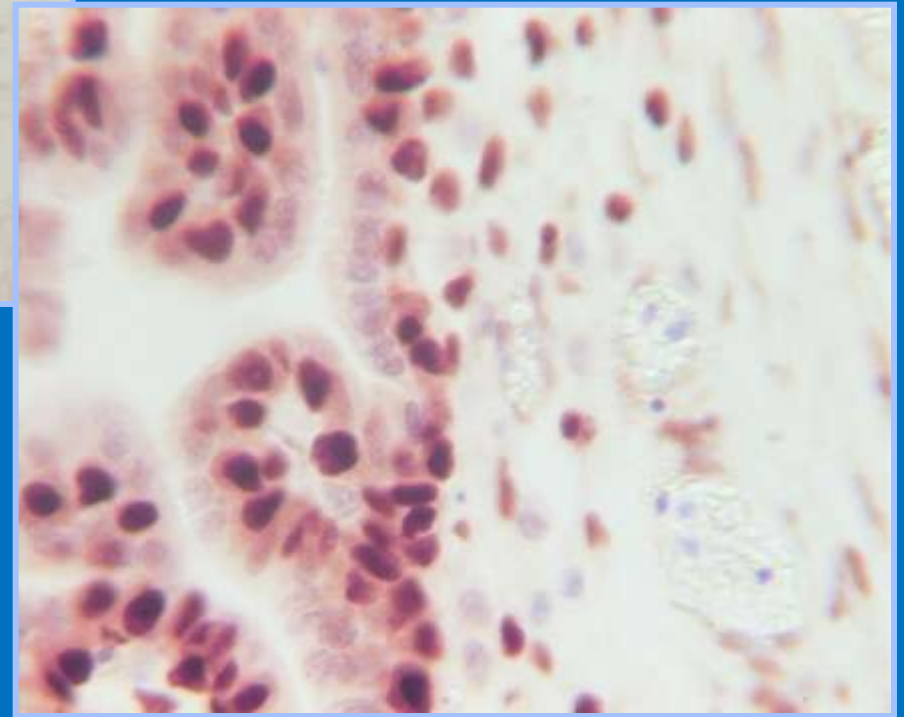
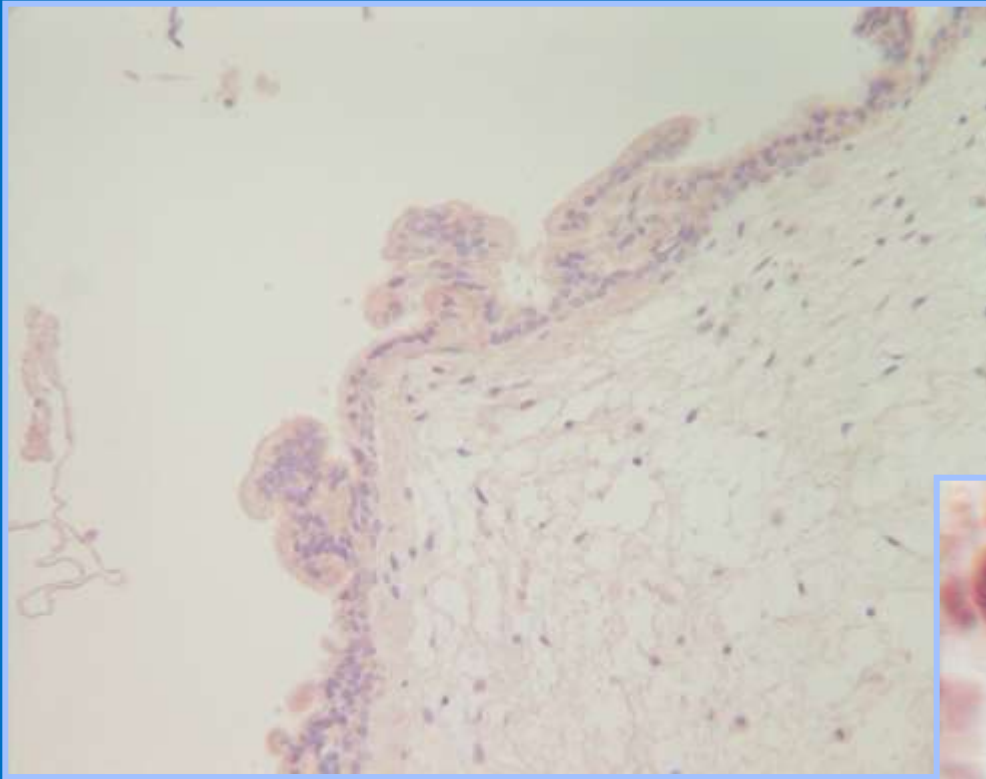
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<b>Suspected diagnosis</b>	<b>Image cytometry</b>	<b>p57<sup>KIP2</sup> status</b>	<b>Revised diagnosis</b>
Partial mole	Triploid	+ve	Partial mole
Complete mole	Triploid	+ve	Partial mole
Partial mole	Diploid	-ve	Complete mole
Partial mole	Diploid	+ve	Hydropic miscarriage

# Complete mole in twin pregnancy

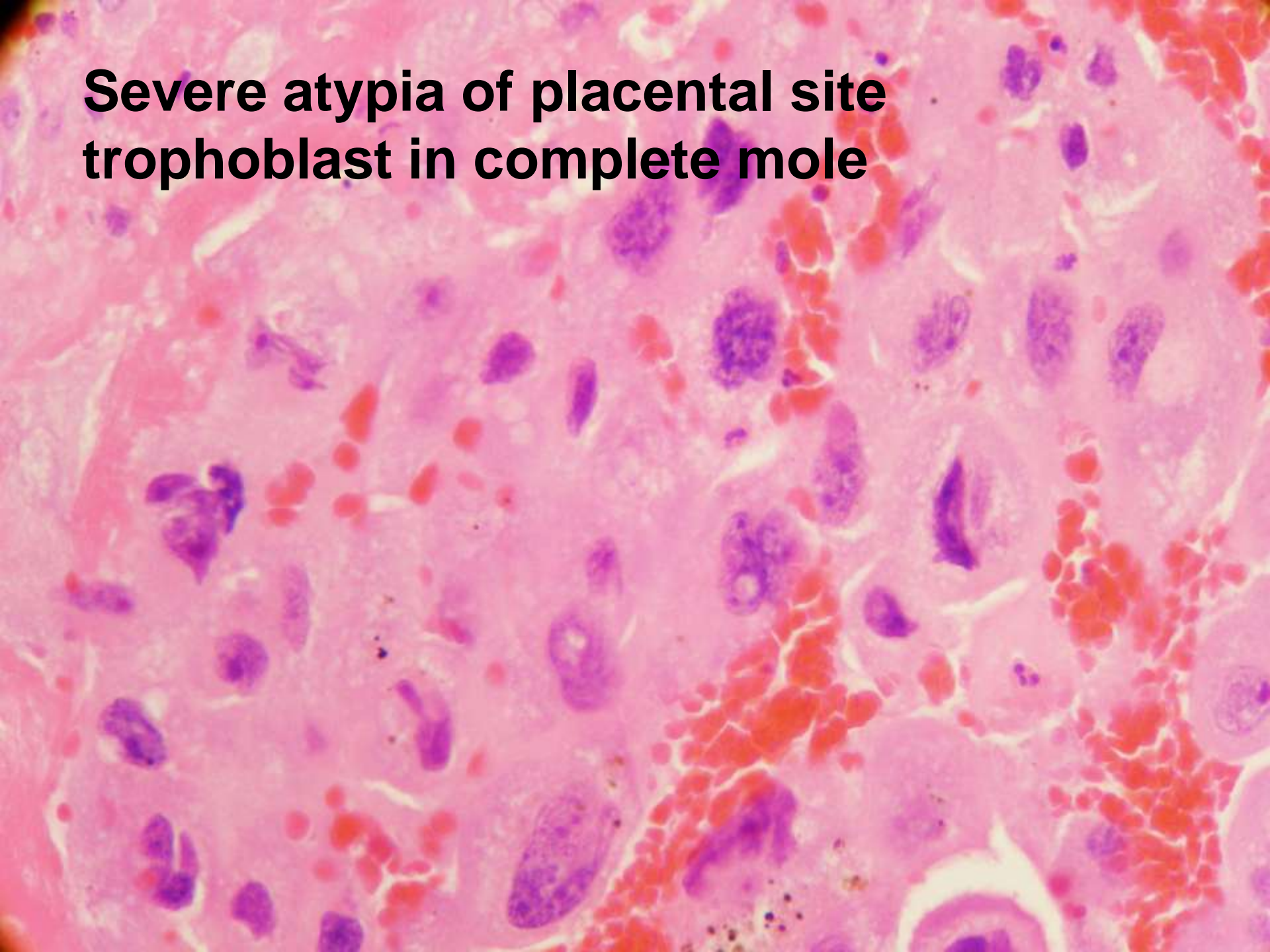
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**Sections stained with P57<sup>(KIP2)</sup> showing negative staining for the complete mole (above) and positive staining for normal placental tissue (right)**

**Severe atypia of placental site trophoblast in complete mole**



# Persistent trophoblastic disease = gestational trophoblastic neoplasia (WHO) not a histopathological diagnosis

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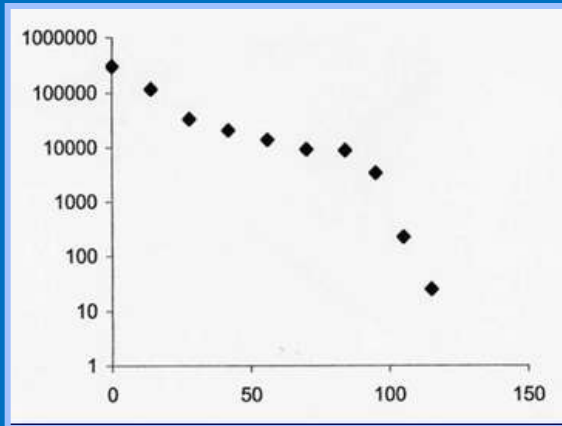
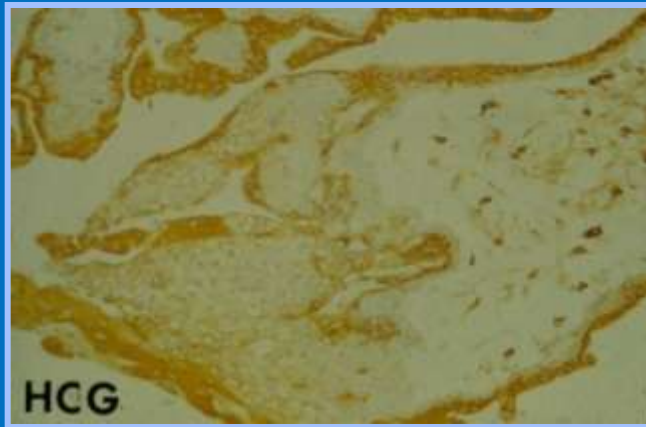
- 15% of patients with complete mole
- 0.5% of patients with partial mole
- majority are invasive moles
- choriocarcinoma

FIGO RISK SCORING	0	1	2	4
Age	< 40	≥ 40	-	-
Antecedent pregnancy	Mole	Abortion	Term	-
Interval months from index pregnancy	< 4	4 - < 7	7 - < 13	≥ 13
Pre-treatment serum hCG (IU/L)	< 10 <sup>3</sup>	10 <sup>3</sup> - < 10 <sup>4</sup>	10 <sup>4</sup> - < 10 <sup>5</sup>	≥ 10 <sup>5</sup>
Largest tumour size (including uterus) cm	< 3	3 - < 5	≥ 5	-
Site of metastases	Lung	Spleen, kidney	Gastro-intestinal	Liver, brain
Number of metastases	-	1-4	5-8	> 8
Previous failed chemotherapy	-	-	Single drug	2 or more drugs

# hCG monitoring of GTD

## Criteria for chemotherapy

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- static or rising hCG after 2nd/3rd uterine evacuation
- hCG >20,000iu after 2nd/3rd uterine evacuation
- persistent uterine haemorrhage with raised hCG
- persistent elevation of hCG 6 months post-uterine evacuation
- pulmonary metastases with static or rising **hCG**





# Hydatidiform mole - predictive factors for PTD (GTN)

- ↑ telomerase activity
- ↓ apoptotic indices (TUNEL & M30 CytoDeath antibody)
- ↑ *Mcl-1* (anti-apoptotic gene)
- ↓ ferritin light polypeptide & IGFBP-1

Cheung *et al*

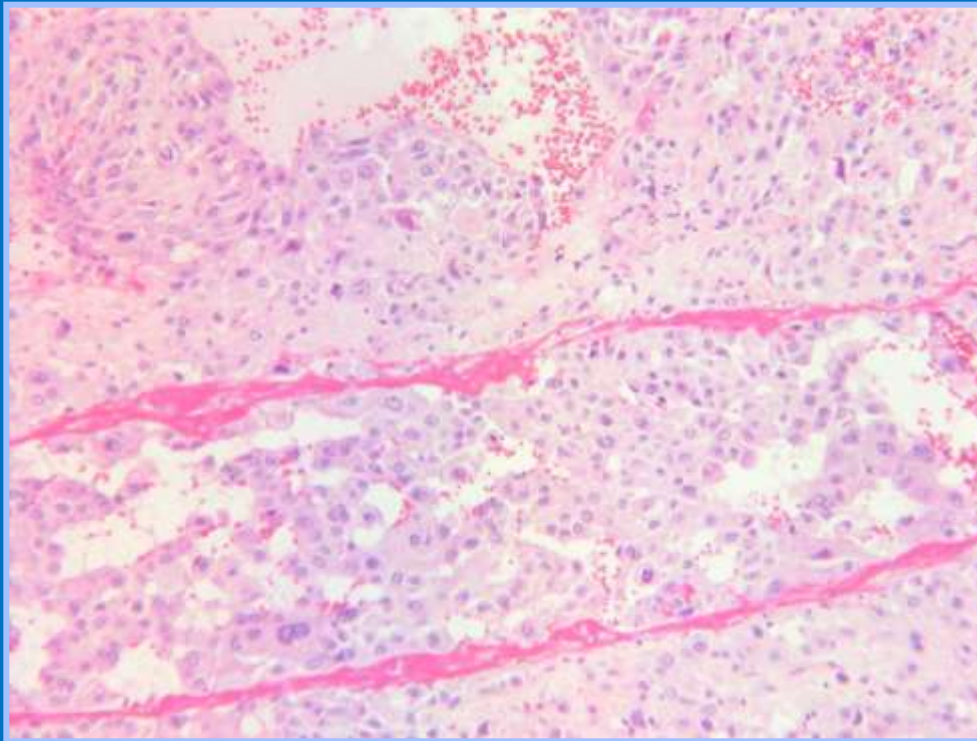
# Placental site trophoblastic tumour

- weeks to years after pregnancy
- average interval 18-30 months
- invasive uterine mass (mean - 5cms diameter)
- paternal allele present
- absence of Y chromosome



## Placental site trophoblastic tumour mirrors properties of normal non-villous trophoblast (extravillous or intermediate trophoblast)

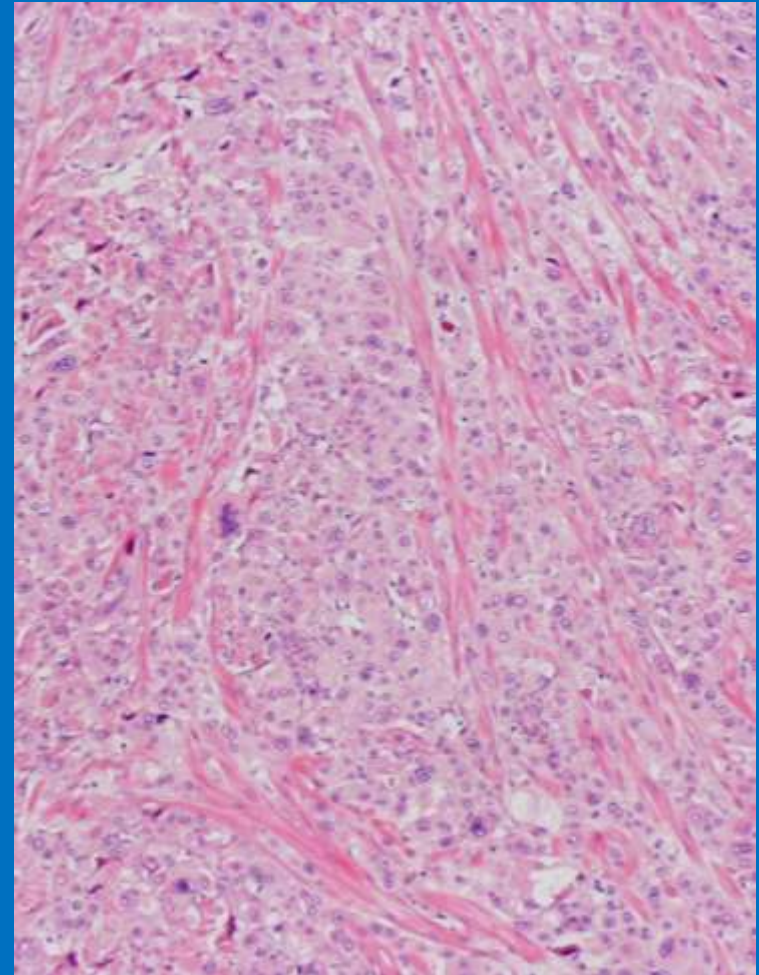
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- occasional binucleate /multinucleate cells
- myometrial infiltration
- intravascular tumour
- fibrinoid necrosis in vessel wall

# Placental site trophoblastic tumour

- cords, islands, sheets of polygonal, round or spindle cells
- scattered mitoses
- Ki67 > 5%
- hPL, PLAP, inhibin +ve
- focal hCG +ve
- p63 - ve



# PSTT

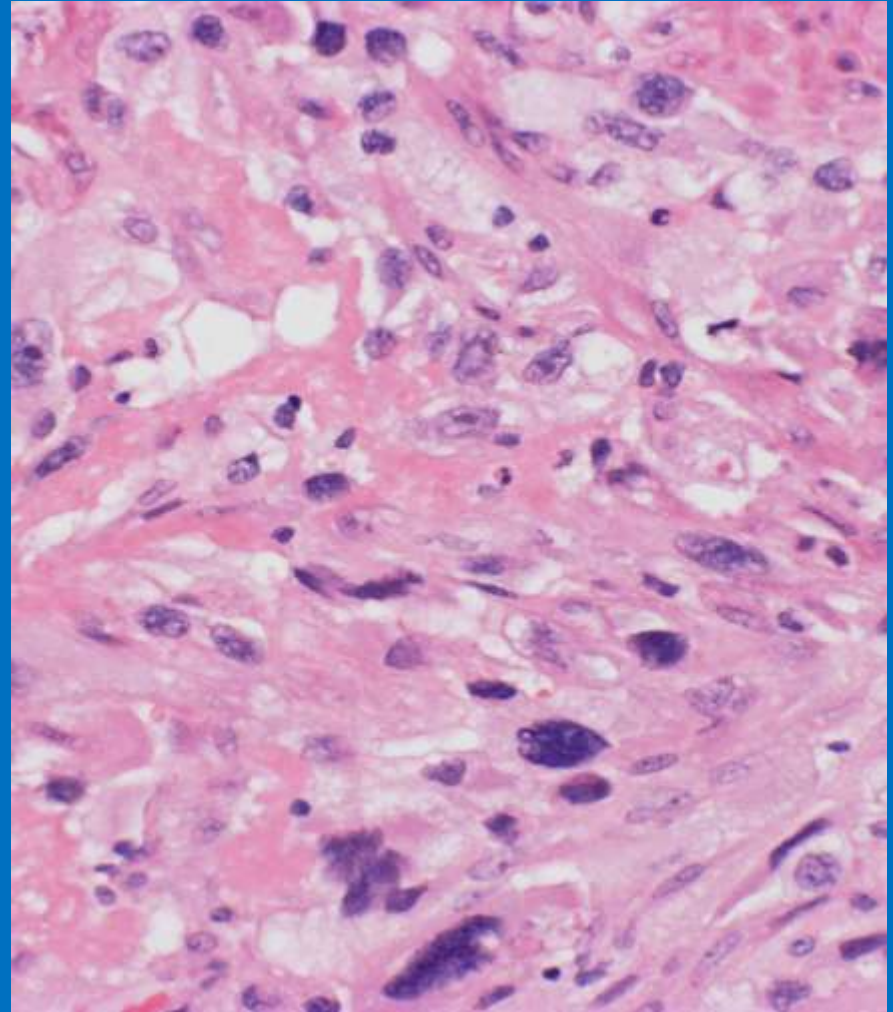
## Compared to Choriocarcinoma

- Slow growing
- Late metastases
- Lymph node involvement more common
- Less chemosensitive
- Less hCG

# Placental site trophoblastic tumour factors associated with poor prognosis

(Baergen et al Gynecol Oncol 2006; 100: 511-520)

- deep invasion
- clear cells
- extensive necrosis
- mitoses+





# PSTT Methods

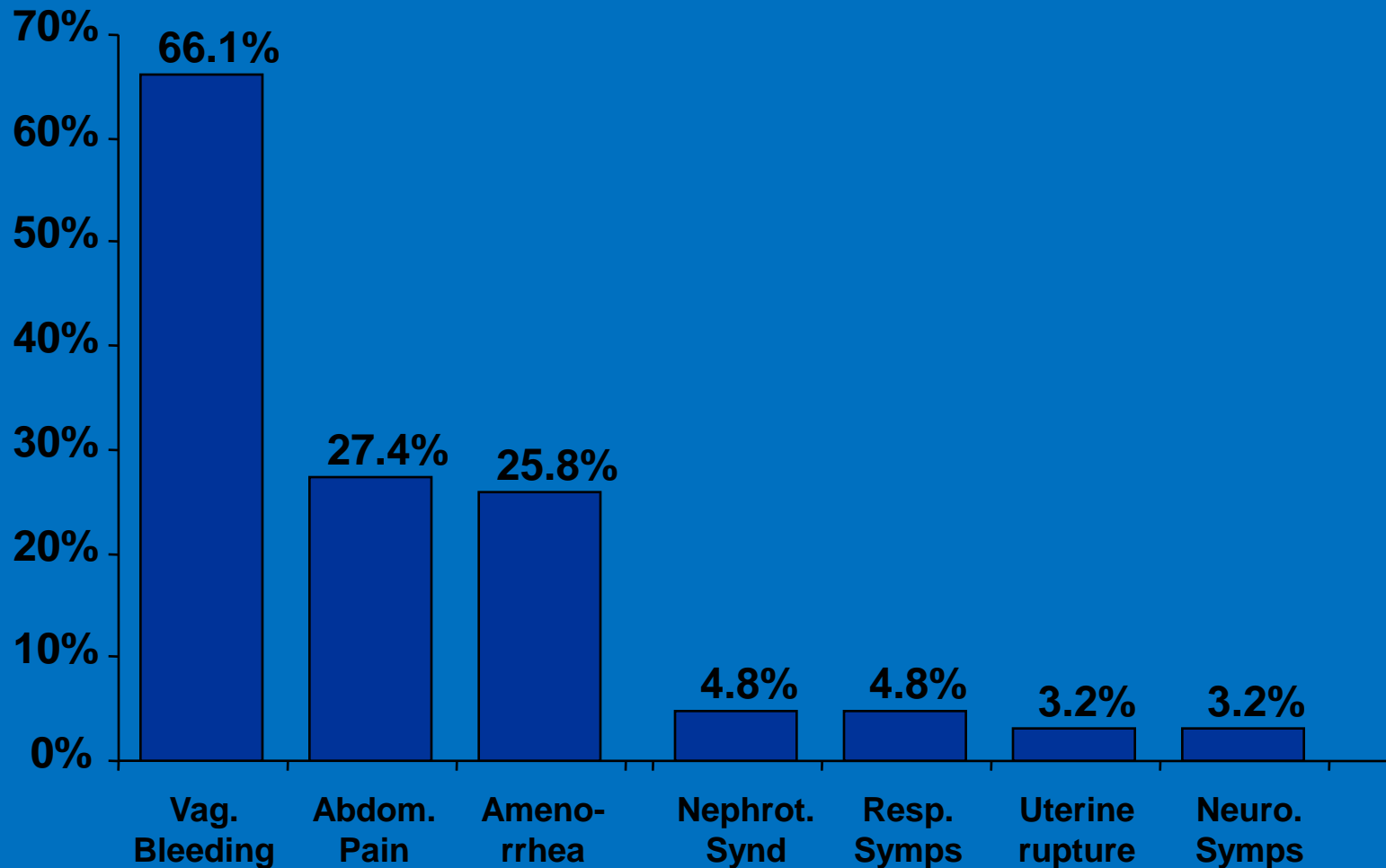
- Retrospective study:
    - 62 patients with PSTT
    - Evaluated and/or treated between 1975 and 2006 in the UK GTD service (35,550 women registered)
    - Pathology centrally reviewed
- Schmid et al Lancet 2009; 374: 48-55



# PSST Patient Characteristics

<b>Characteristic</b>	<b>No. of patients</b>	<b>(%)</b>
<b>Age, years</b>		
Median	34.6	
Range	20-54	
<b>Antecedent Pregnancy</b>		
Complete Mole	8	(13%)
Partial Mole	1	(2%)
Termination	6	(10%)
Miscarriage/Stillbirth	10	(16%)
Term	37	(60%)

# PSST Presenting Symptoms



# PSST Patient Characteristics

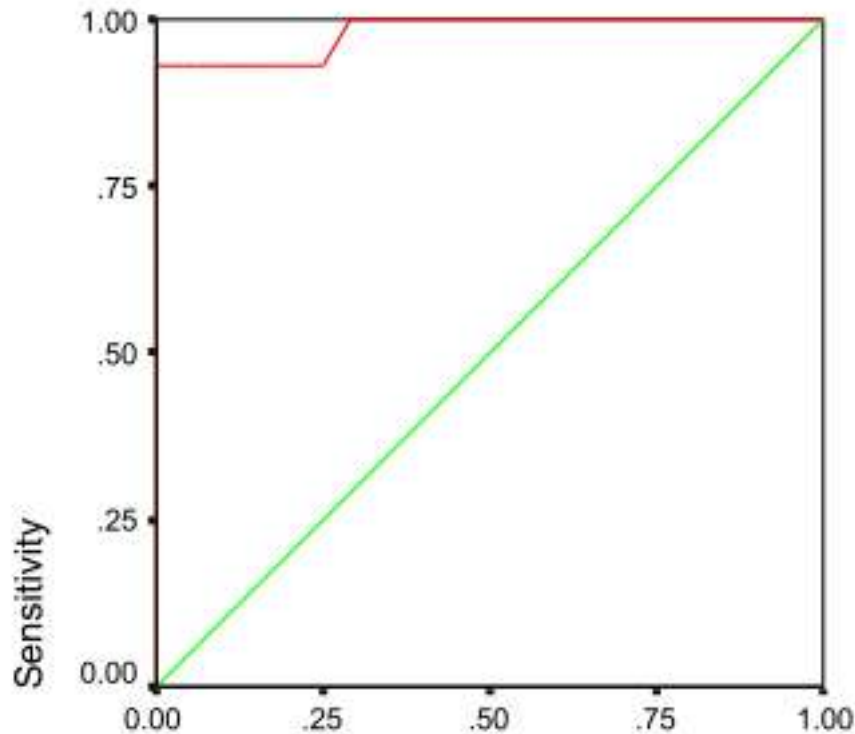
<b>Interval to Antecedent Pregnancy</b>		
Median	18	
Range	2-264	
≤ 12 months	15	(24%)
13-47 months	34	(55%)
≥ 48 months	13	(21%)
<b>Disease manifestation</b>		
No extra-uterine disease	36	(58%)
Uterine and extra-uterine, pelvic disease	5	(8%)
Distant metastases	21	(34%)

# PSST Diagnostic Material

- Diagnosis established following
  - uterine evacuation (n=38, 61%),
  - hysterectomy (n=19, 31%)
  - or tumour biopsy (n=5, 8%).

# 48 months from causative pregnancy is critical

ROC Curve For Interval from antecedent preg



1 - Specificity

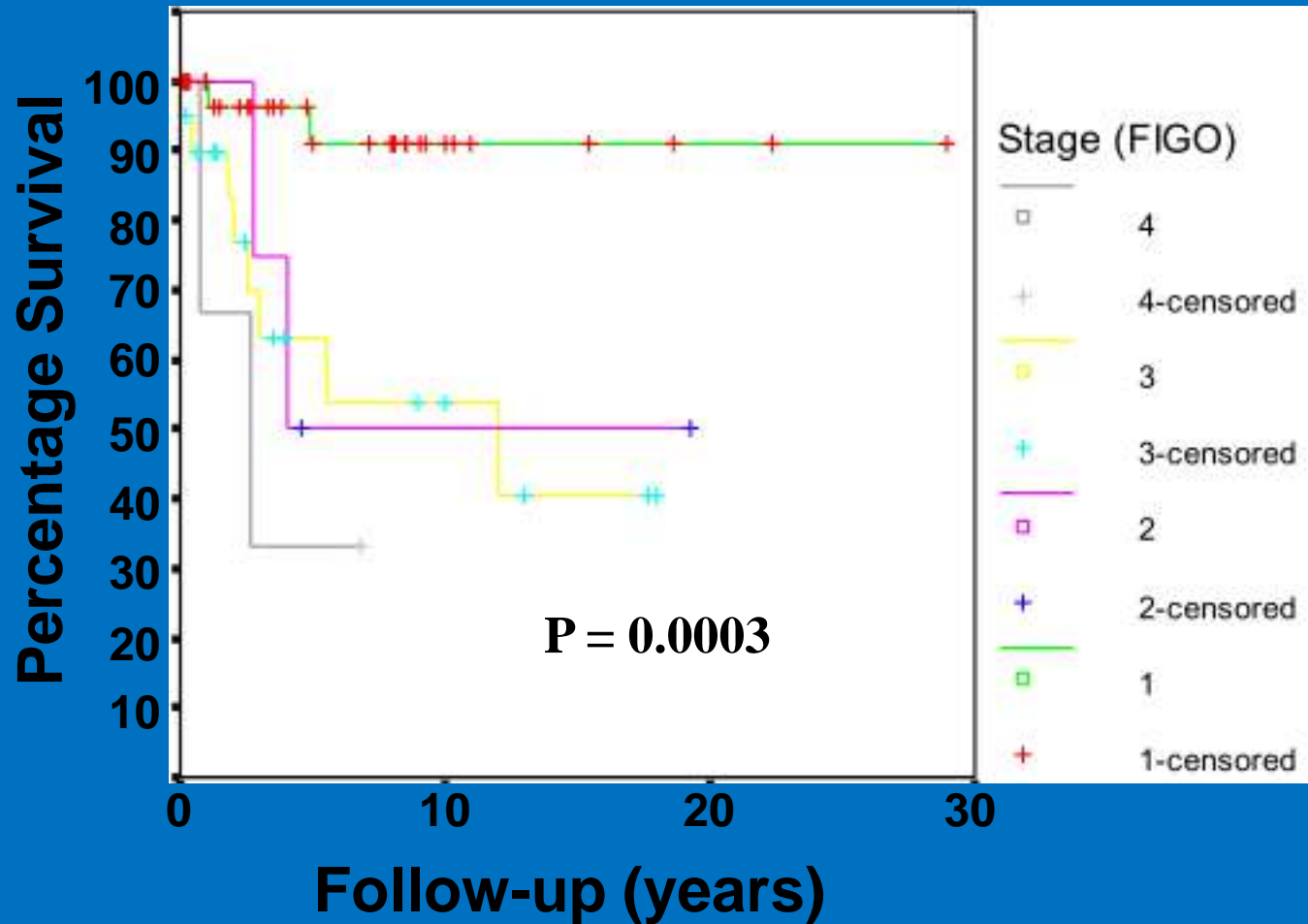
Diagonal segments are produced by ties.

## 48 month cut-off

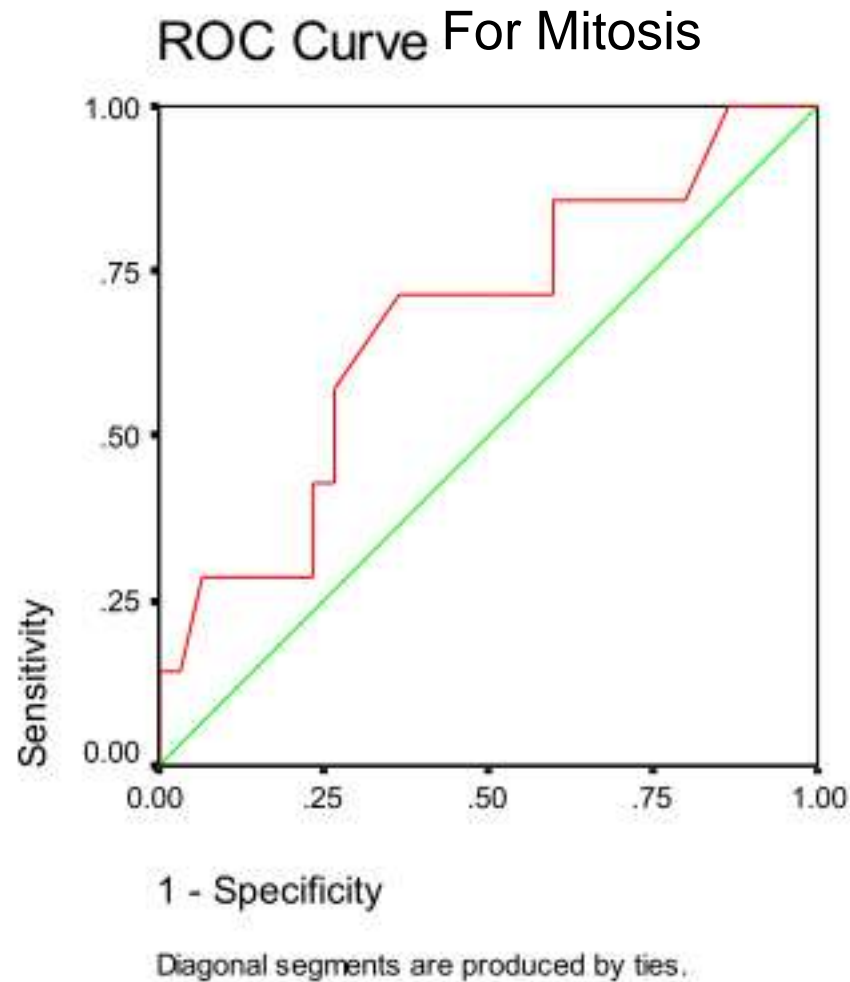
Specificity 100%  
Sensitivity 93%

Time	Dead	OS
< 48	1/49	98%
≥ 48	13/13	0%

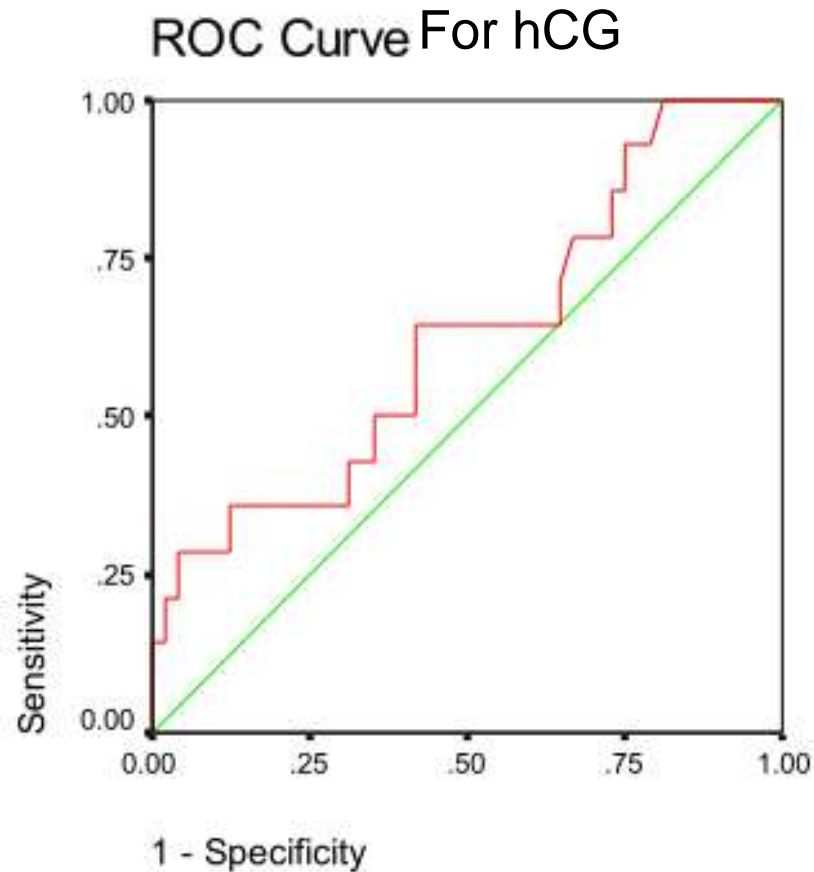
# Stage predicts survival



# Mitosis no clear cut-point



# hCG no clear cut-point



Diagonal segments are produced by ties.



# Univariate analysis

Variable	Significance
Interval $\geq$ 48 months*	$p < 0.00001$
Age $\geq$ 36 yrs	$p < 0.00001$
hCG (continuous)	$p = 0.014$
FIGO Stage	$p = 0.0003$
No of mets	$p = 0.0002$
Mitosis (continuous)	$p = 0.008$

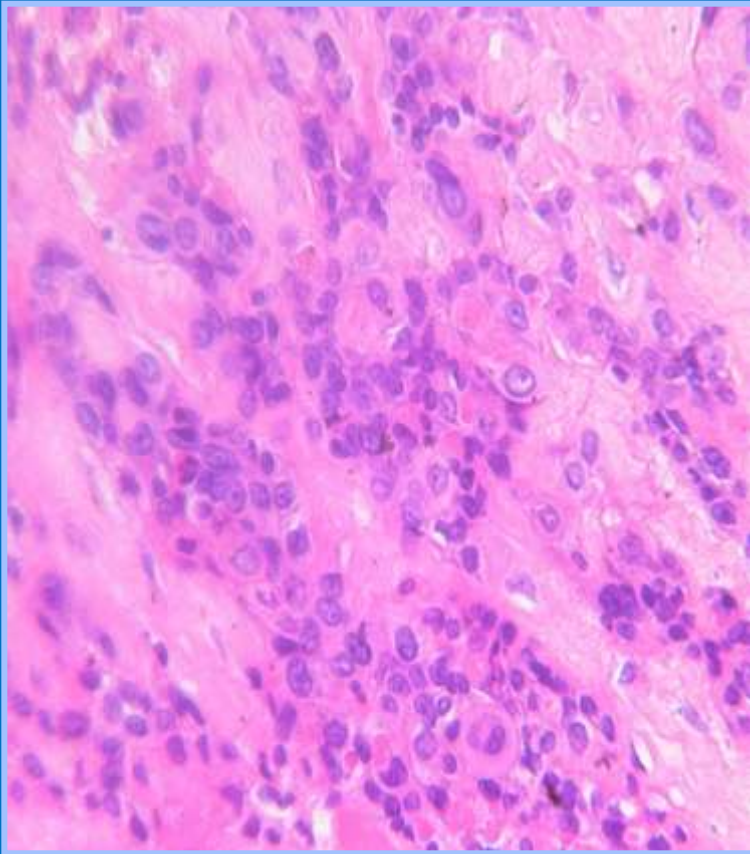
\* remained significant on multivariate analysis

# PSTT

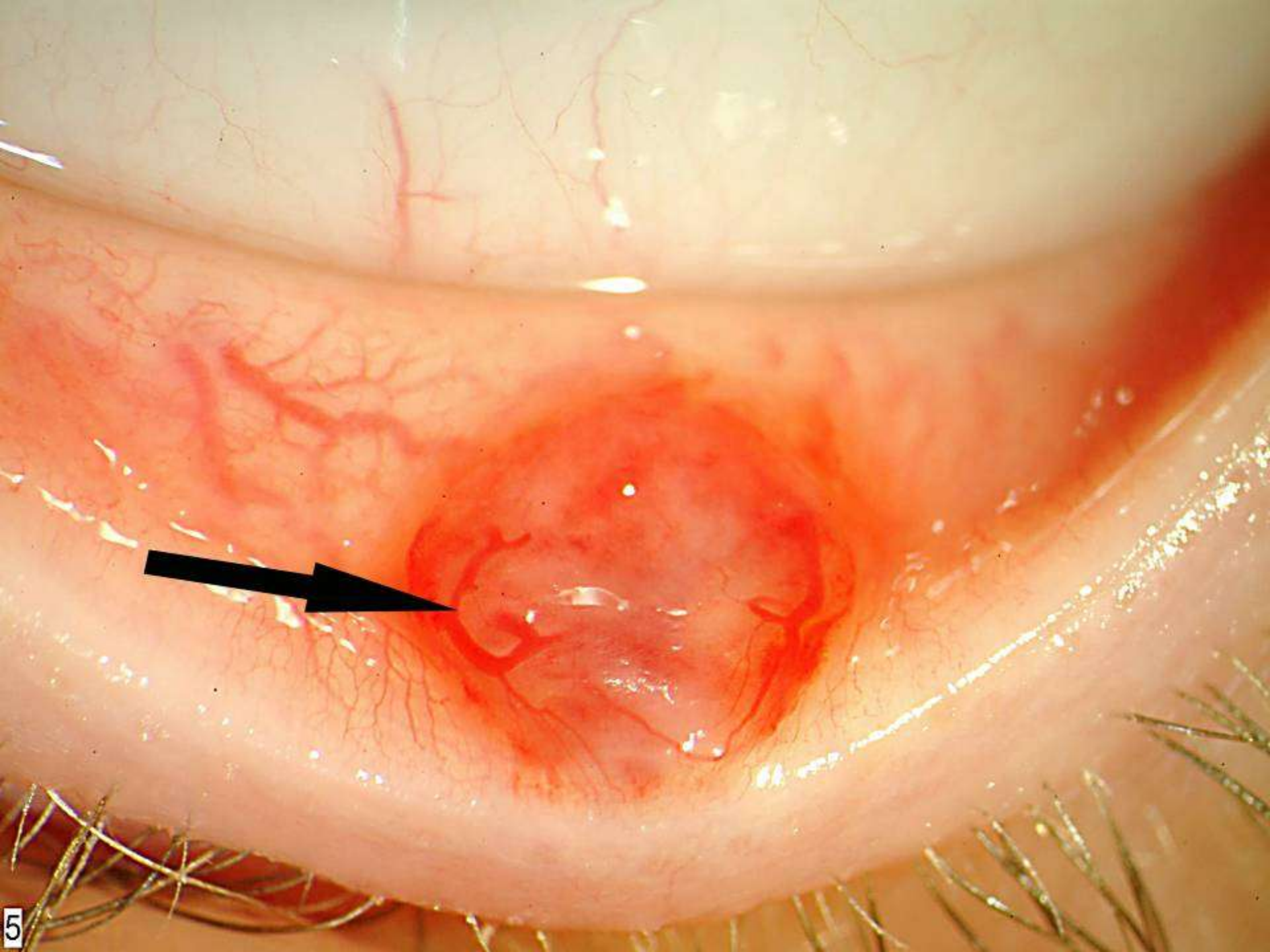
- FIGO risk score – not applicable
- Stage I disease – surgery is sufficient unless there are other risk factors
- Stage II, III & IV – combined surgery and chemotherapy
- Chemotherapy not as effective compared with other forms of GTD
- Why 48 months since antecedent pregnancy is the optimum discriminator for survival is unclear

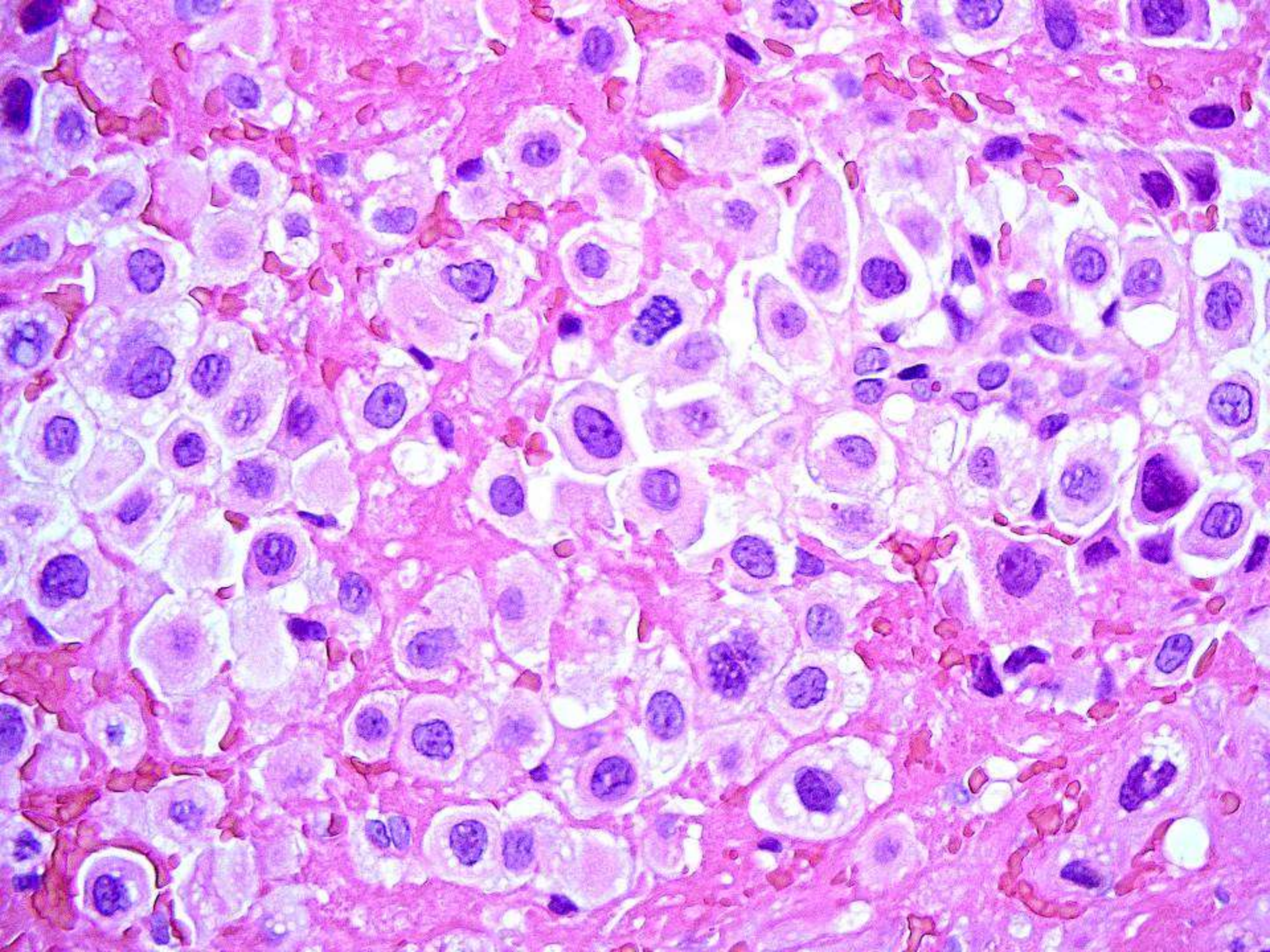
# Epithelioid trophoblastic tumour

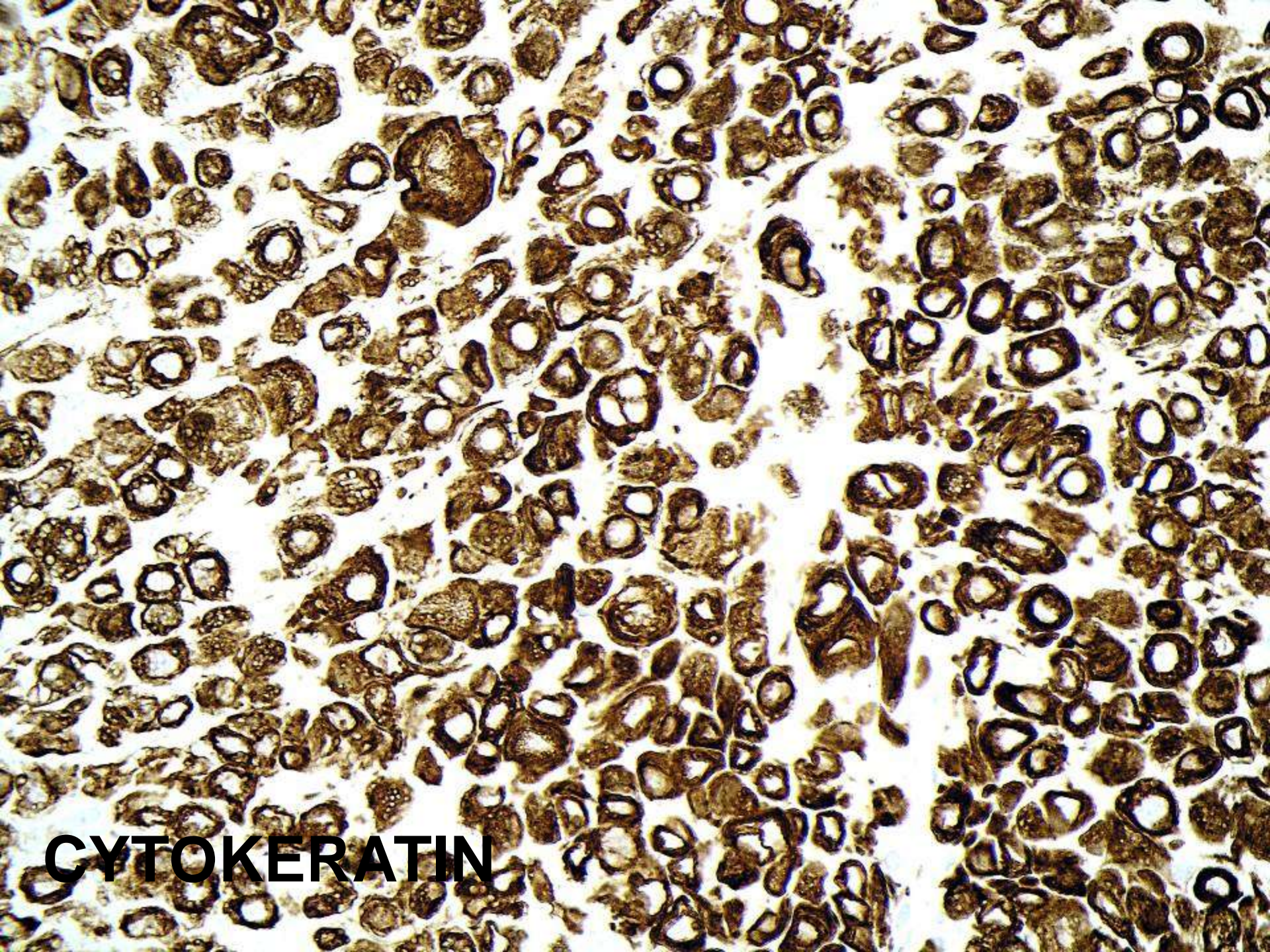
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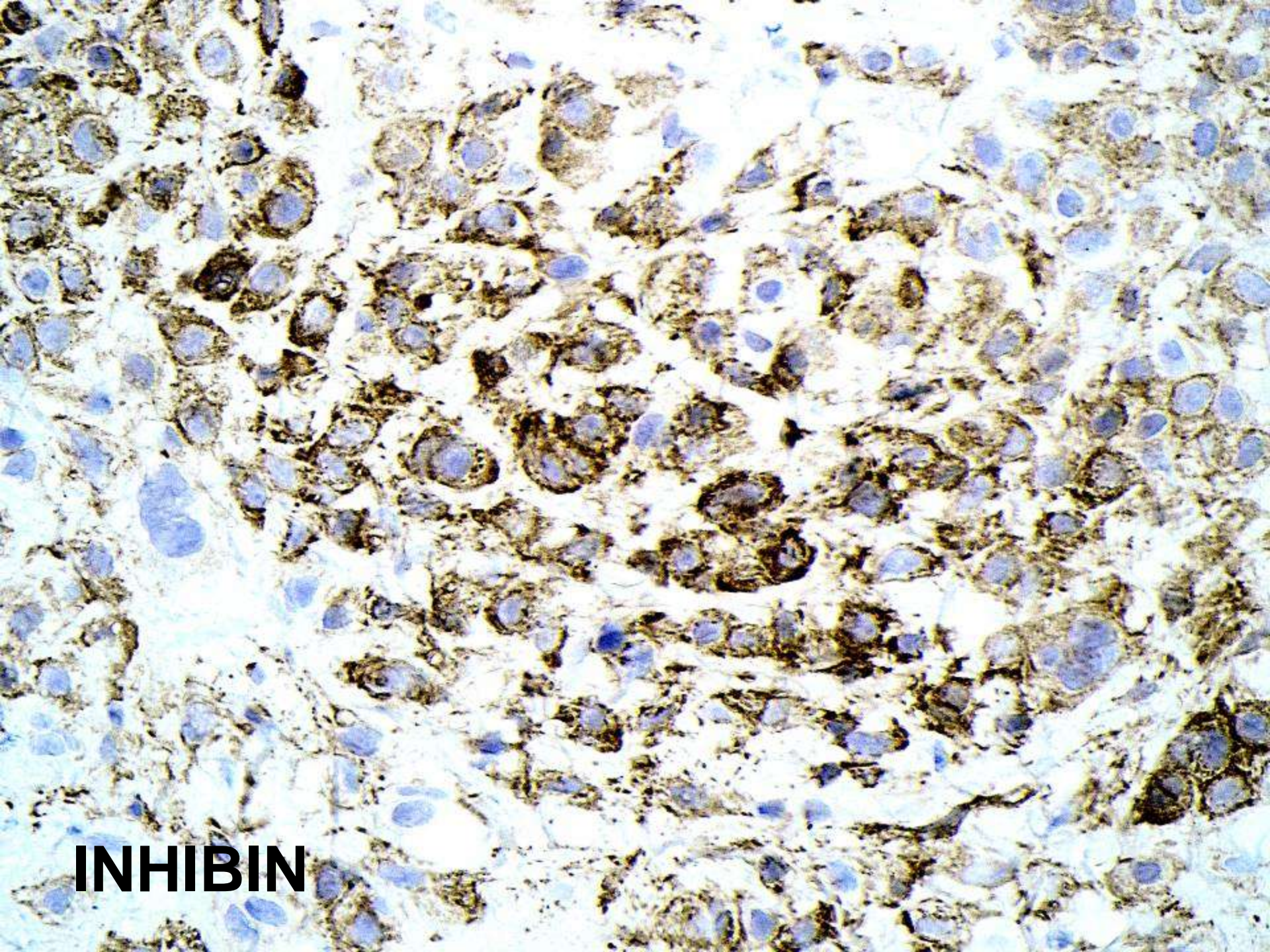
- cells resemble chorion laeve
- nodular islands of trophoblast surrounded by extensive necrosis
- hyaline-like matrix
- cells smaller & less pleomorphic than PSTT
- p63 positive



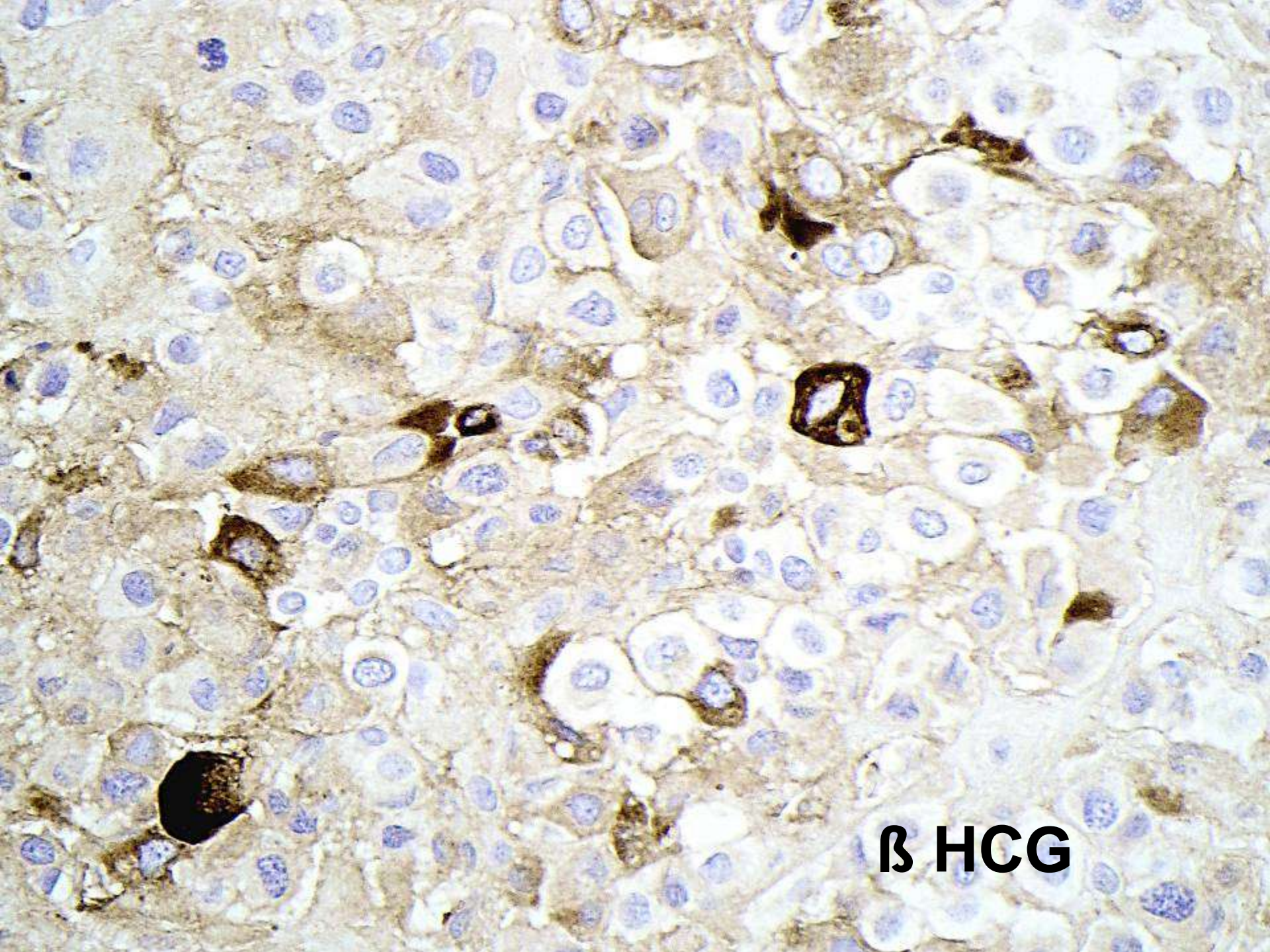




**CYTOKERATIN**



**INHIBIN**

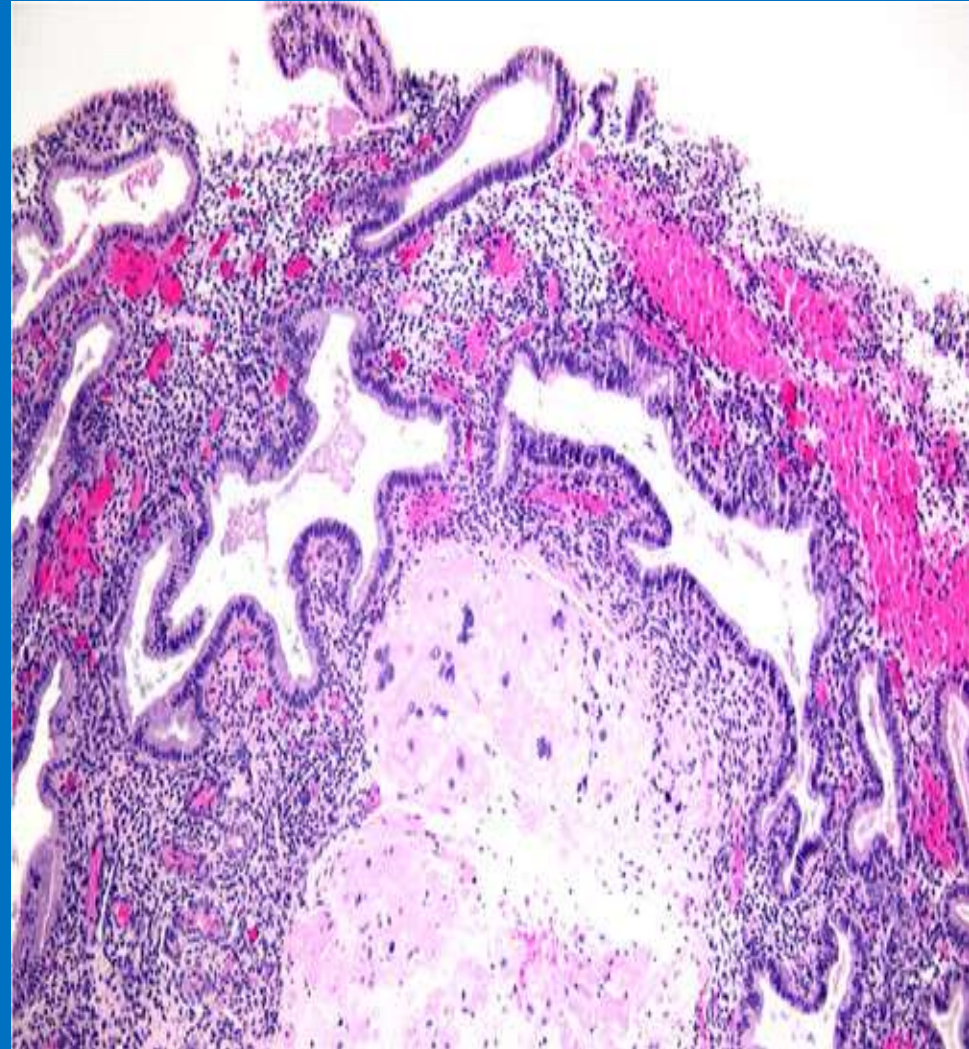


**β HCG**



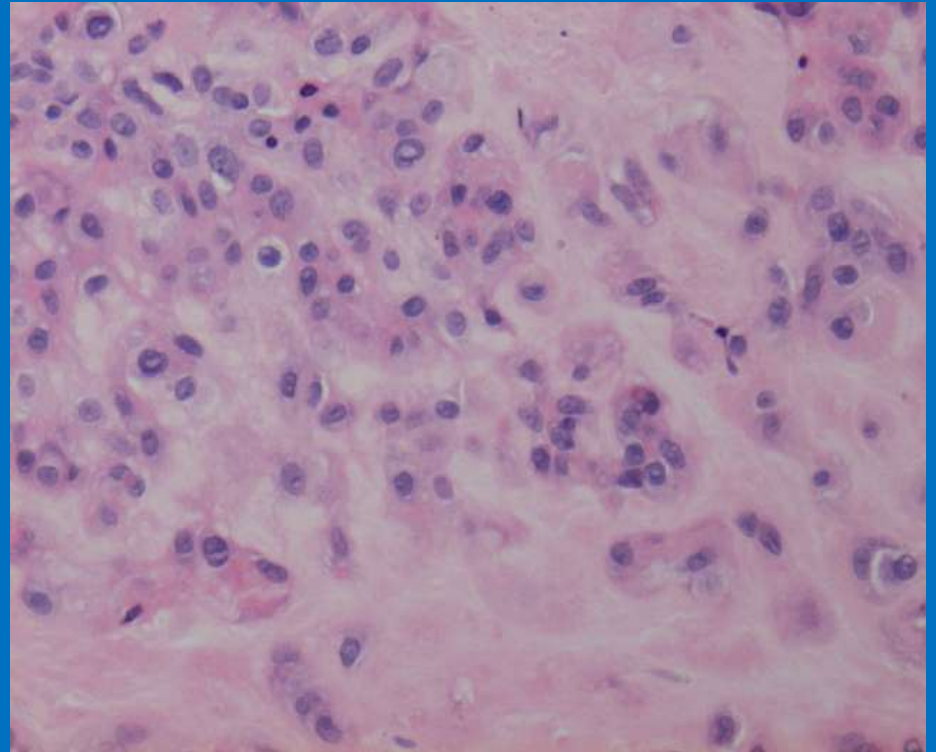
# Placental site nodule

- usually incidental
- months / years post pregnancy
- small, well circumscribed
- hyalinised



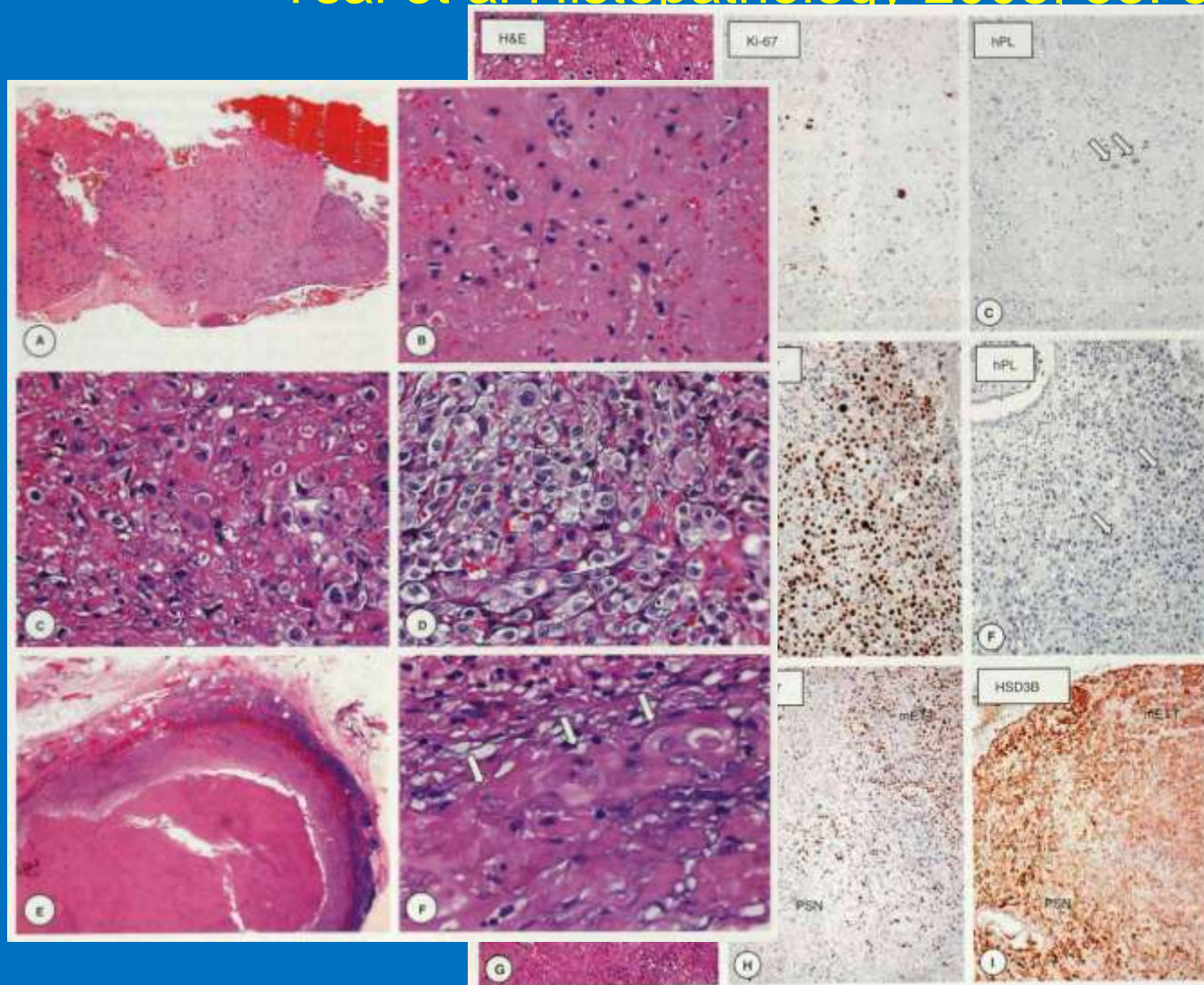
# Placental site nodule

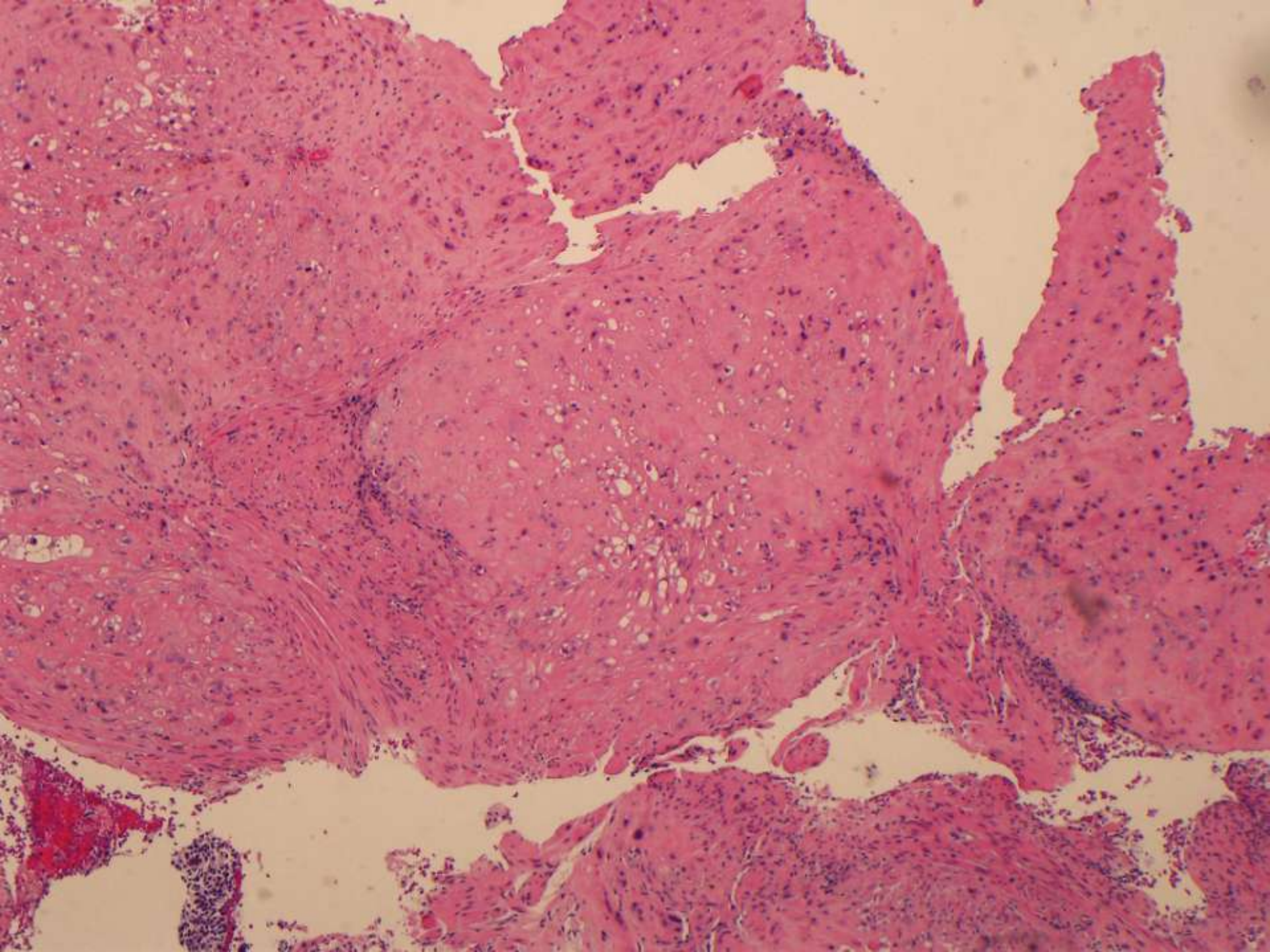
- single cells, clusters or cords of bland, uniform cells
- no infiltration
- no mitoses
- Ki67 < 5%

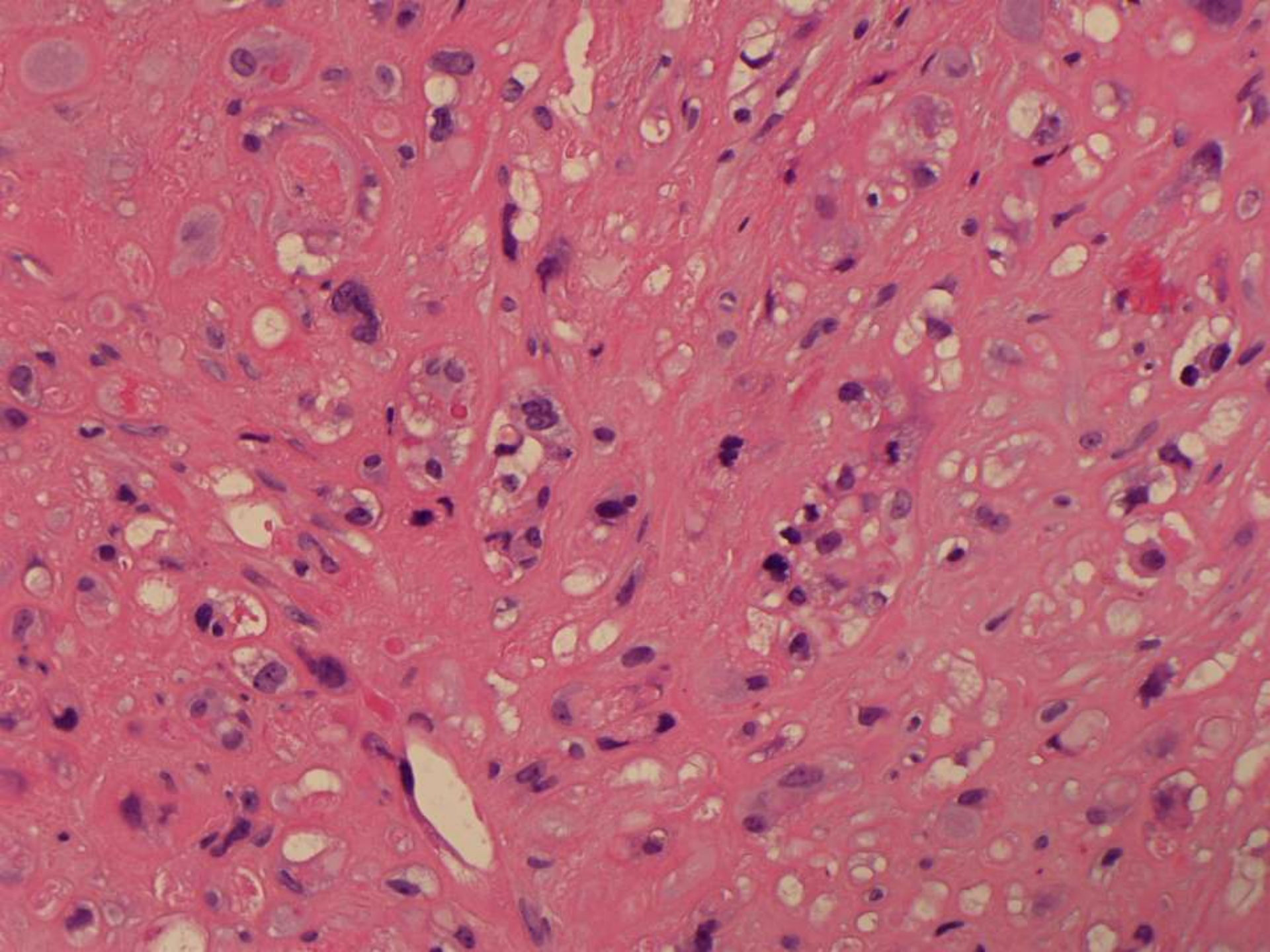


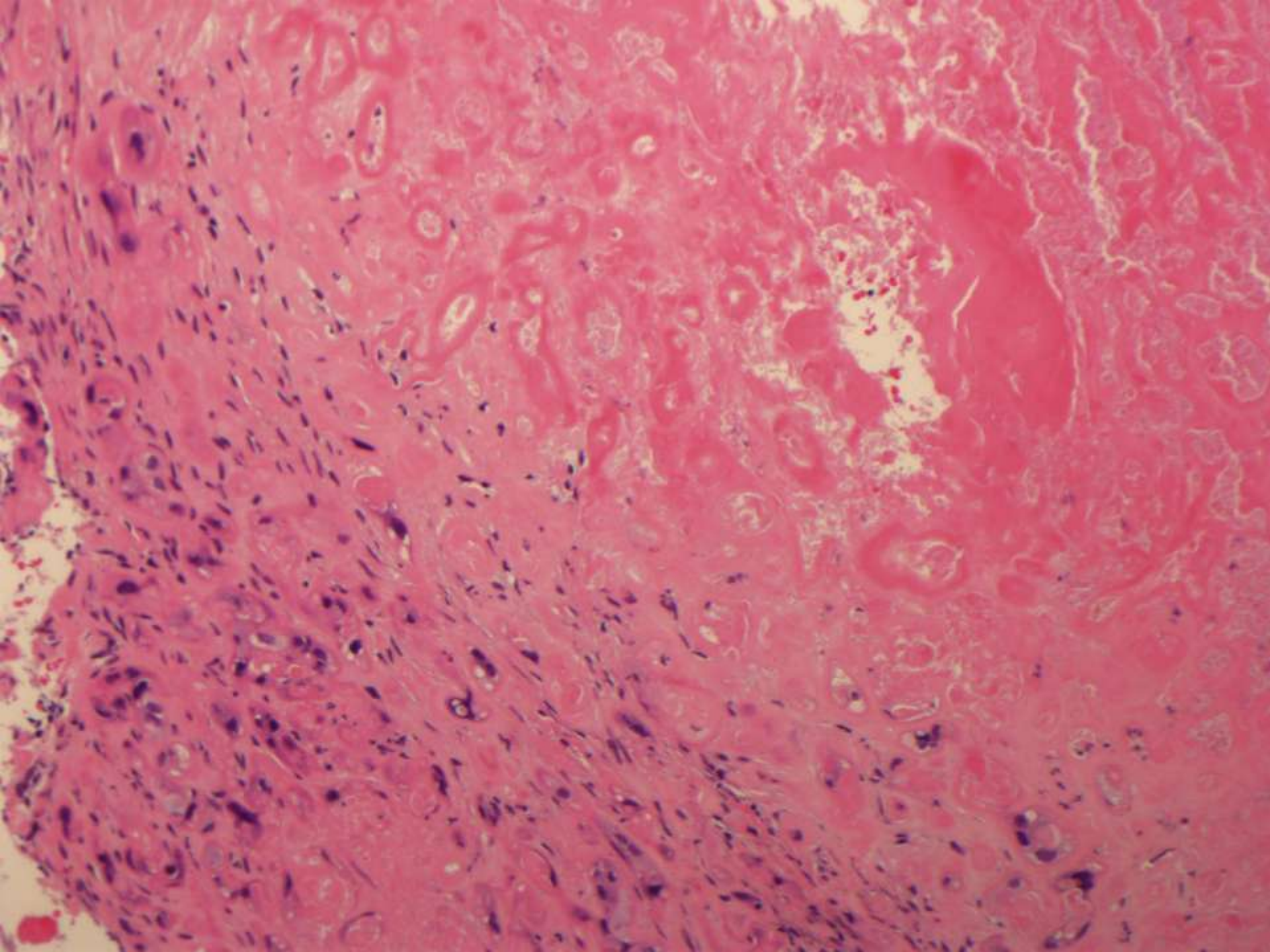
# Placental site nodule transformed into a malignant epithelioid trophoblastic tumour with pelvic lymph node and lung metastasis

Tsai et al *Histopathology* 2008; 53: 601-604









Placental site nodule v atypical  
placental site nodule v epithelioid  
trophoblastic tumour

- significant areas of necrosis
- increased Ki-67
- foci of calcification
- increased Cyclin E expression

# Placental site nodule v Epithelioid trophoblastic tumour

