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The Role of Lymphadenectomy in Gynaecological Cancer Surgery

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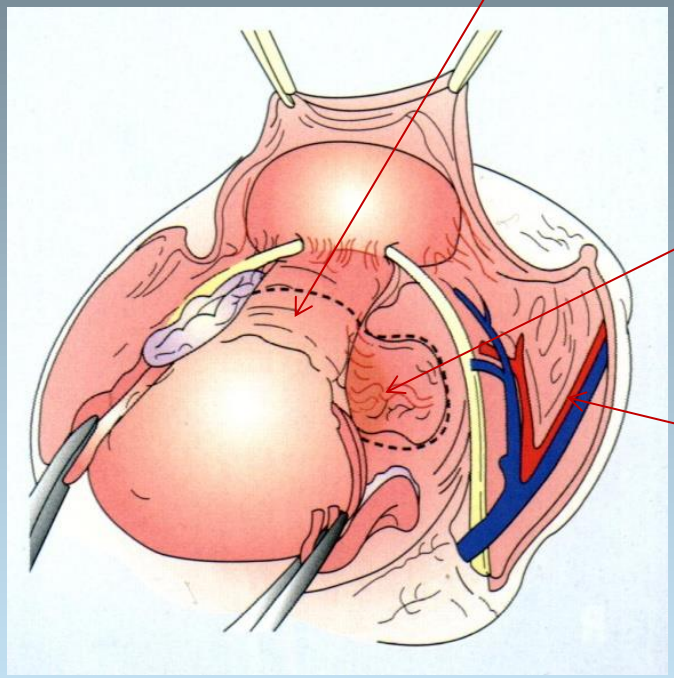
THE NORTH LONDON CANCER NETWORK

Principles of surgical treatment -

1. Remove the primary tumour



2. Consider if there might be spread to the local area –
wide excision for margins

3. Consider if there might be spread to the lymph nodes

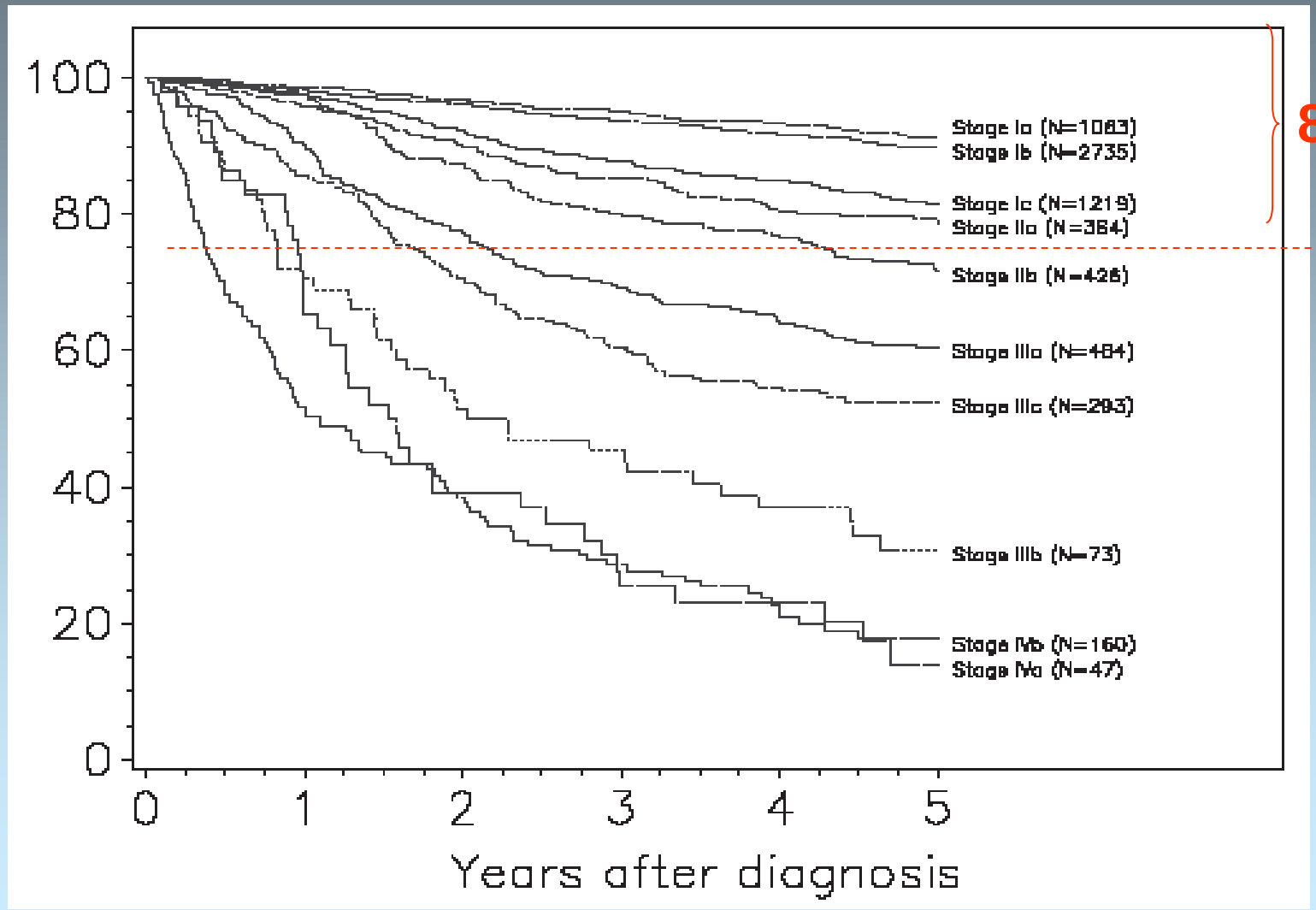
Rationale to remove nodes -

- Determine the need for adjuvant treatments
- Therapeutic effect
- Document the extent of disease spread
  - Allow comparative evaluation / trials
- Can we use sentinel node in gynaecology?

The role of nodal surgery

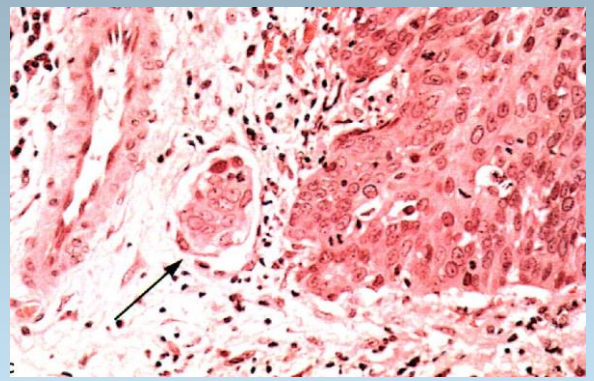
- Endometrial cancer
  - Select adjuvant treatments
  - ? Therapeutic effect
- Ovarian cancer
  - Select adjuvant treatment in early stage disease
  - Therapeutic effect in late stage disease
- Cervical cancer
  - Select adjuvant treatment
  - Development of sentinel nodes
- Vulval cancer
  - Sentinel node technique to guide adjuvant treatment

Endometrial Cancer
-survival curves: 6864 cases treated 1996-8
(FIGO annual report Int J Gyn Obs 2003)



Endometrial Cancer – risk factors for spread

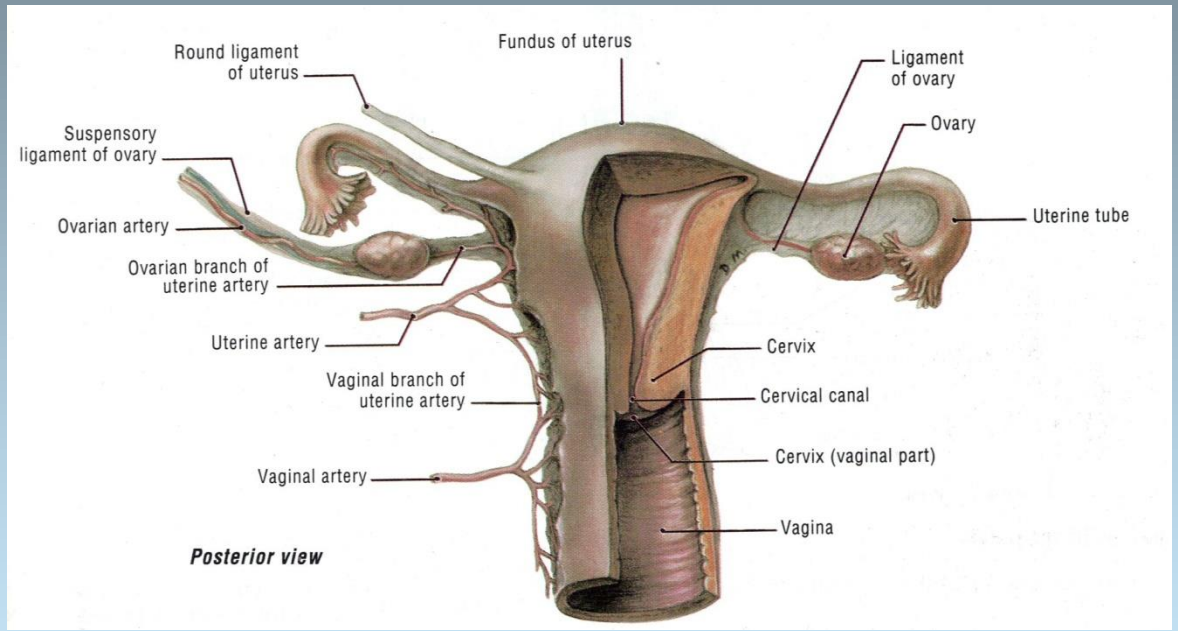
- Size > 2cm
- G3 – endometroid, serous, carcino sarcoma, clear cell
- Depth invasion > 50%
- LVSI
- Stage 2 – cervix involved



What should nodal dissection be?

Not standardised at present

Should depend on the patterns of spread



Fundal invasion

⟶ PA nodes

Mid / lower uterus

⟶ iliac basins

Main route of Spread via nodes – pelvic nodal metastases

- Creasman et al 1987

	G1	G2	G3
Inner	3	5	9
Middle	0	9	4
Outer	11	19	34

Spread – PA nodal metastases

- Creasman et al 1987

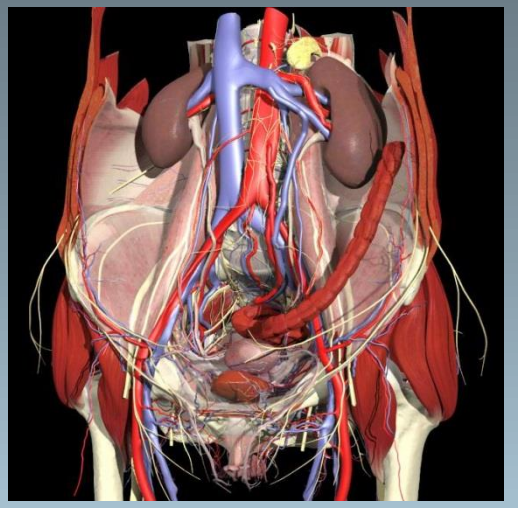
	G1	G2	G3
Inner	1	4	4
Middle	5	0	0
Outer	6	14	23

What nodes to remove –

If pelvic nodes +ve PA nodes +ve in 47%

If positive PA nodes

Area between IMA and renal vessels +ve 77%



If area between IMA and renals +ve

Ipsilateral below IMA - ve 60%

Ipsilateral common iliacs - ve 71%

Isolated PA nodes +ve 16%

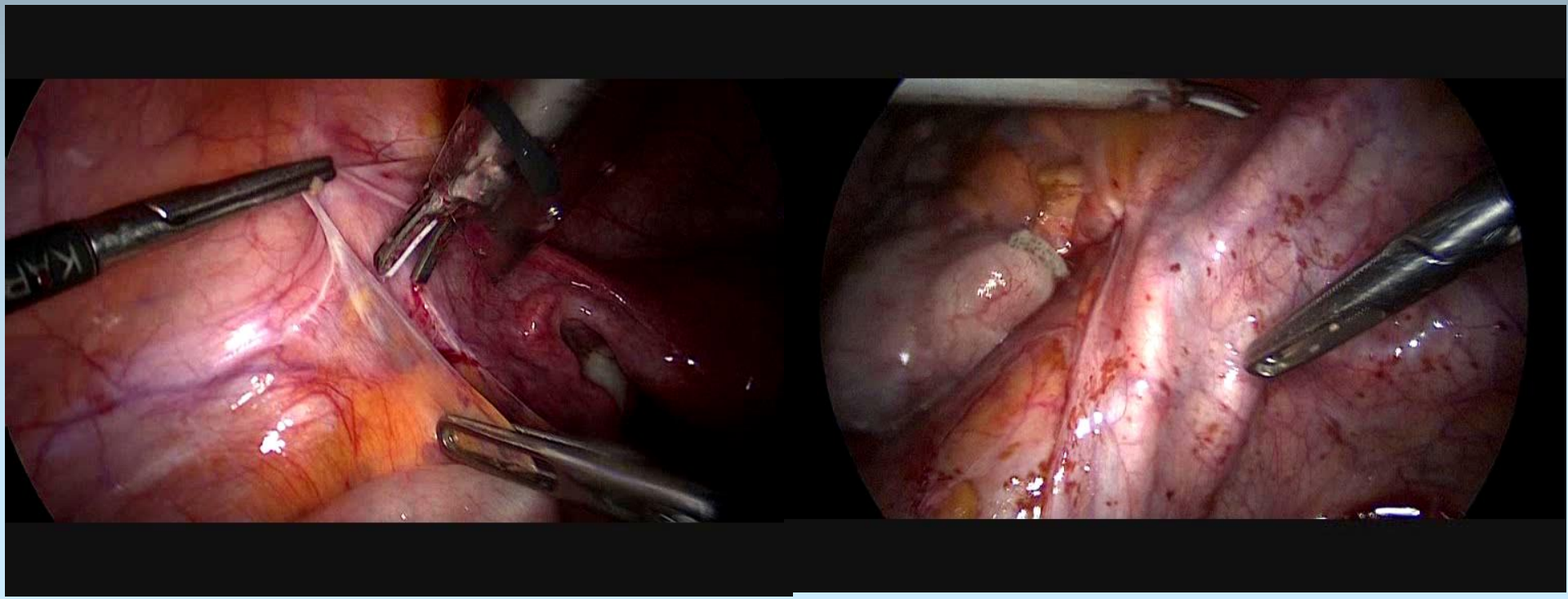
Tissue connected to gonadal vessels +ve 28%

What should nodal dissection be - conclusion

Pelvic node dissection

Para aortic node dissection up to renal vessels

Include tissue along gonadal vessels



Determine adjuvant treatment

+ve nodes

- **Increase treatment - extended RT or Chemo**

40% survival if extended RT for +ve PA nodes

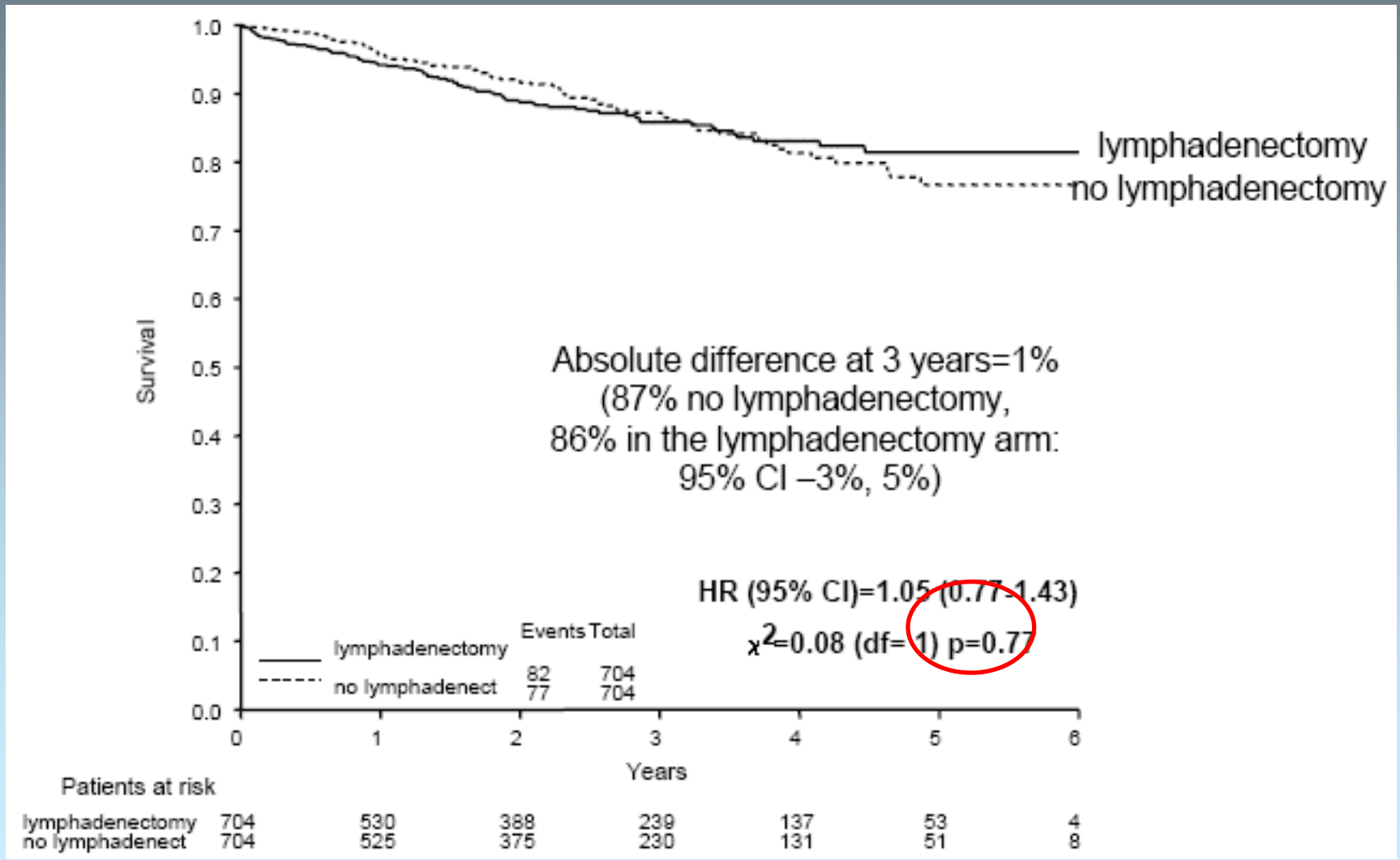
Rose et al 1992

-ve nodes

- **Decrease treatment - vault brachy / no RT**

A therapeutic role - randomised trials

ASTEC surgical results: Overall survival



A therapeutic role - randomised trials

ASTEC patient and surgery details

- only 20% pt G3 or 1c
- median number of nodes = 12

A therapeutic role - randomised trials

Panici et al results: Overall survival

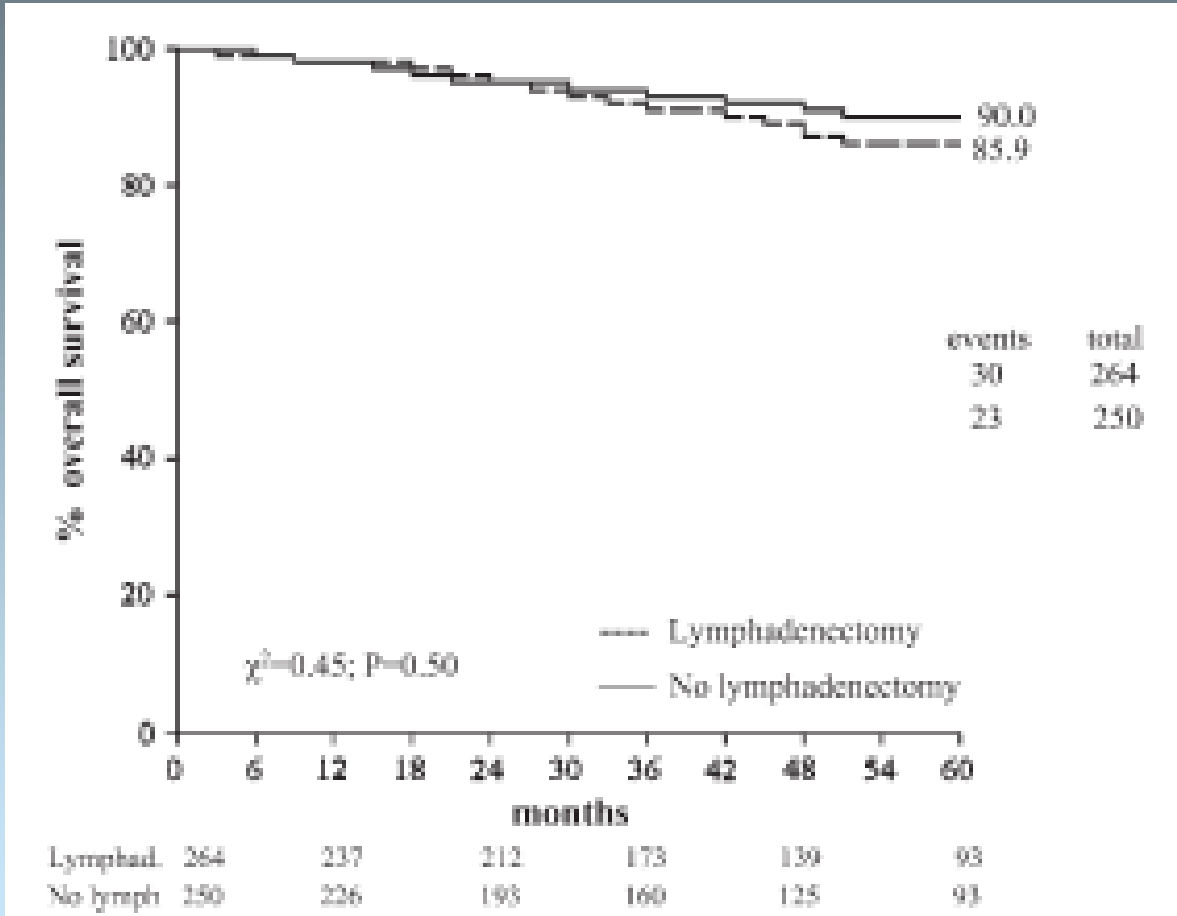


Figure 3. Overall survival for patients with clinical early-stage endometrial cancer undergoing systematic pelvic lymphadenectomy (Lymphad.) vs those undergoing resection of bulky lymph nodes only (No lymph). All statistical tests were two-sided.

A therapeutic role - randomised trials

Panici et al patients and surgery details

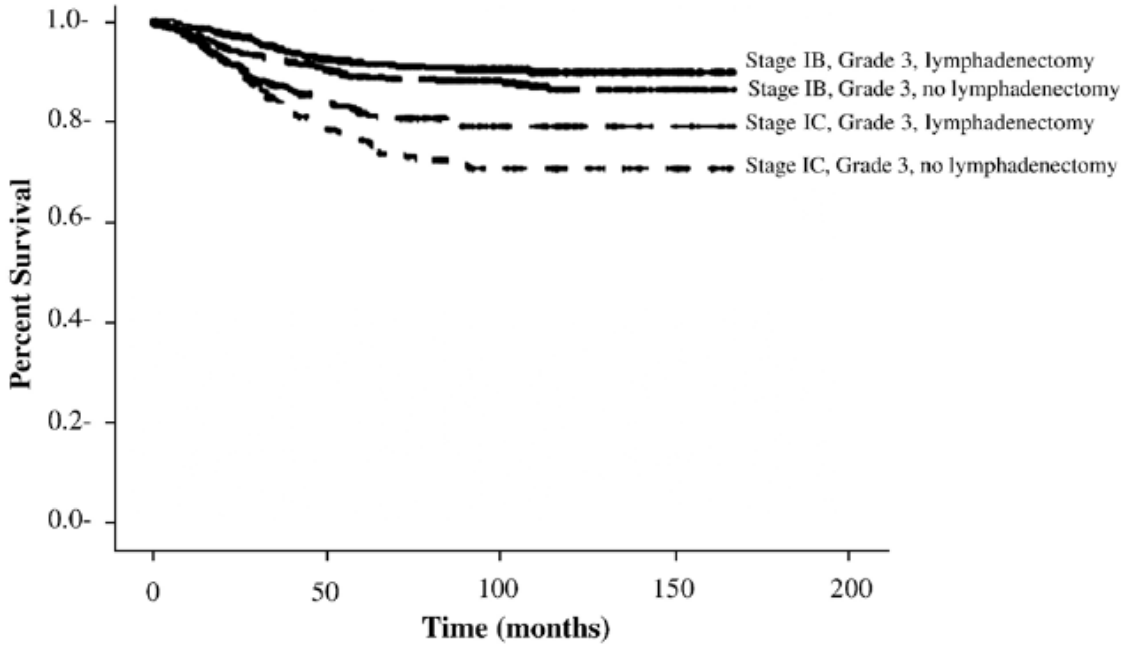
- 50% deep invasion
- 33% G3

- mean nodes 26

A therapeutic role – retrospective cohort studies

Chan et al 2007

No effect in low risk disease
Depends on numbers of nodes
Depends on extent of nodal dissection



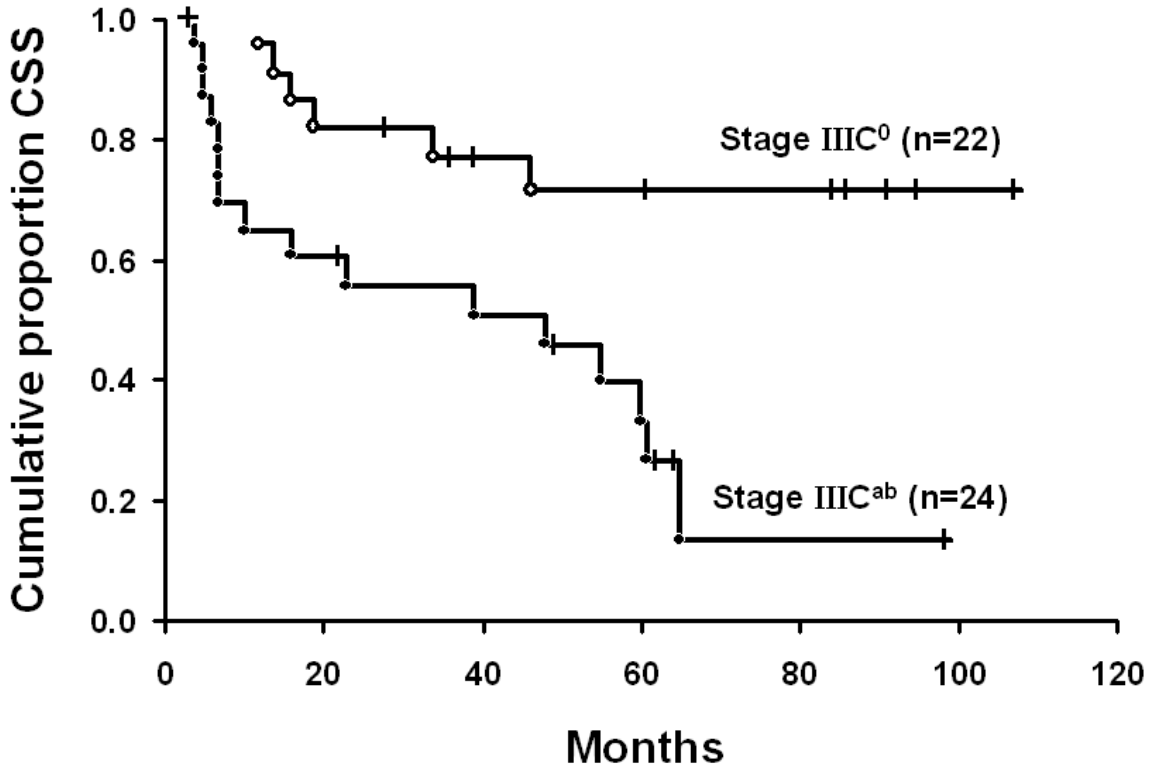
5-year disease-specific survival:

	Lymphadenectomy	No Lymphadenectomy	p-value
Stage IB grade3	91.7% (n=1,070)	89.1% (n=852)	p=0.048
Stage IC grade3	81.7% (n=483)	76.3% (n=401)	p=0.058

Fig. 1. Kaplan–Meier disease-specific survival of stage I grade 3 endometrioid uterine cancer patients based on lymphadenectomy.

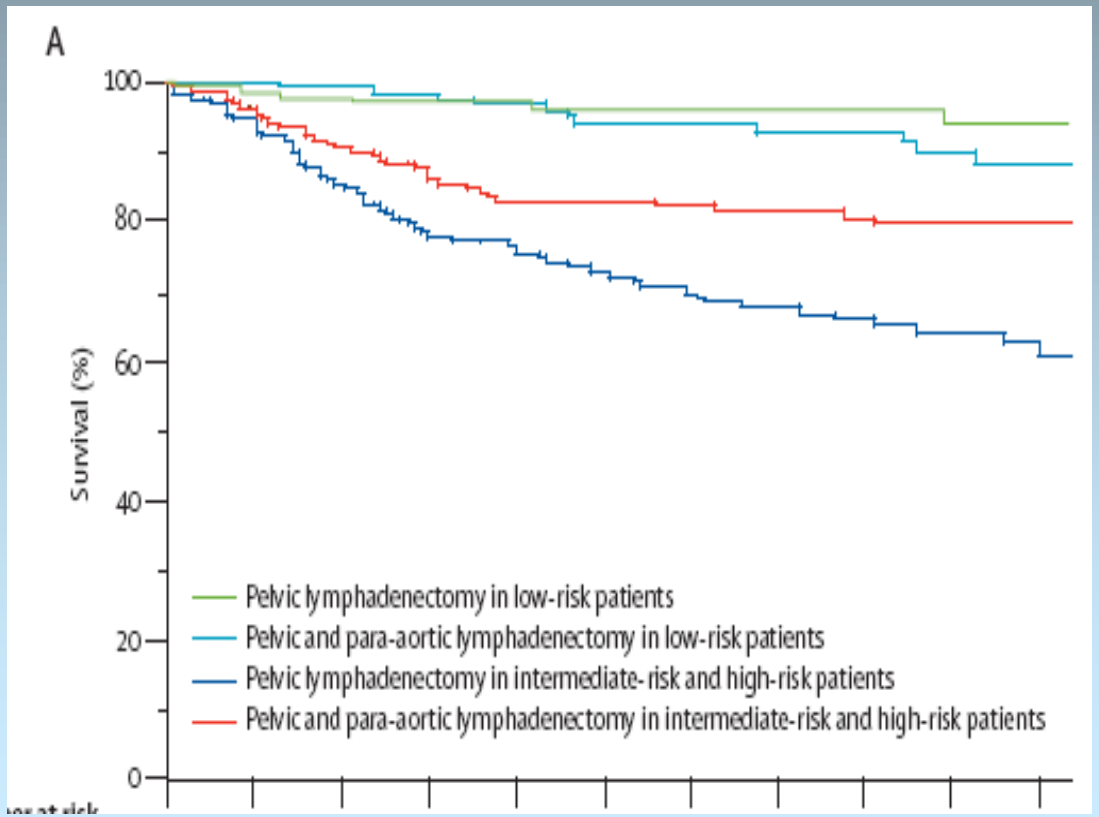
A therapeutic role – retrospective cohort studies

Extended PA dissection vs limited PA procedure Mayo clinic data



A therapeutic role – retrospective cohort studies

SEPAL study –
pelvic node vs. pelvic / PA node dissection



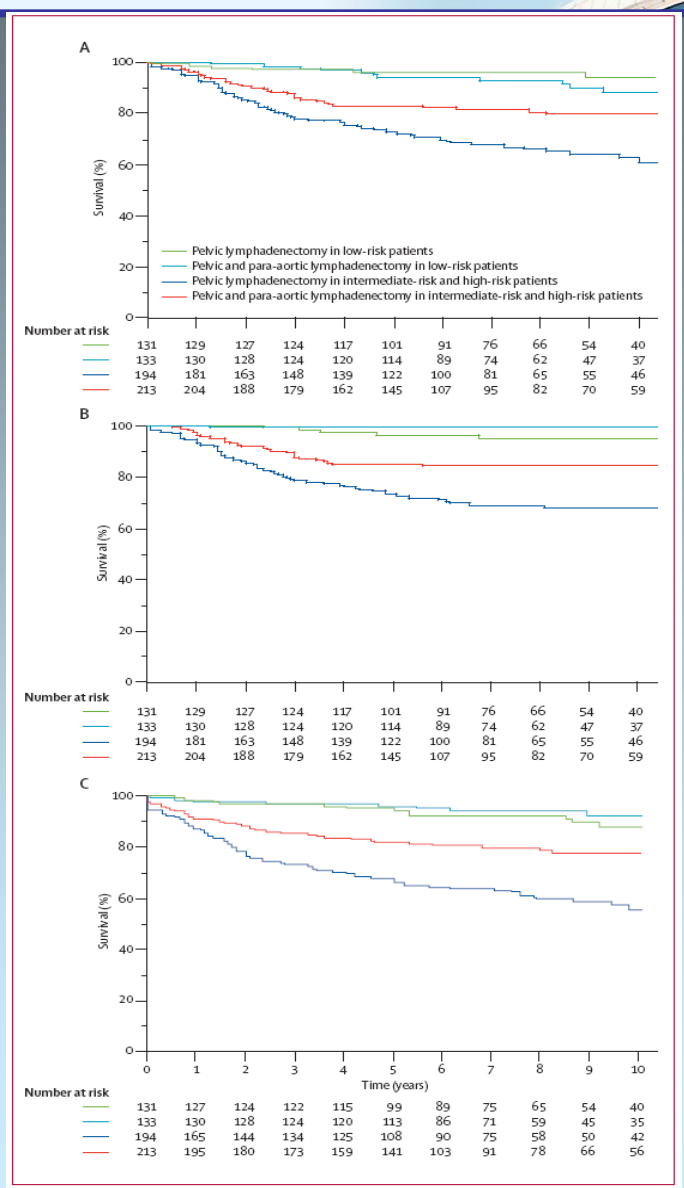


Figure 3: Kaplan-Meier analysis of overall (A), disease-specific (B), and recurrence-free (C) survival for patients with endometrial carcinoma according to type of lymphadenectomy and risk of recurrence

A therapeutic role – retrospective cohort studies

SEPAL study – pelvic node vs. pelvic / PA node dissection

	Number of deaths/ number of patients in group		Hazard ratio (95% CI)	p value
	Pelvic lymphadenectomy	Pelvic and para-aortic lymphadenectomy		
Low risk	13/131	6/133	0·45 (0·17–1·19)	0·11
Intermediate risk	32/124	13/116	0·43 (0·23–0·82)	0·0106
Radiotherapy	21/56	0/1	..	..
Chemotherapy	7/42	12/82	0·68 (0·26–1·73)	0·43
High risk	38/70	30/97	0·50 (0·31–0·81)	0·0051
Radiotherapy	15/19	0/1	..	..
Chemotherapy	20/46	20/81	0·53 (0·28–0·99)	0·0448
Total	83/325	49/346	0·53 (0·38–0·76)	0·0005

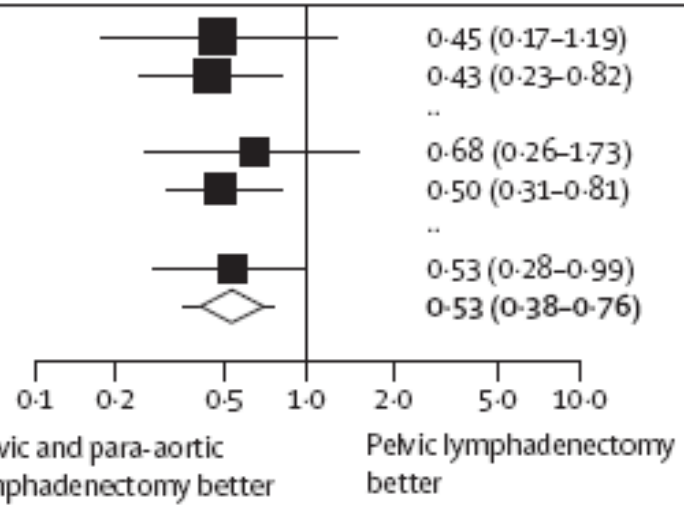


Figure 2: Cox regression analysis of overall survival with pelvic and para-aortic lymphadenectomy compared with pelvic lymphadenectomy alone according to risk of recurrence

..=data not available.

SEPAL study

- retrospective, cluster study, long time period
- selection bias
- no surgery/morbidity details
- difference in chemo rates

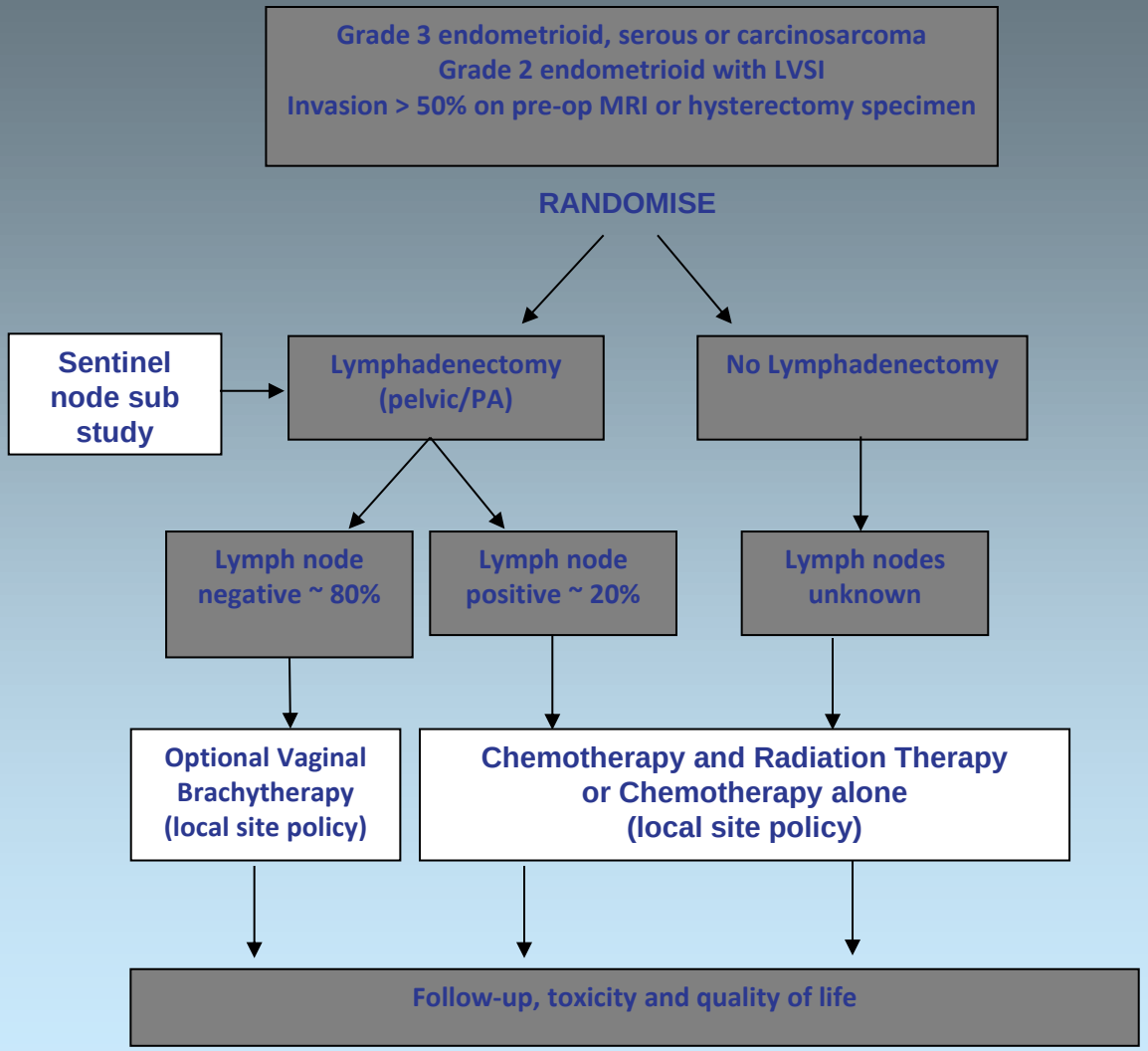
STATEC

Selective Targeting of Adjuvant Therapy for Endometrial Cancer

- Tailoring adjuvant therapy based on node status may limit toxicity with equal survival
- Improvement in survival may require systemic therapy
- Lymphadenectomy is not independently therapeutic

- Sentinel node biopsy may be as effective as full lymphadenectomy to triage patients to adjuvant therapy

STATEC


Grade 3 endometrioid, serous or carcinosarcoma
Grade 2 endometrioid with LVSI
Invasion > 50% on pre-op MRI or hysterectomy specimen
RANDOMISE
Sentinel node sub study
Lymphadenectomy (pelvic/PA)
No Lymphadenectomy
Lymph node negative ~ 80%
Lymph node positive ~ 20%
Lymph nodes unknown
Optional Vaginal Brachytherapy (local site policy)
Chemotherapy and Radiation Therapy or Chemotherapy alone (local site policy)
Follow-up, toxicity and quality of life

STATEC

- Laparoscopic, robotic, or open
- Anatomical landmarks - above IMA expected but not mandated
- Quality assurance – photo graphs, centre review if inadequate
- Adjuvant treatment – Portec regime, randomisation by centre
- Sentinel node – Te99, blue dye, indocyanin green

Conclusions: Endometrial cancer

Full dissection of pelvic and para aortic nodes

- **Is not helpful in low risk disease**
  - **2cm, G1-2, <50% invasion, no LVSI**
- **But in high risk disease**
  - **Can guide adjuvant treatment**
  - **Is not therapeutic in randomised studies**
  - **Is therapeutic in retrospective case series studies**
- **STATEC – tailoring adjuvant therapy to limit toxicity**

Ovarian cancer – Early Stage

Apparent early stage - Isolated ovarian abnormality:

remove ovary +/- other ovary and uterus
+ washings
+ pelvic/pa nodes, omentectomy

- 20-25% upstaged
- usually to Stage 3 (+ve nodes = 3c or omentum = 3a)
- determines need for chemo

Aletti et al 2006
- surgeons operating in same centre
194 cases

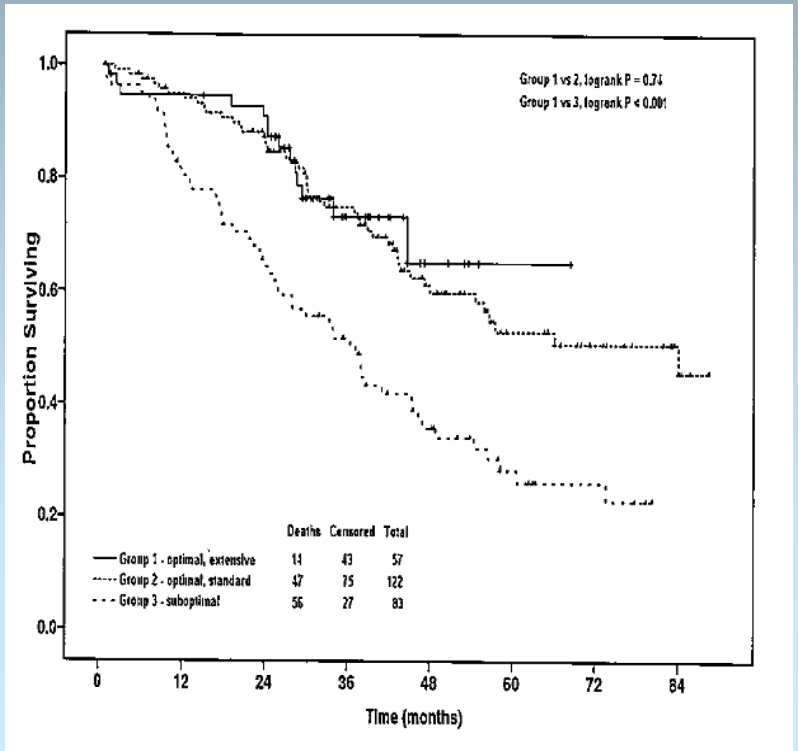
Surgery type	% achieving optimal debulk
Standard	51%
URS	84.5%

Multivariate analysis –
Equally extensive disease and good performance status

Significant survival benefit $p < 0.001$
For surgeons frequently performing URS

Bristow et al 2002 – meta analysis

Every 10% improvement in optimal debulking rate
=
5% improvement in overall survival



Cervical cancer – guiding adjuvant treatment

Pelvic nodes in stage 1a2 and 1b1

+ve nodes

- **Increase treatment - chemo RT**

-ve nodes

- **Surgery alone - less morbidity**

Cervical cancer – guiding adjuvant treatment
Pelvic nodes in stage 1a2 and 1b1

? Need for block dissection of lymph nodes

- Sentinel node – blue dye and technesium – laparoscopic

If positive, abandon surgery for chemo RT

If negative, continue pelvic node dissection

Rob et al, Gynecol Oncol 2005

Sentinel node technique – more sensitive, detects unusual sites of drainage

? Should become standard practice

Gortzak-Uzan Gynecol Oncol 2010
87 cases with controls - 17% vs 7%
Cibula et al Gynecol Oncol 2012 645 pt
Bats et al Ann Surg Oncol 2013 145 pt

Cervical cancer – guiding adjuvant treatment
Para aortic nodes in stage 1b2 and above

Laparoscopic retro peritoneal para-aortic lymphadenectomy

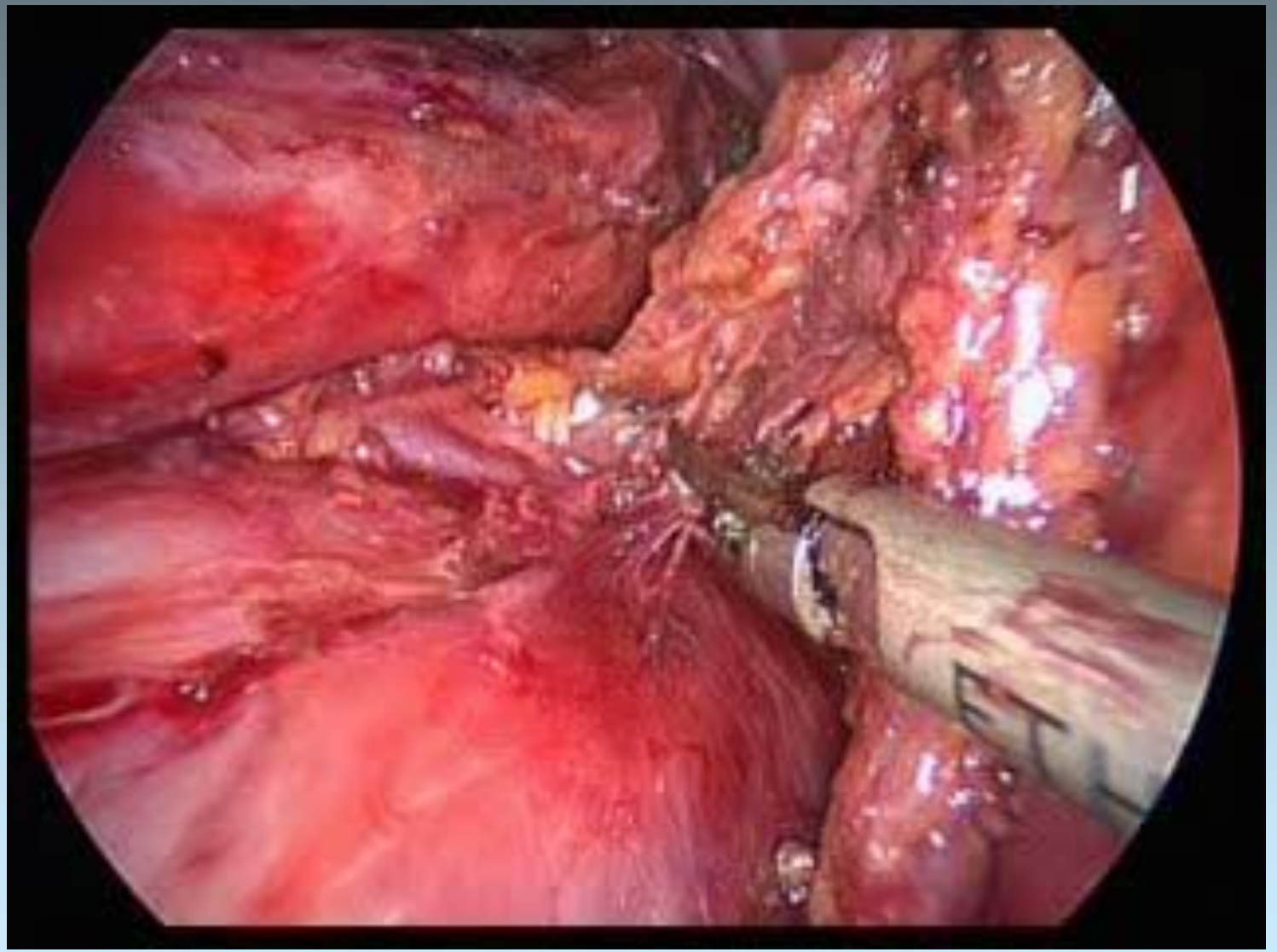
Stage 2b onwards treated by Chemo-Radiotherapy

Stage 2b - radiologically negative para-aortic nodes,

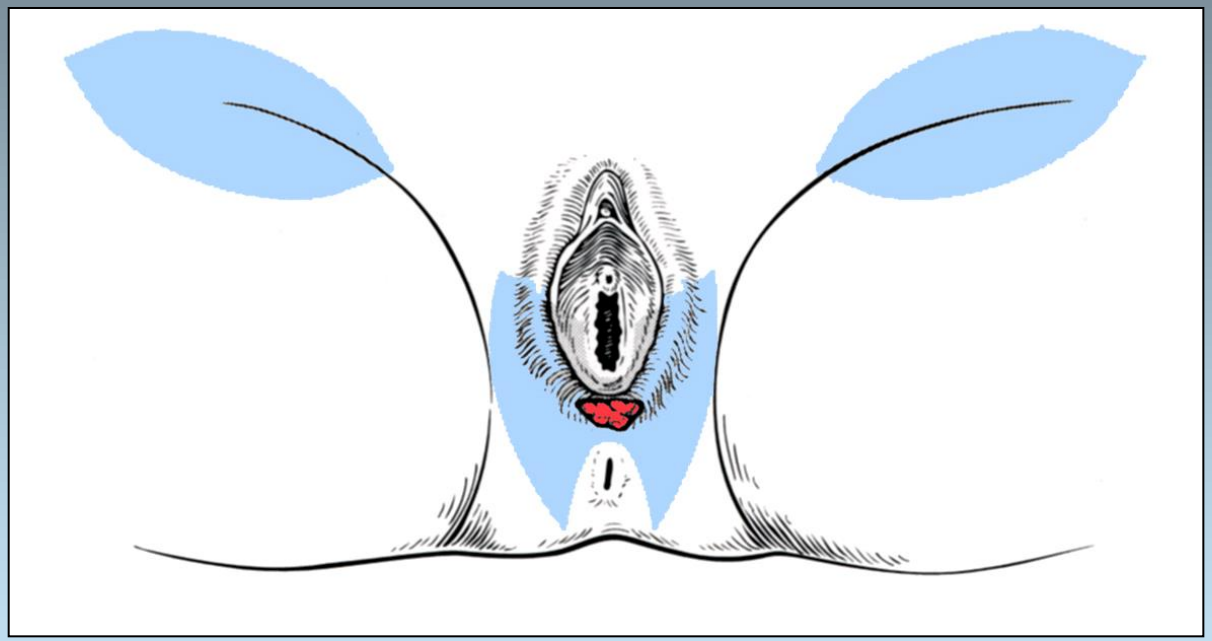
+ve histologically 15%

- para-aortic radiotherapy

Retro peritoneal Para aortic node dissection

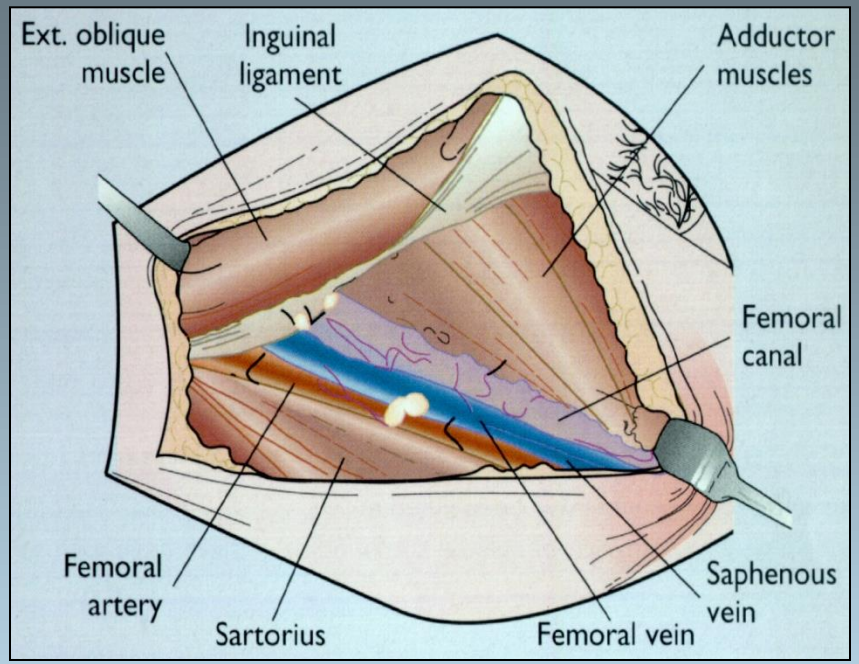


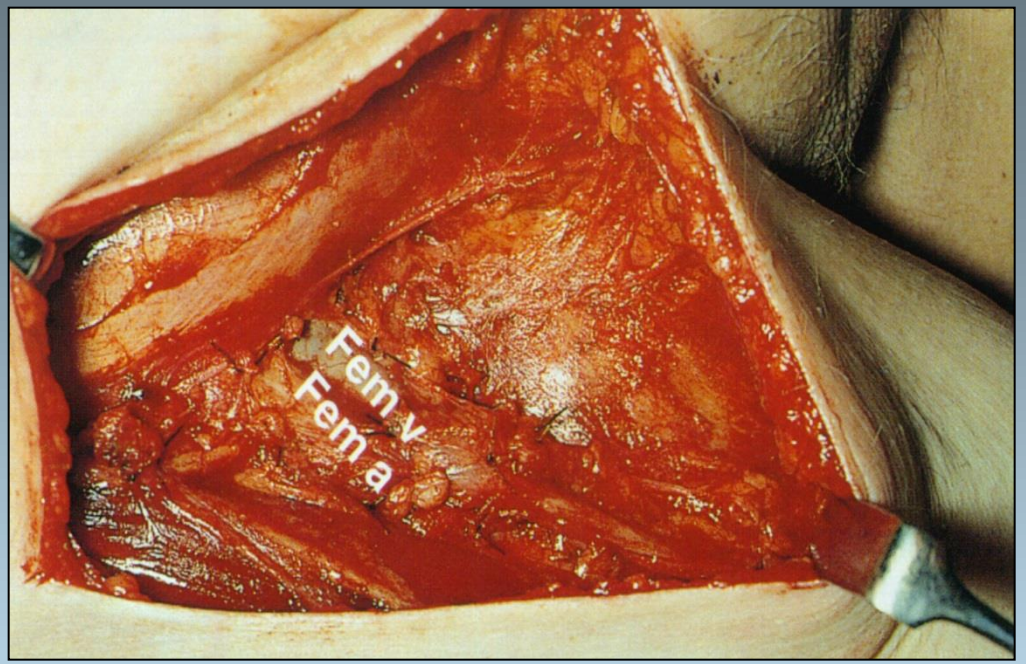
Vulval cancer –
radical local excision + groin node staging

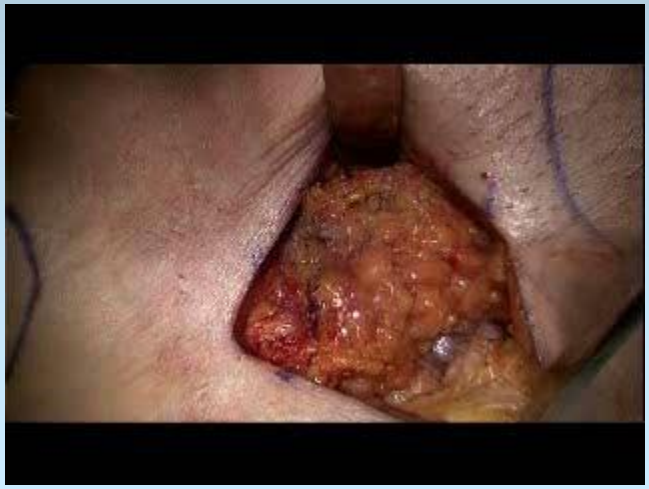


Radiation to groins and pelvis if nodes +ve

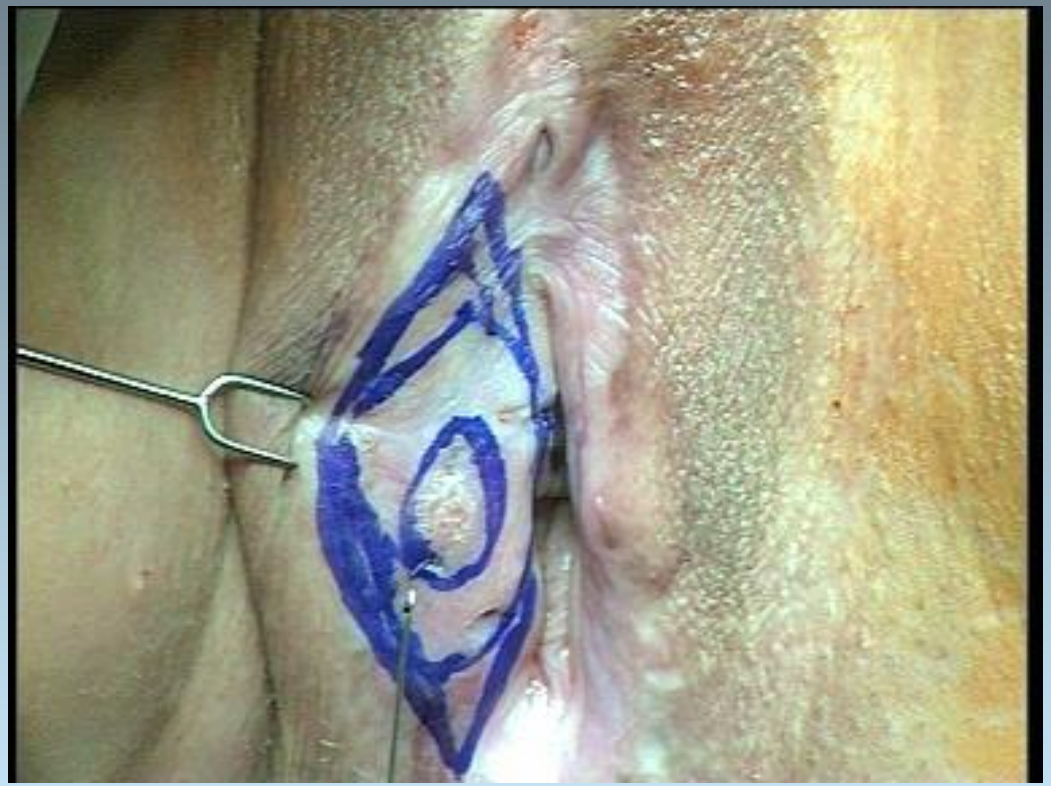
Traditional groin node operation







Sentinel node surgery



Radiation to groins and pelvis if sentinel node positive
GROINSS study

Conclusions

- Endometrial cancer
  - Select adjuvant treatments to minimise morbidity of adjuvant treatments
  - Therapeutic effect seen in retrospective trials
- Ovarian cancer
  - Select adjuvant treatment in early stage disease
  - Debulking in stage 3/4 - Therapeutic effect
- Cervical cancer
  - Select / Guide adjuvant treatment
  - Development of sentinel nodes
- Vulval cancer
  - Sentinel node technique to guide adjuvant treatment

New markers provide new answers in malignant ovarian germ cell tumours

ugr

Francisco F Nogales
University of Granada

WHO 2014

Germ cell tumours	
Dysgerminoma	9060/3
Yolk sac tumour	9071/3
Embryonal carcinoma	9070/3
Non-gestational choriocarcinoma	9100/3
Mature teratoma	9080/0
Immature teratoma	9080/3
Mixed germ cell tumour	9085/3
Monodermal teratoma and somatic-type tumours arising from a dermoid cyst	
Struma ovarii, benign	9090/0
Struma ovarii, malignant	9090/3
Carcinoid	8240/3
Strumal carcinoid	9091/1
Mucinous carcinoid	8243/3
Neuroectodermal-type tumours	
Sebaceous tumours	
Sebaceous adenoma	8410/0
Sebaceous carcinoma	8410/3
Other rare monodermal teratomas	
Carcinomas	
Squamous cell carcinoma	8070/3
Others	
Germ cell - sex cord-stromal tumours	
Gonadoblastoma, including gonadoblastoma with malignant germ cell tumour	9073/1
Mixed germ cell-sex cord-stromal tumour, unclassified	8594/1*

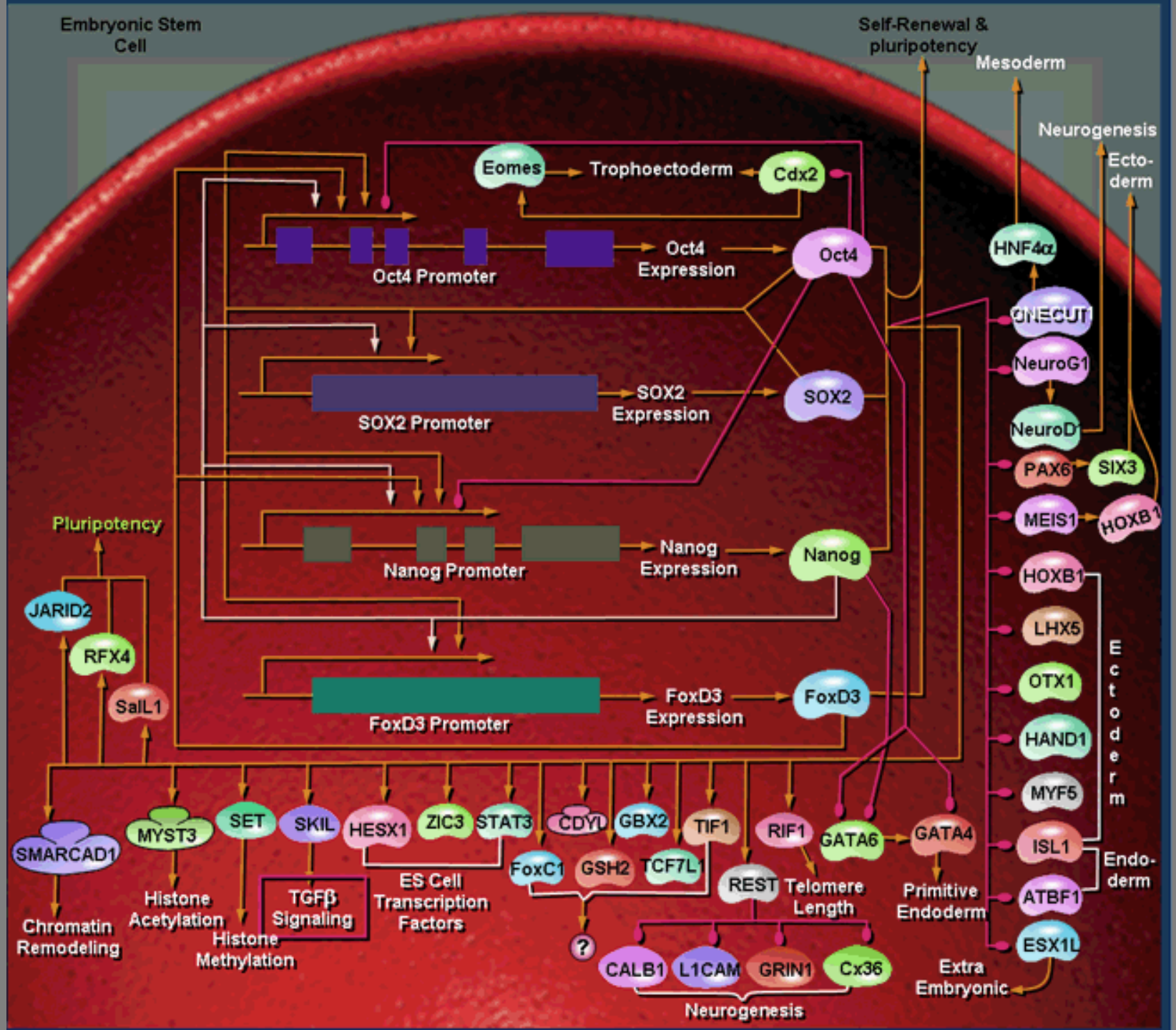
"Germ cell tumours are caricatures of normal embryonal development……" (Pierce 1971)

- **Models of comparative embryology/pathology**

1958,1962

"Germ cell tumours are caricatures of normal embryonal development……" (Pierce 1971)

- **Every normal developmental embryonal stage is caricaturized by a specific GCT type**
- **Each stage has characteristic markers (both stage-specific (SS) and pluripotency -PPM-)**
- **Analysis of expression of these markers (PPM and SS) will lead to a more accurate diagnosis of GCT types**
- **Additional demonstration of tissue-specific markers complement and fine-tune diagnosis based on a PPM expression**

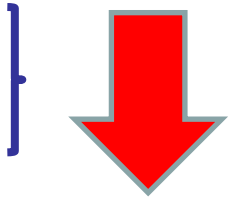

Embryonic Stem Cell
Self-Renewal & pluripotency
Mesoderm
Neurogenesis
Ecto-derm
Eomes
Trophoectoderm
Cdx2
Oct4 Promoter
Oct4 Expression
Oct4
HNF4α
ONECUT
NeuroG1
NeuroD
SOX2 Promoter
SOX2 Expression
SOX2
PAX6
SIX3
MEIS1
HOXB1
Pluripotency
Nanog Promoter
Nanog Expression
Nanog
JARID2
RFX4
SalL1
FoxD3 Promoter
FoxD3 Expression
FoxD3
HOXB1
LHX5
OTX1
HAND1
MYF5
ISL1
ATBF1
ESX1L
Ectoderm
Endo-derm
SMARCAD1
MYST3
SET
SKIL
HESX1
ZIC3
STAT3
CDYL
GBX2
TIF1
RIF1
GATA6
GATA4
FoxC1
GSH2
TCF7L1
REST
Telomere Length
Primitive Endoderm
Extra Embryonic
Chromatin Remodeling
Histone Acetylation
Histone Methylation
TGFβ Signaling
ES Cell Transcription Factors
?
CALB1
L1CAM
GRIN1
Cx36
Neurogenesis
www.SABiosciences.com

Diagnostic self-renewal and pluripotency markers

OCT4 aka POU5F1, OCT3 or OTF3

- Nuclear transcription factor - chromosome 6p21.3
- Blastocyst differentiation
  - Embryonal stem cells of the "inner cell mass"
  - epiblast

gastrulation



Primordial germ cells

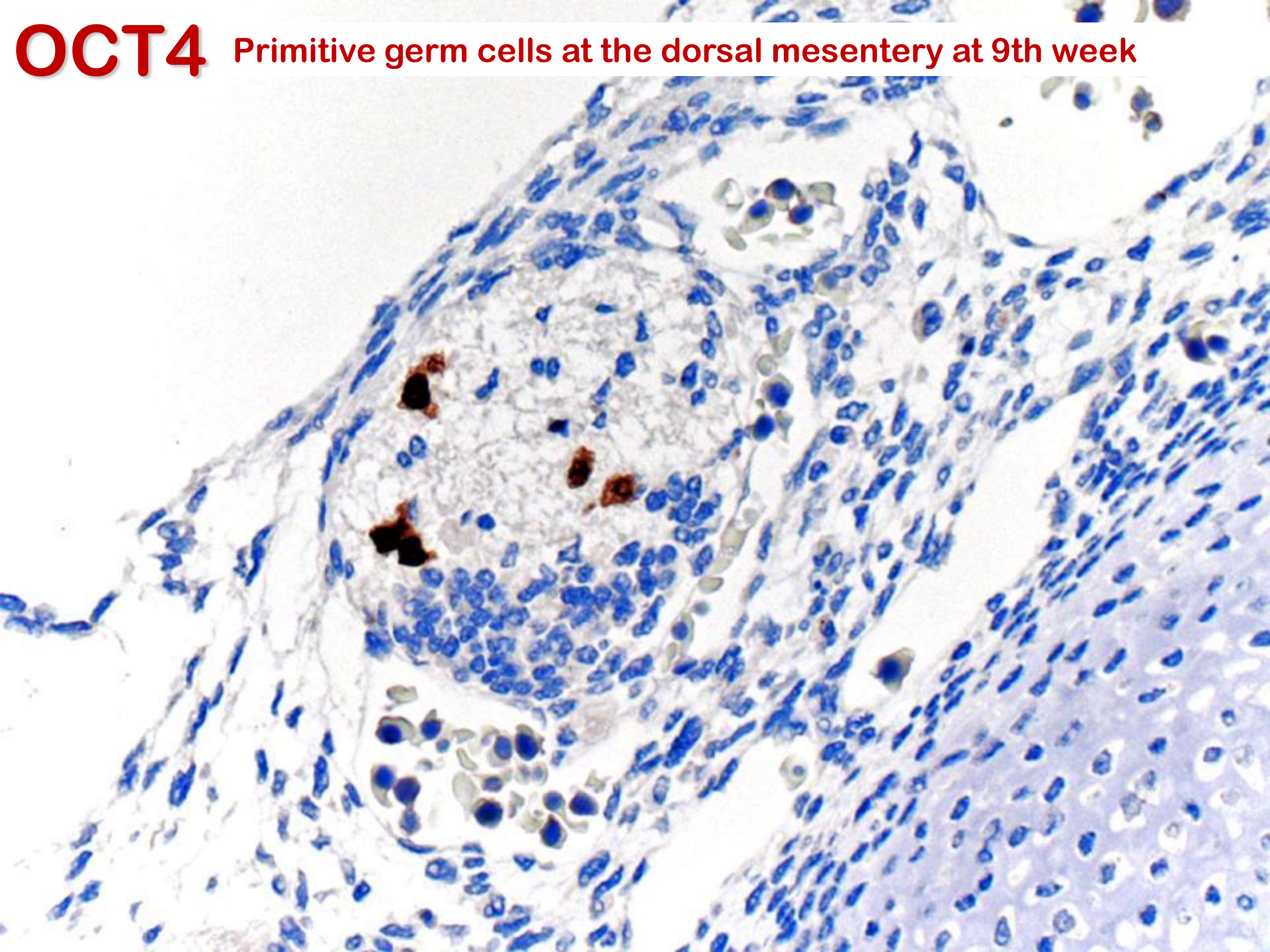
- Inducing pluripotency

Induces pluripotency of mature cells into iPSC

- Earliest marker (Germinoma & Emb Ca.)

OCT4

Primitive germ cells at the dorsal mesentery at 9th week

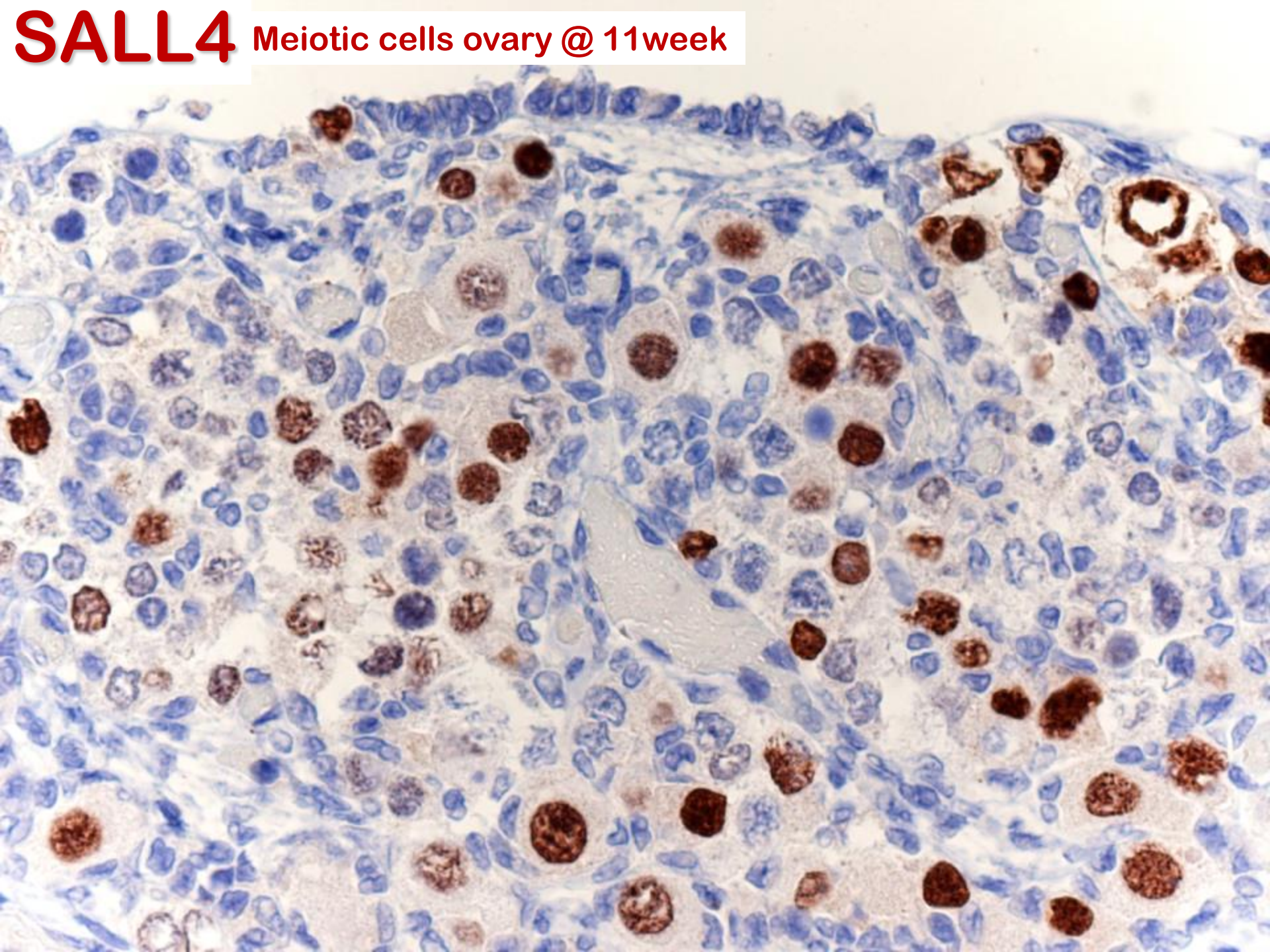


SALL4

- Family of three genes SALL - chromosome 20q13
- Expressed by cells of epiblast and primordial germ cells
  - Mandatory for endodermal differentiation
  - Not implicated in trophectoderm differentiation

- **Expressed by primordial germ cells and embryonal cells retaining pluripotency.**

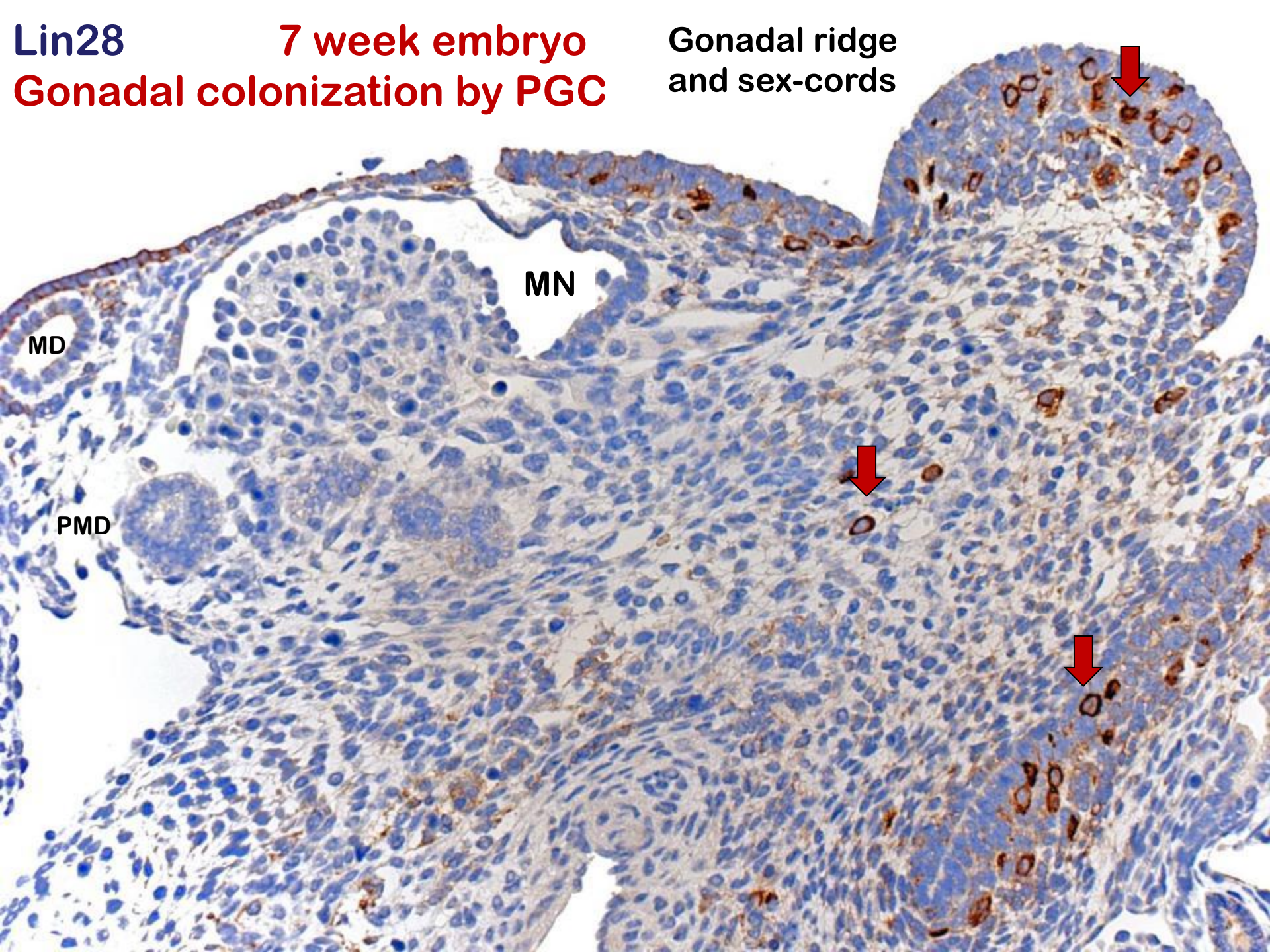
SALL4 Meiotic cells ovary @ 11week



Lin28

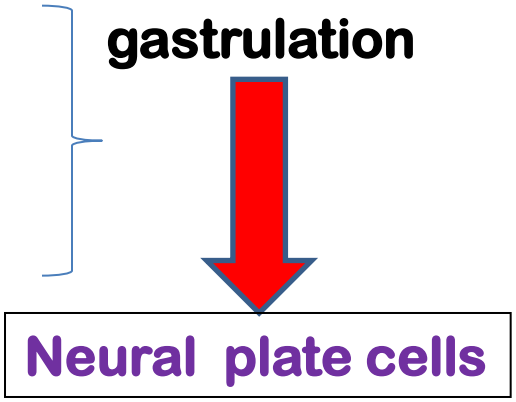
- miRNA binding protein
- Blocks let-7 miRNA activity
- Let-7 diminishes proliferation and induces differentiation
- Lin28 increases proliferation and induces pluripotency

- **Equivalent marker to SALL 4 (exceptions)**


Lin28
7 week embryo
Gonadal colonization by PGC
Gonadal ridge
and sex-cords
MN
MD
PMD

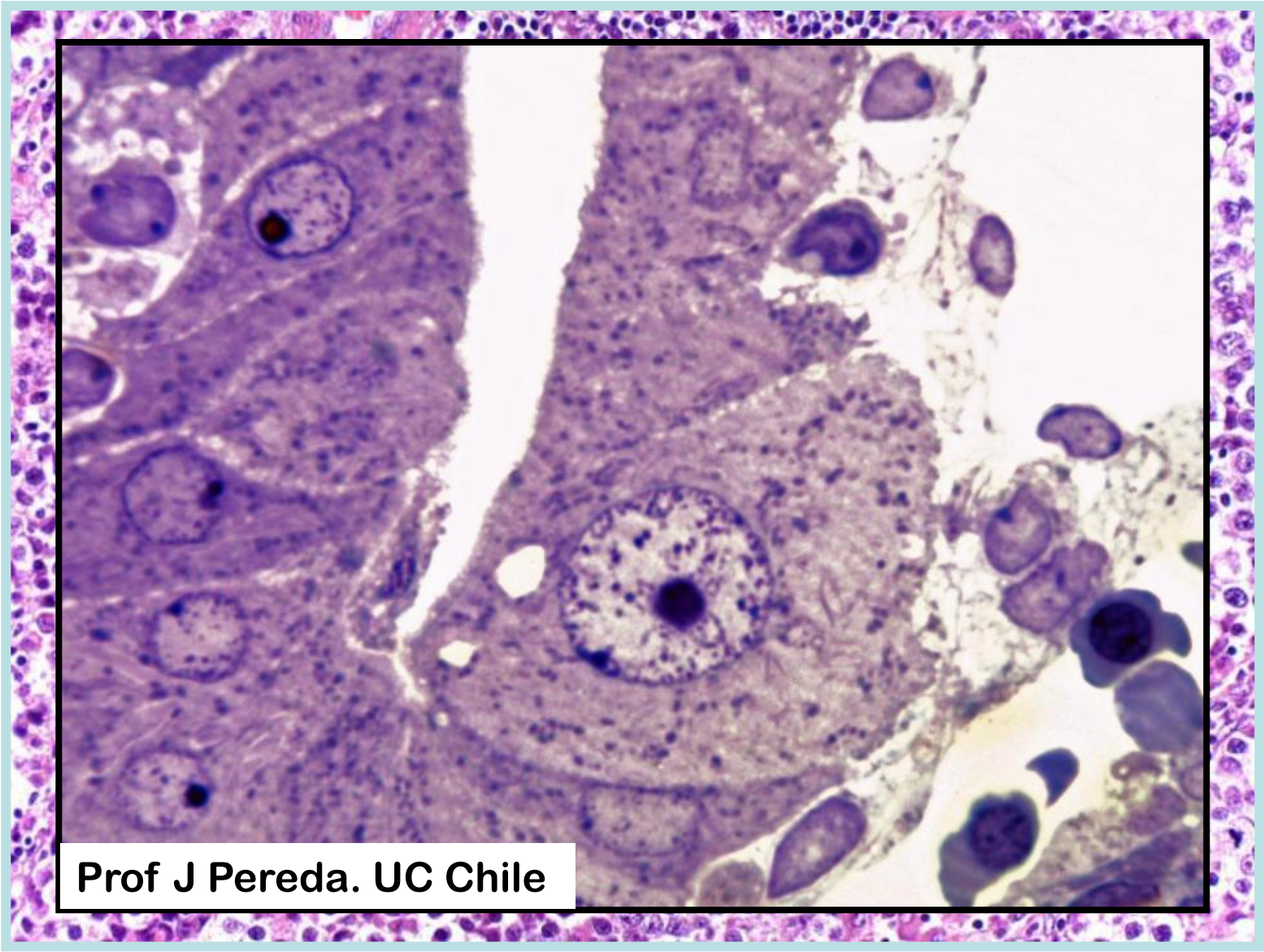
SOX2

- Factor SRY-box2
- Nuclear transcription factor- chromosome 3q26.33
- Responsible for
  - Development of the "inner cell mass"
- Differentiation of the trophectoderm together with CDX2

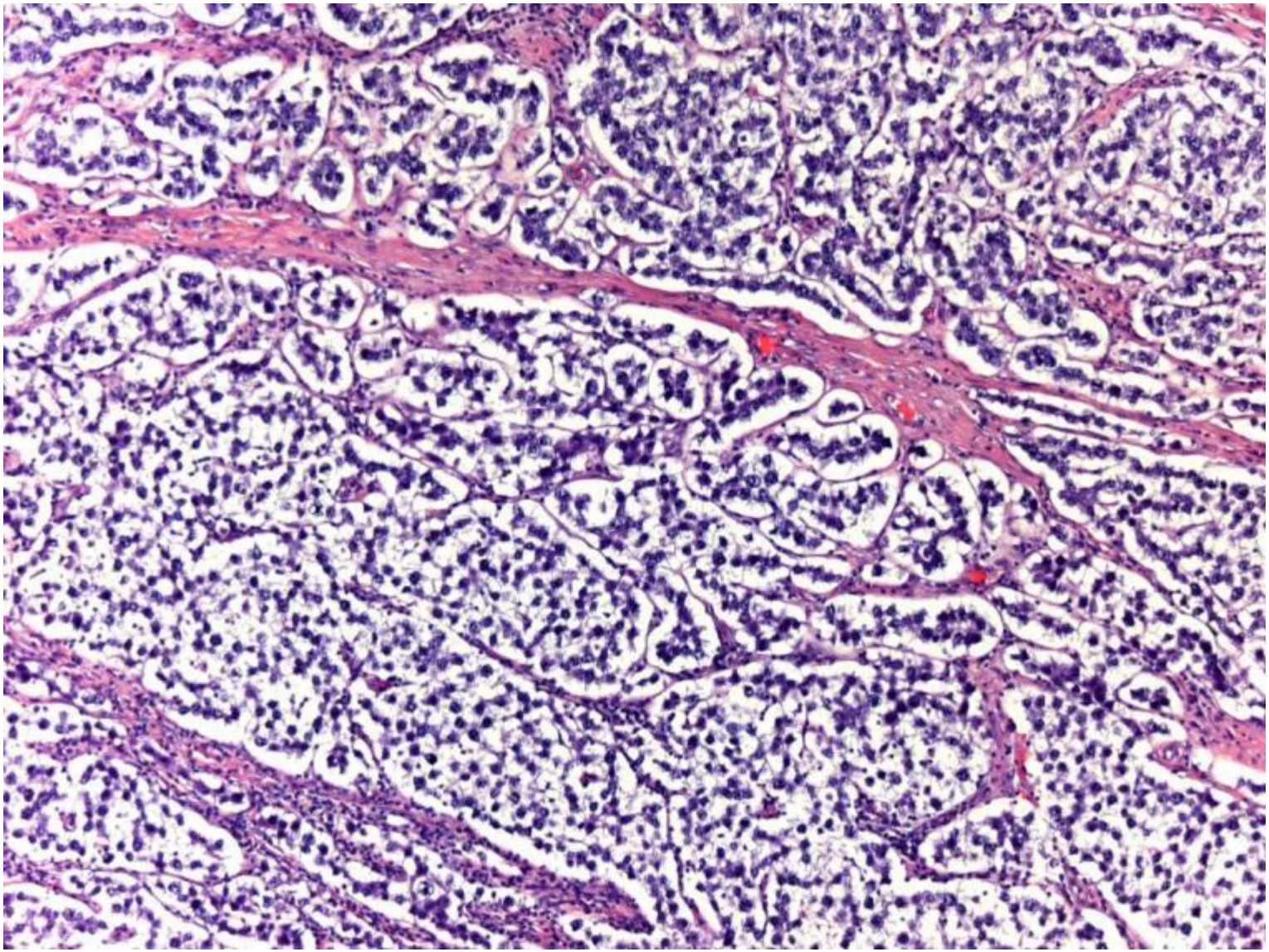


- Expression lost in primordial germ cells
- Ideal marker for embryonal Ca and immature neuroepithelium

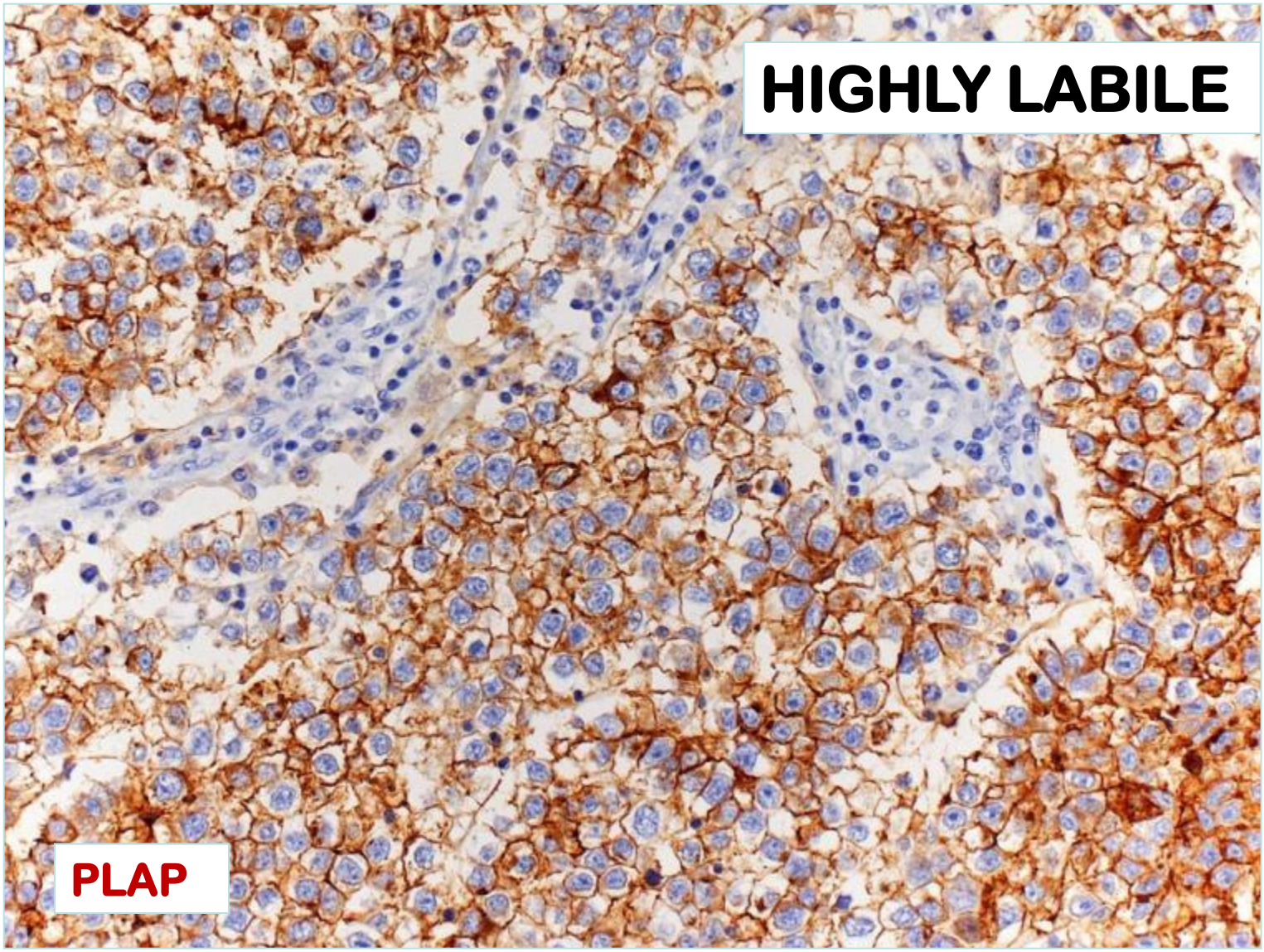
Dysgerminoma



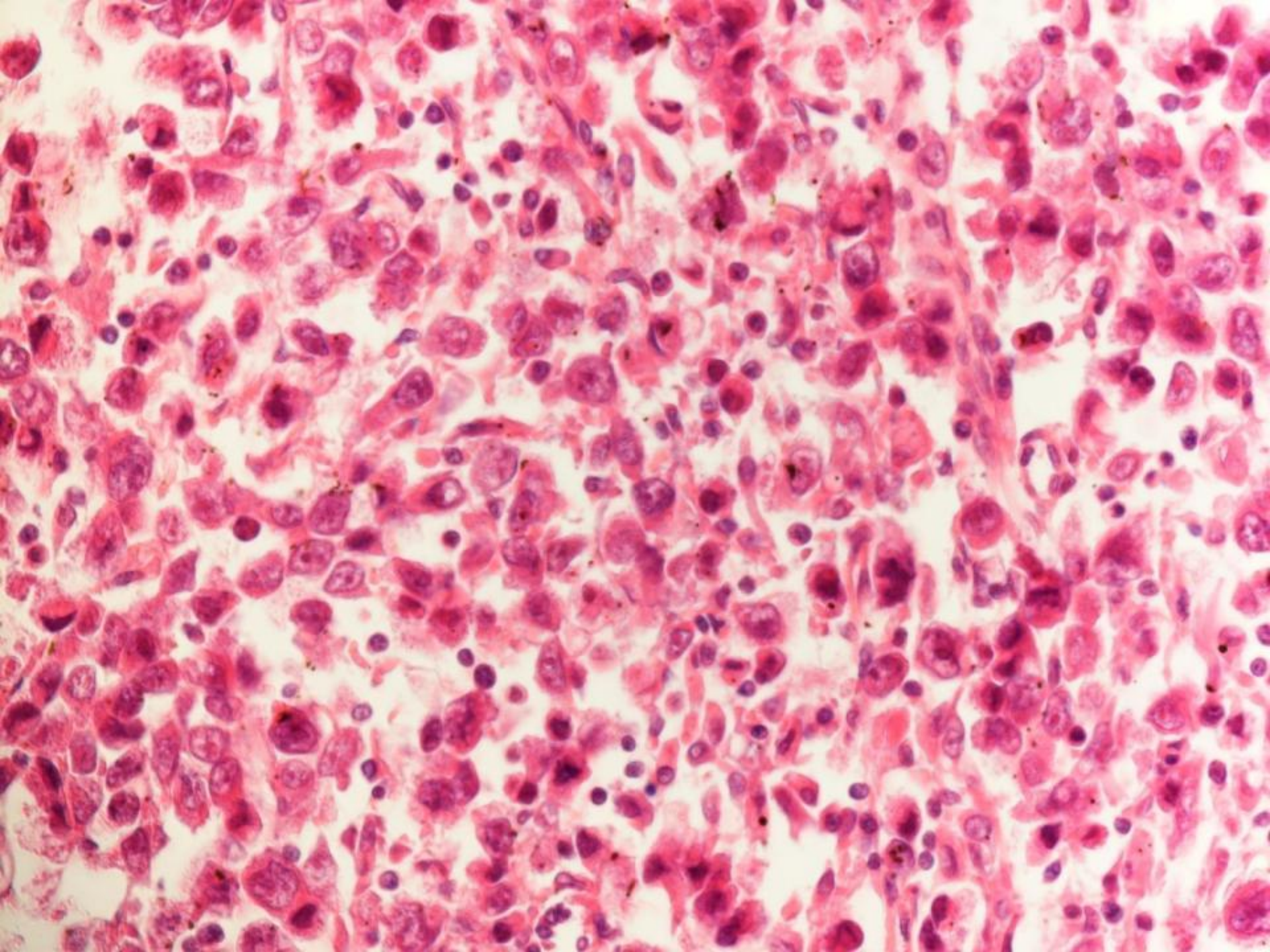
Dysgerminoma variability

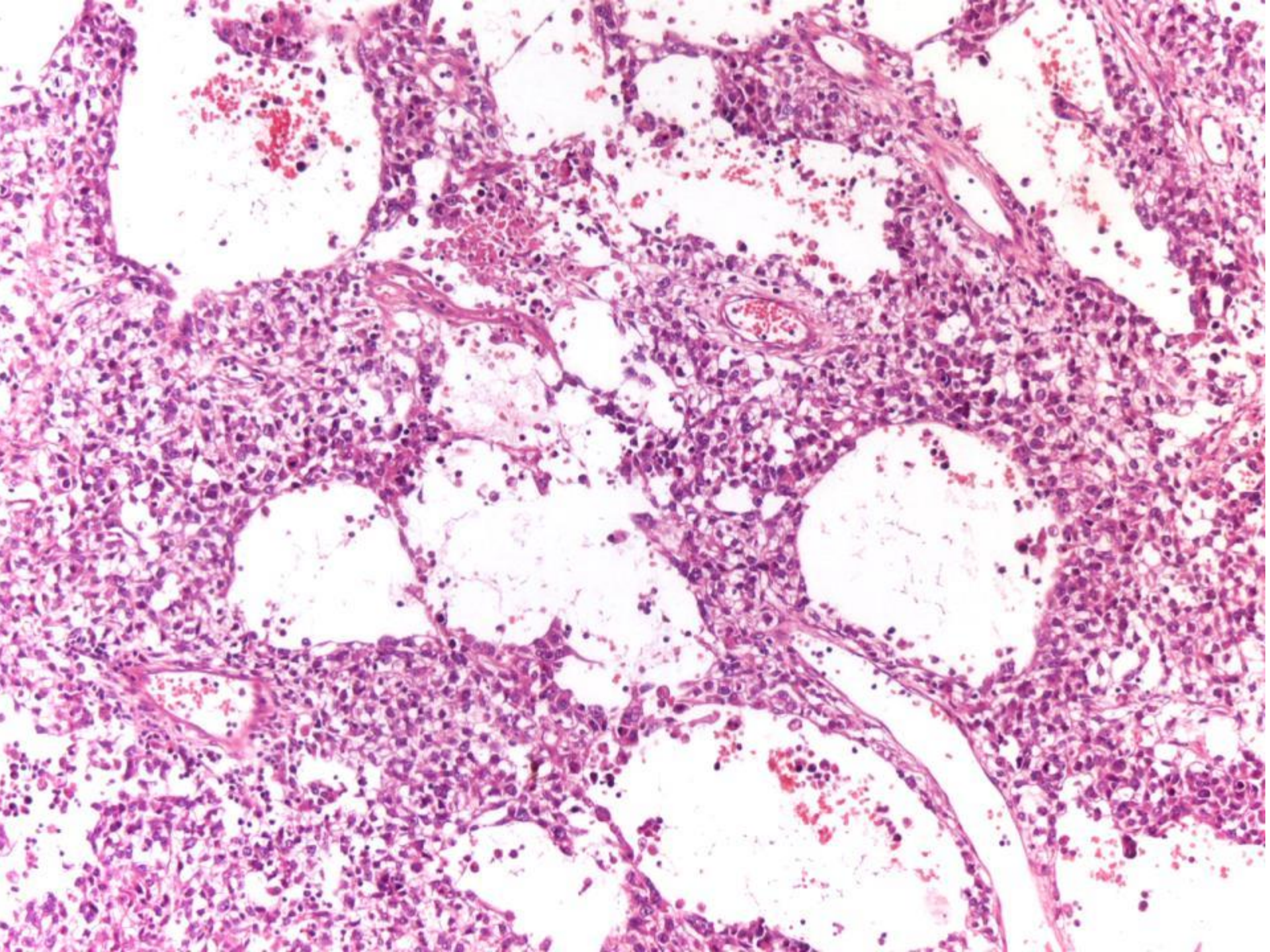


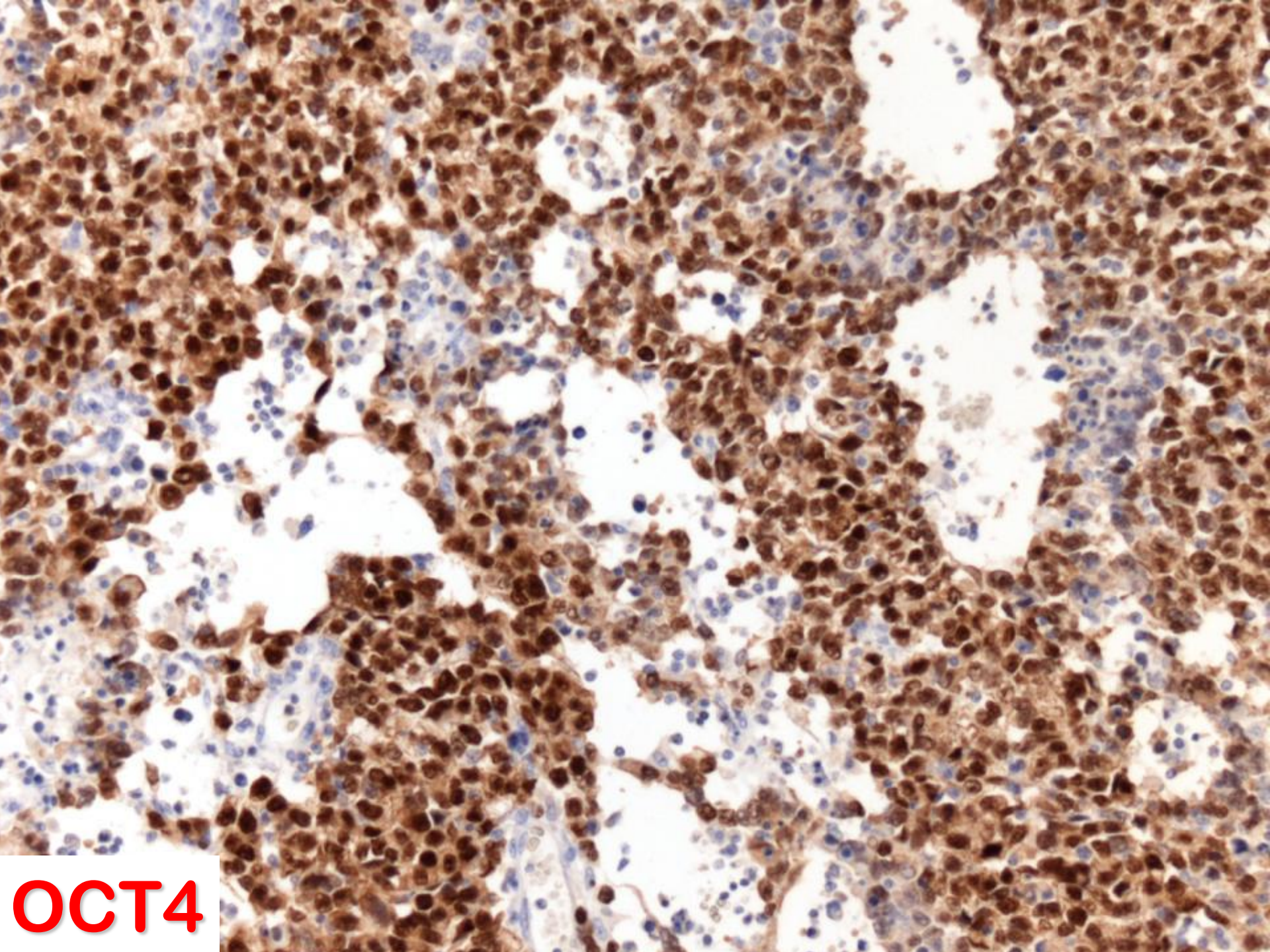
Dysgerminoma - Immuno

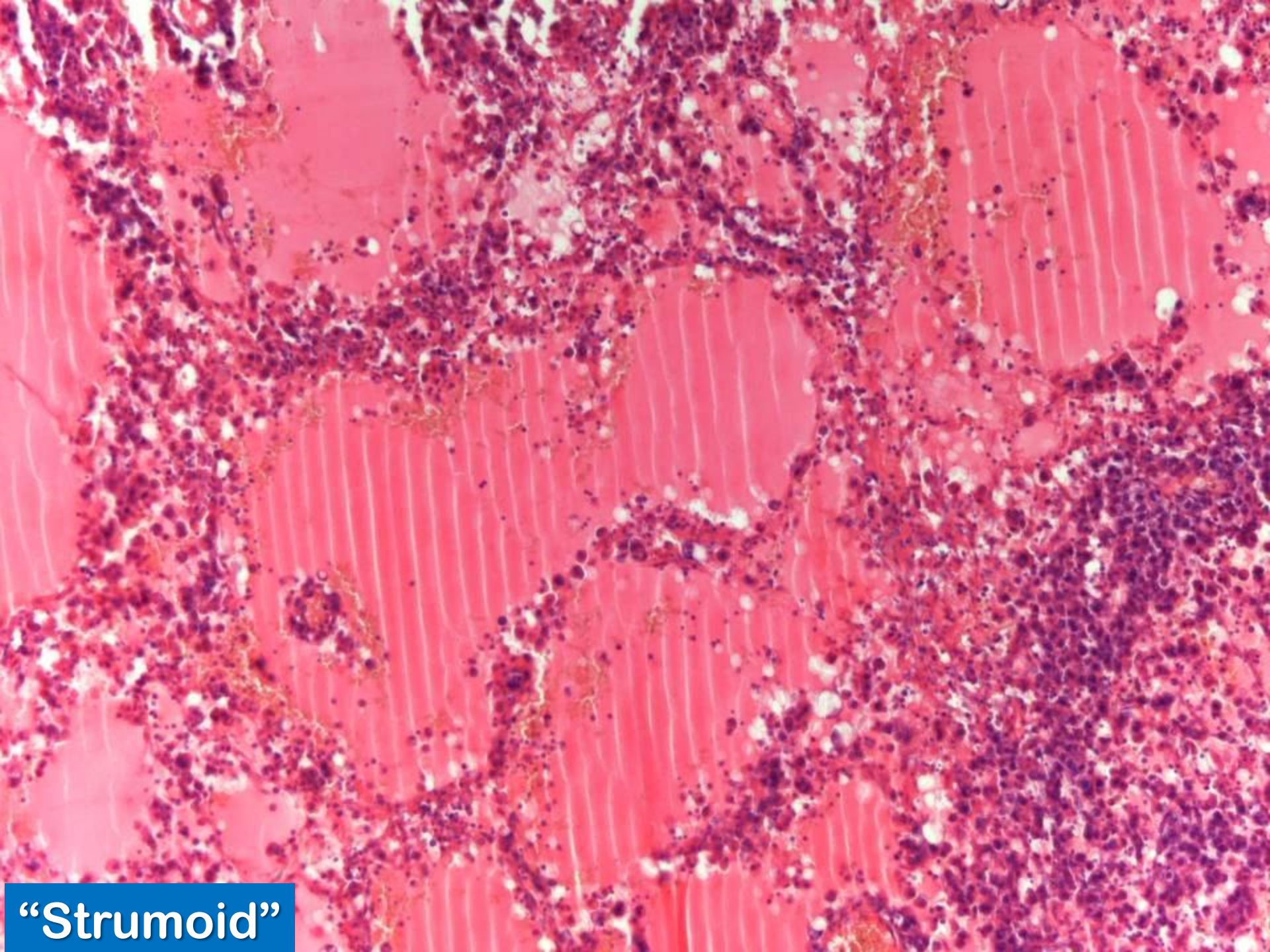


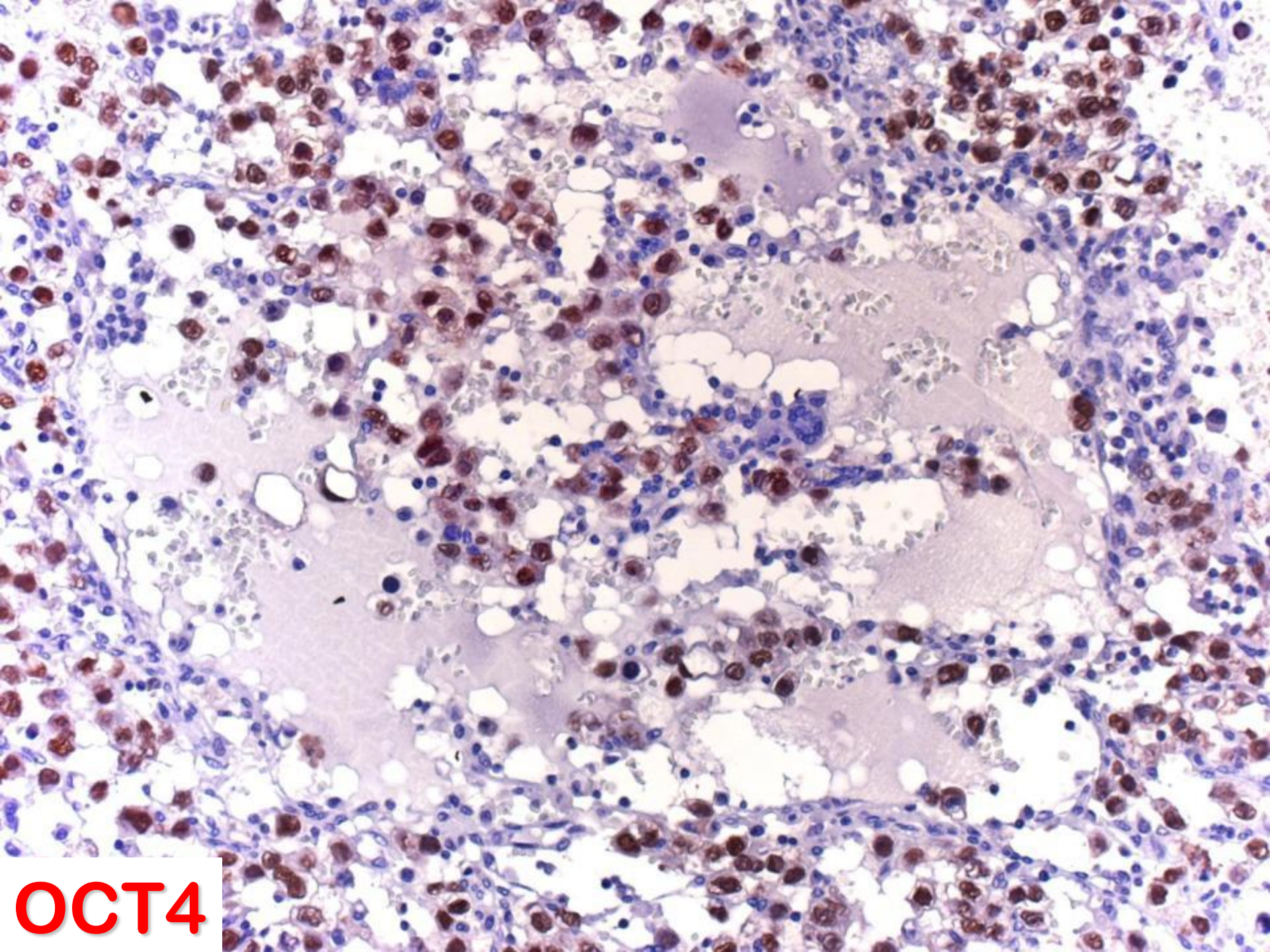
Misinterpretations

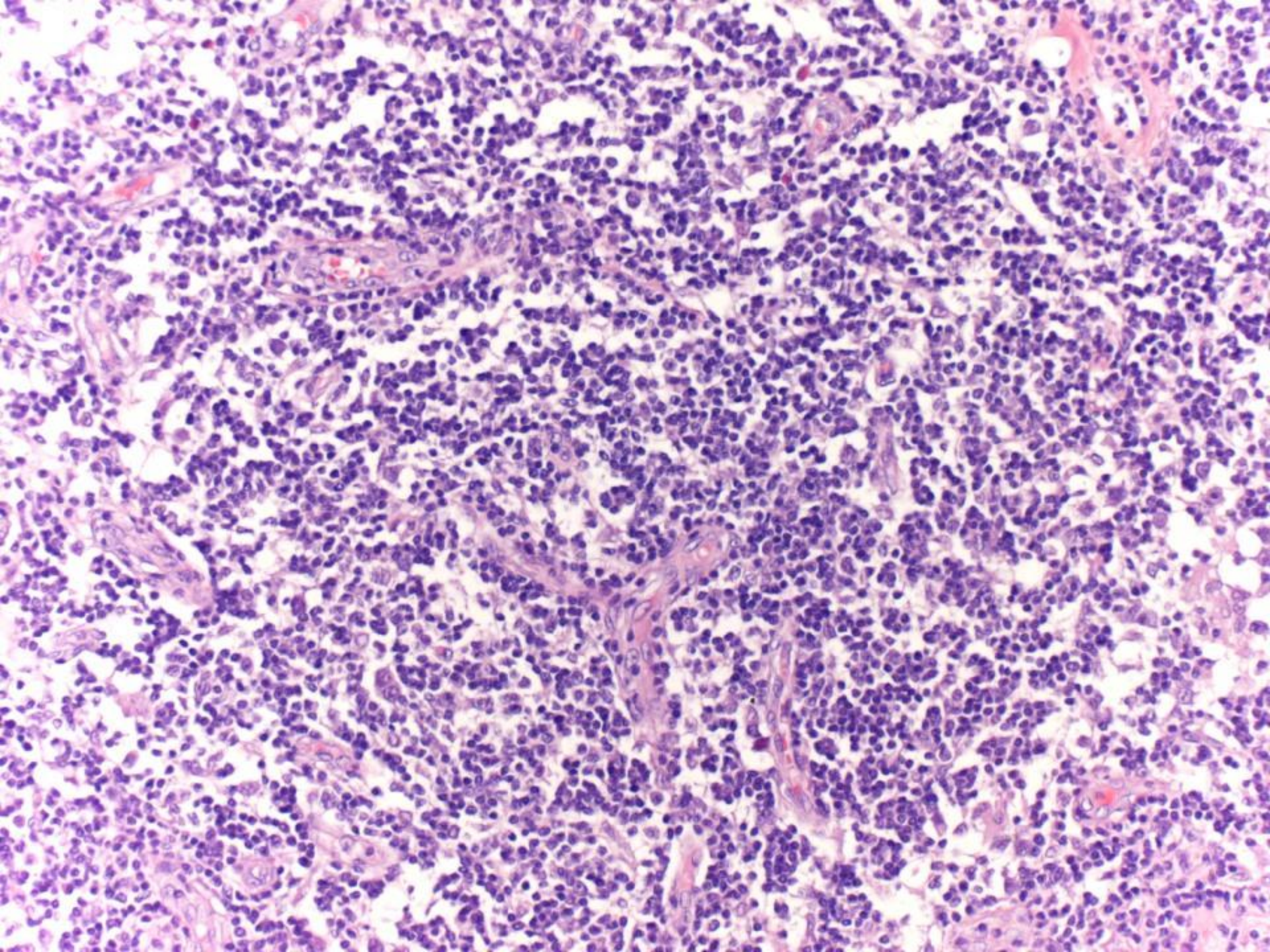


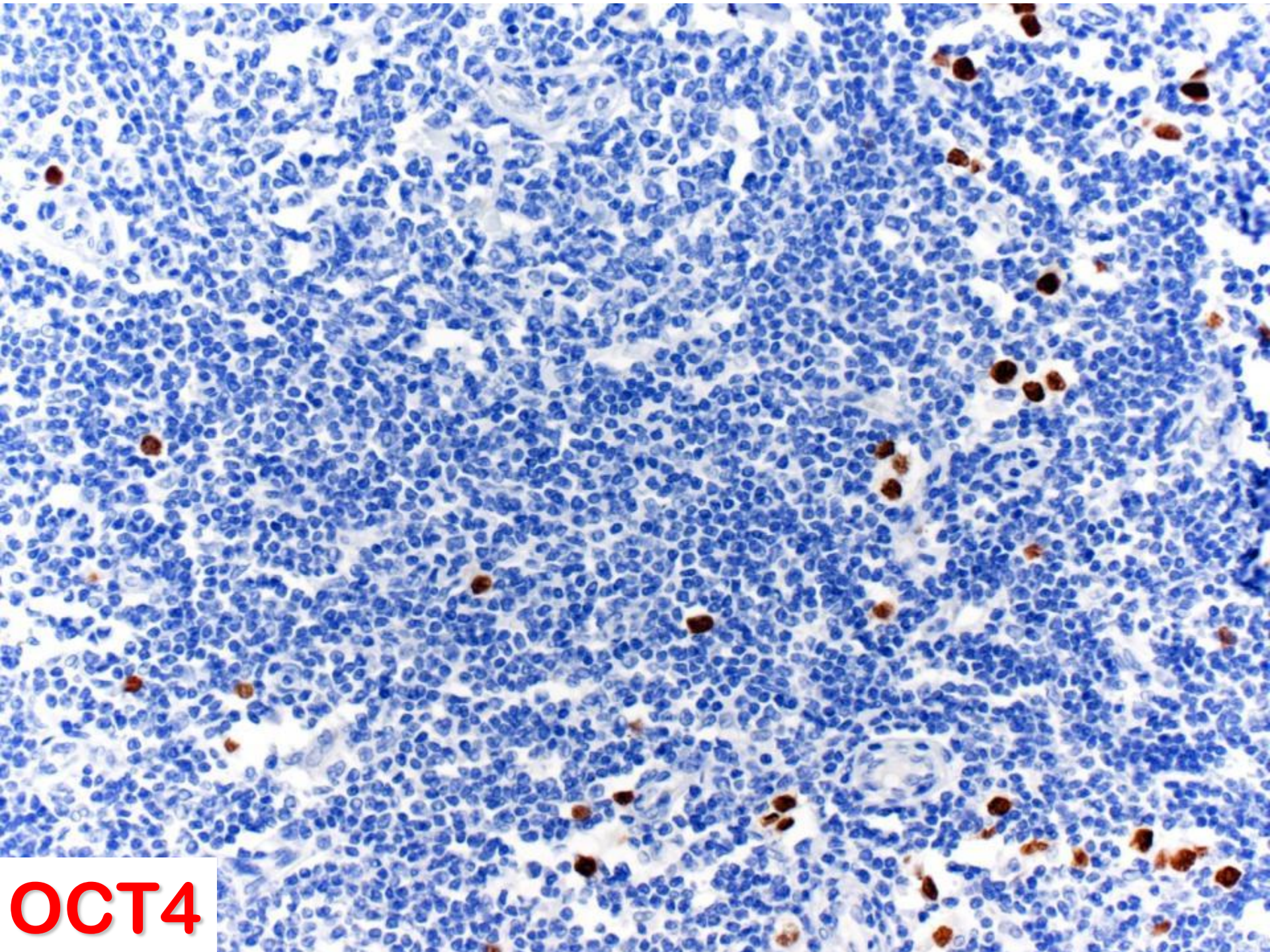



OCT4

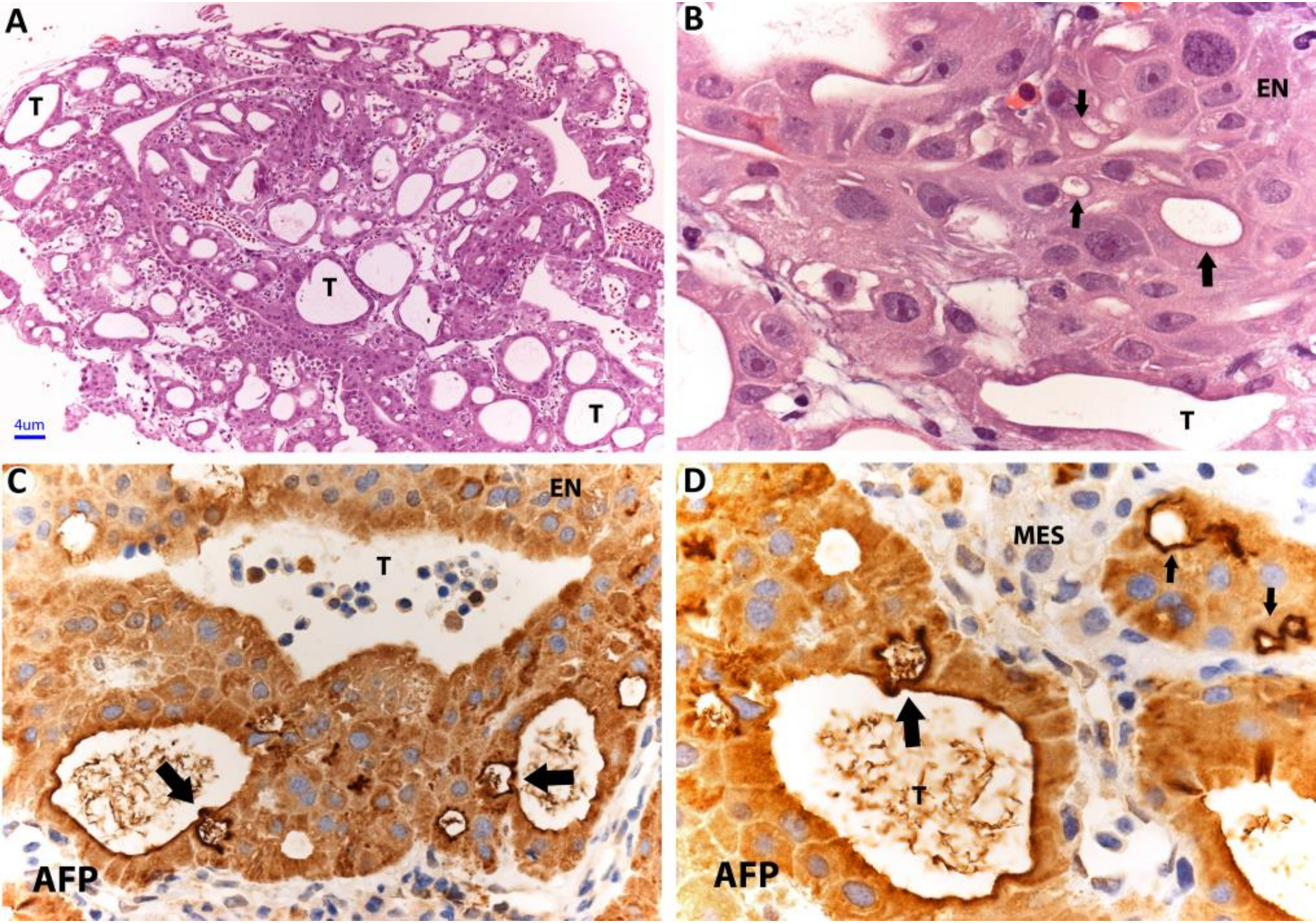

“Strumoid”


OCT4




OCT4

Yolk sac tumours
The primitive endodermal tumours


A
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B
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AFP
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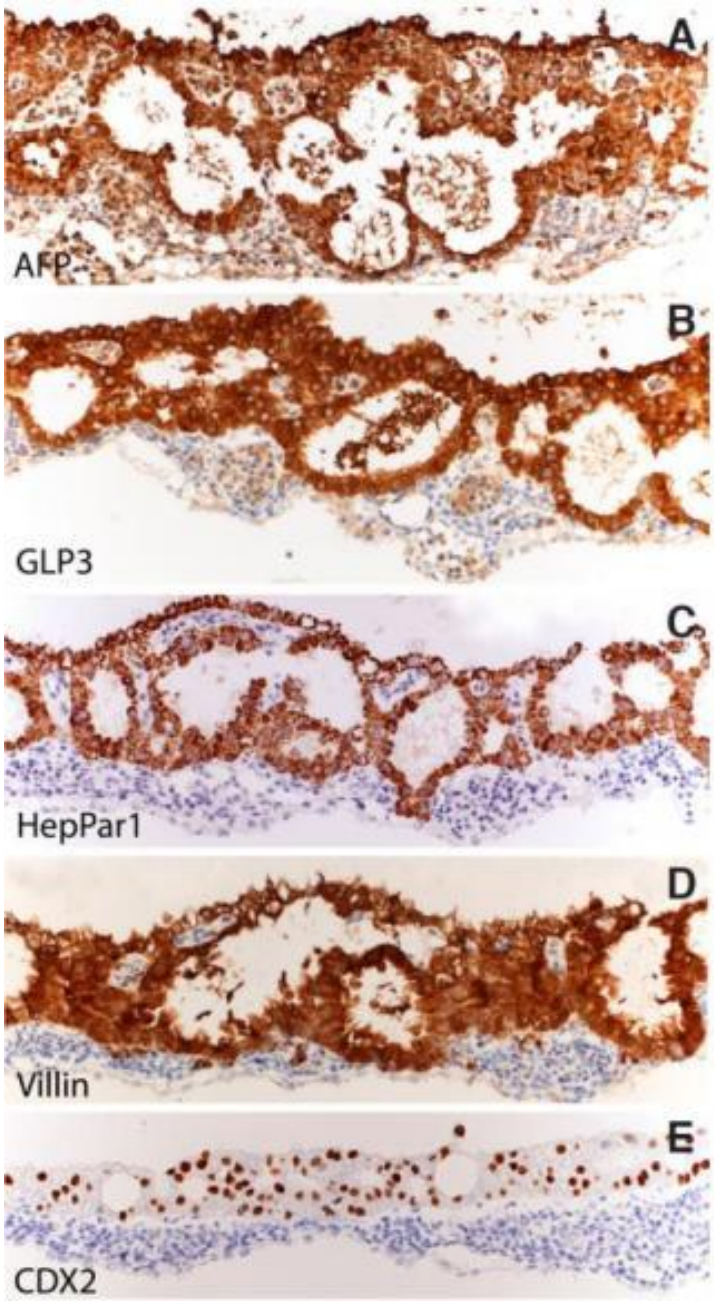
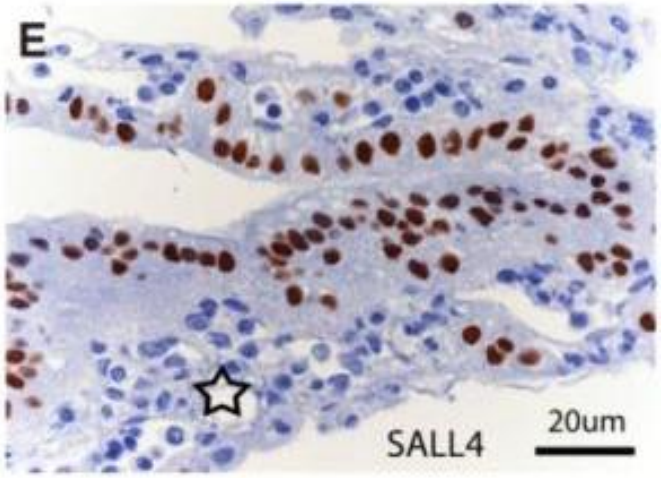
AFP





SHYS IMMUNOPHENOTYPE

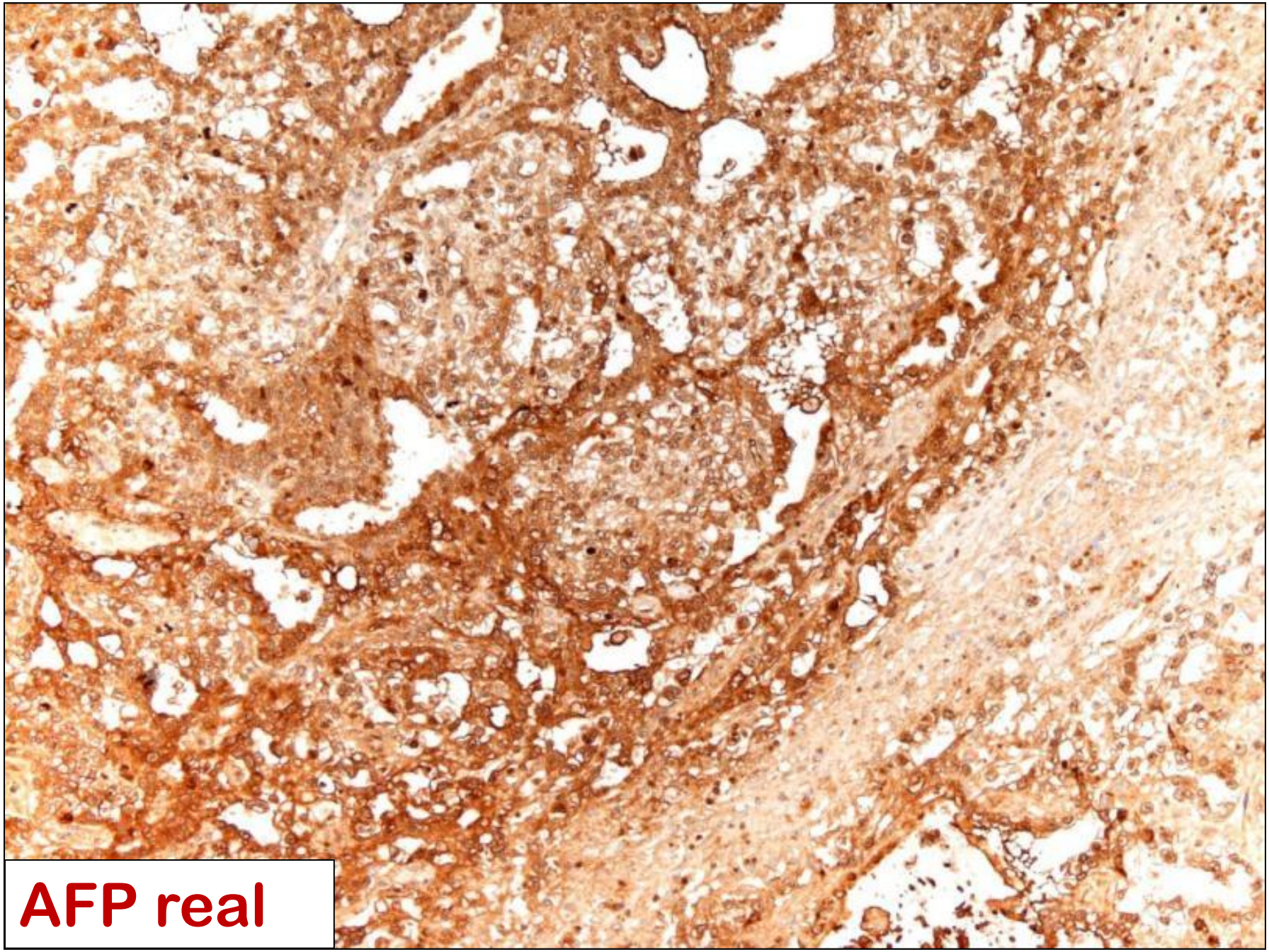
		ANTIBODIES						
Week	#	AFP	GLP3	HepPar-1	Villin	CDX2	SALL4	D2-40
5-6	1	1/1	-	-	-	-	-	-
7-8	15	15/15	15/15	12/14*	11/12*	10/14*	10/13*	15/15
9-11	10	10/10	10/10	9/10	5/9*	9/10	3/8*	8/9*

All antibodies, except for podoplanin D2-40, were expressed in the endodermal layer. Only podoplanin was positive in the mesothelium.

(*) In some cases, step sections failed to produce a sufficient number of slides to complete the study of some antibodies

Alpha-foetoprotein (AFP)

- Member of the albuminoid gene superfamily secreted by both primitive and SHYS
- Functional binding and transport of ligands
- Immunohistochemical gold standard of YST. However, its negativity does not exclude a diagnosis of YST. Expression is often patchy


AFP real

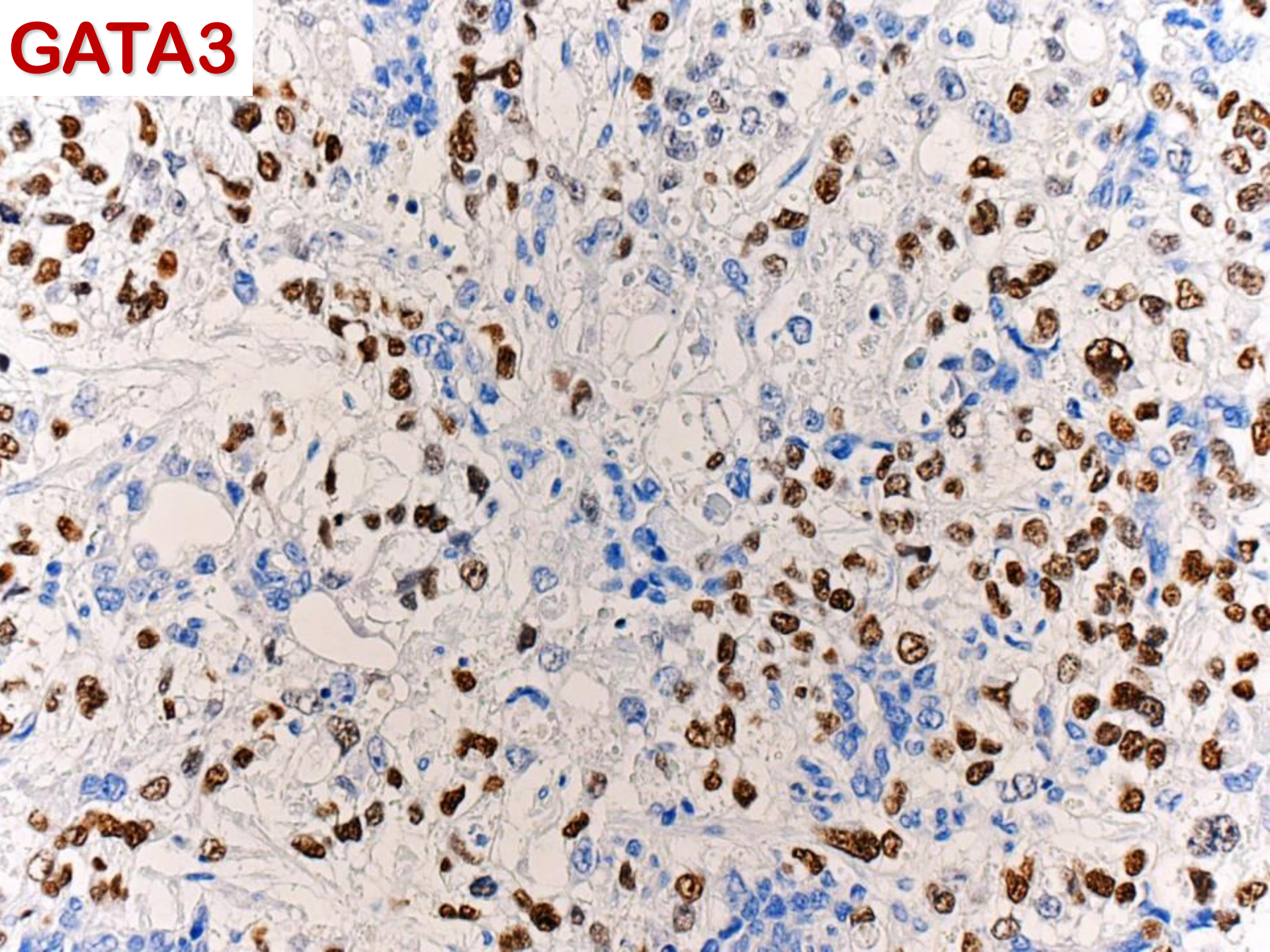
Glypican 3 (GPC3)

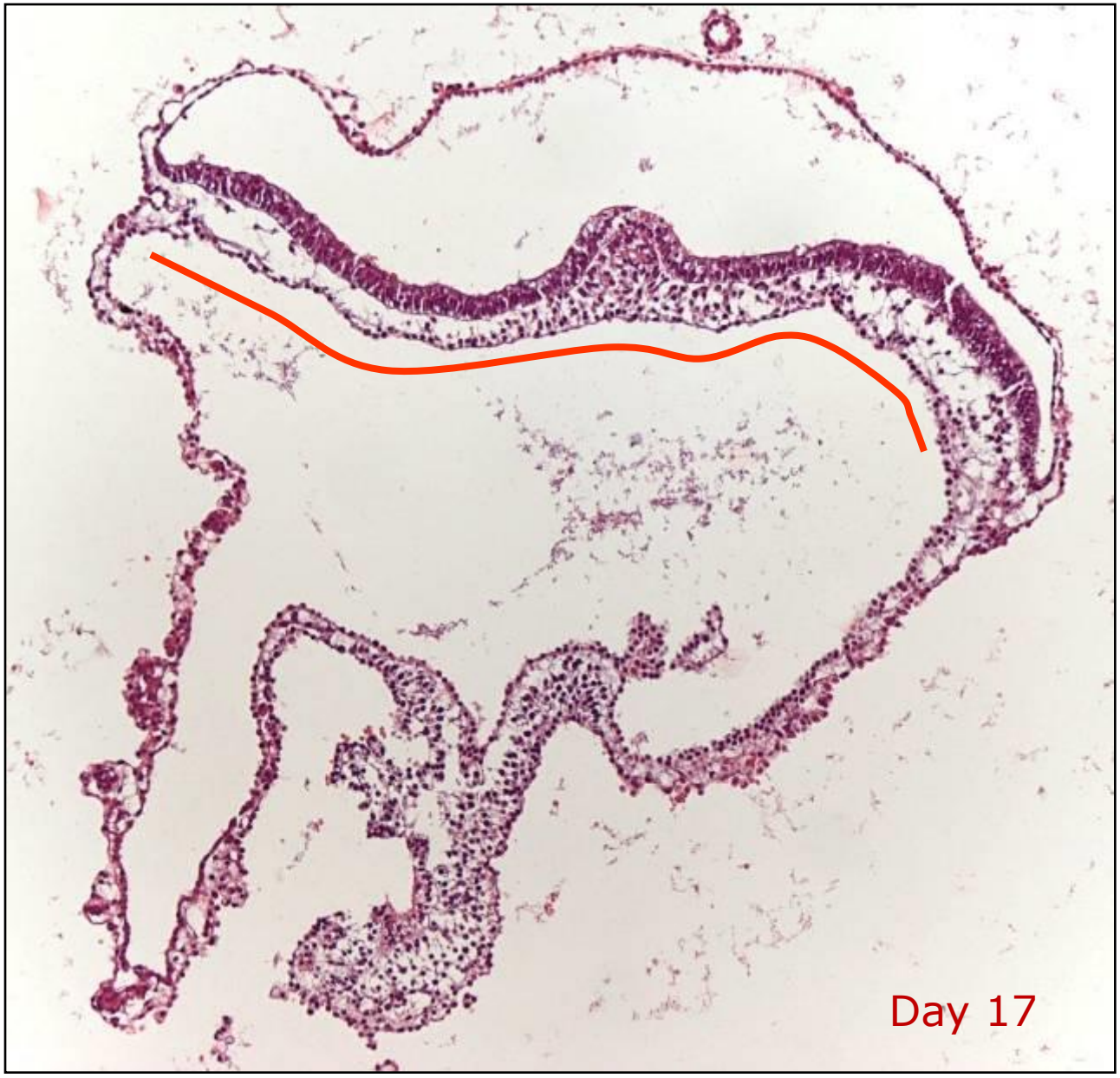
- Expressed in 8-11th week SHYS, but also in developing liver, lung, pancreas, neuroectodermal epithelium and syncytiotrophoblast.
- GPC3 is a sensitive but non-specific marker for YSTs and, to a certain extent, it parallels AFP distribution.
- Consequently, it is positive in other embryonal tumours: neuro, medullo- and nephroblastoma

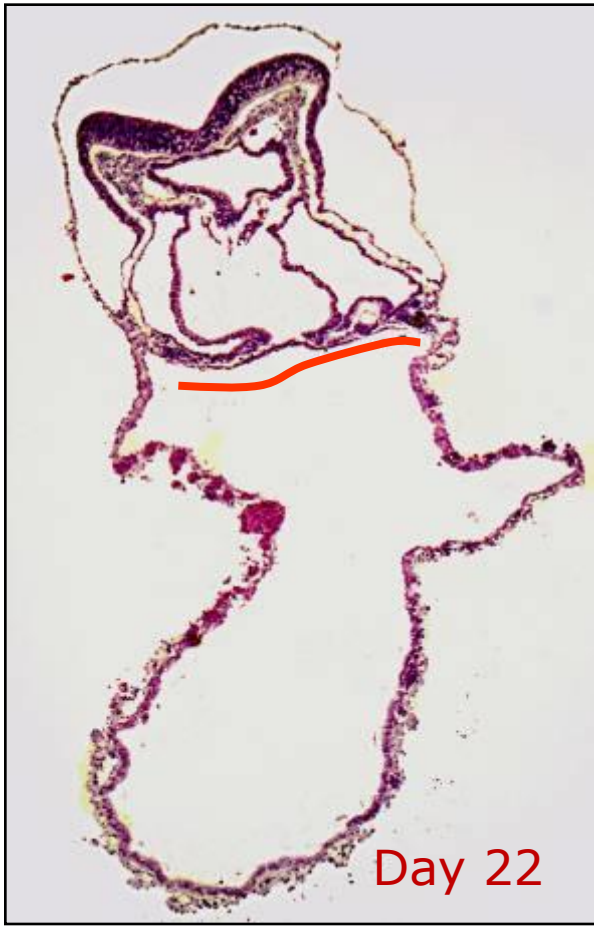
GATA3

- Transcription factor
- GATA3 participates in differentiation
  - Breast epithelium, urothelium
  - T-cell development

Am J Surg Pathol 2014;38:13


GATA3


Day 17


Day 22

Germ cell tumours

J. Prat
D. Cao
S.G. Carinelli
F.F. Nogales
R. Vang
C.J. Zaloudek

Yolk sac tumour

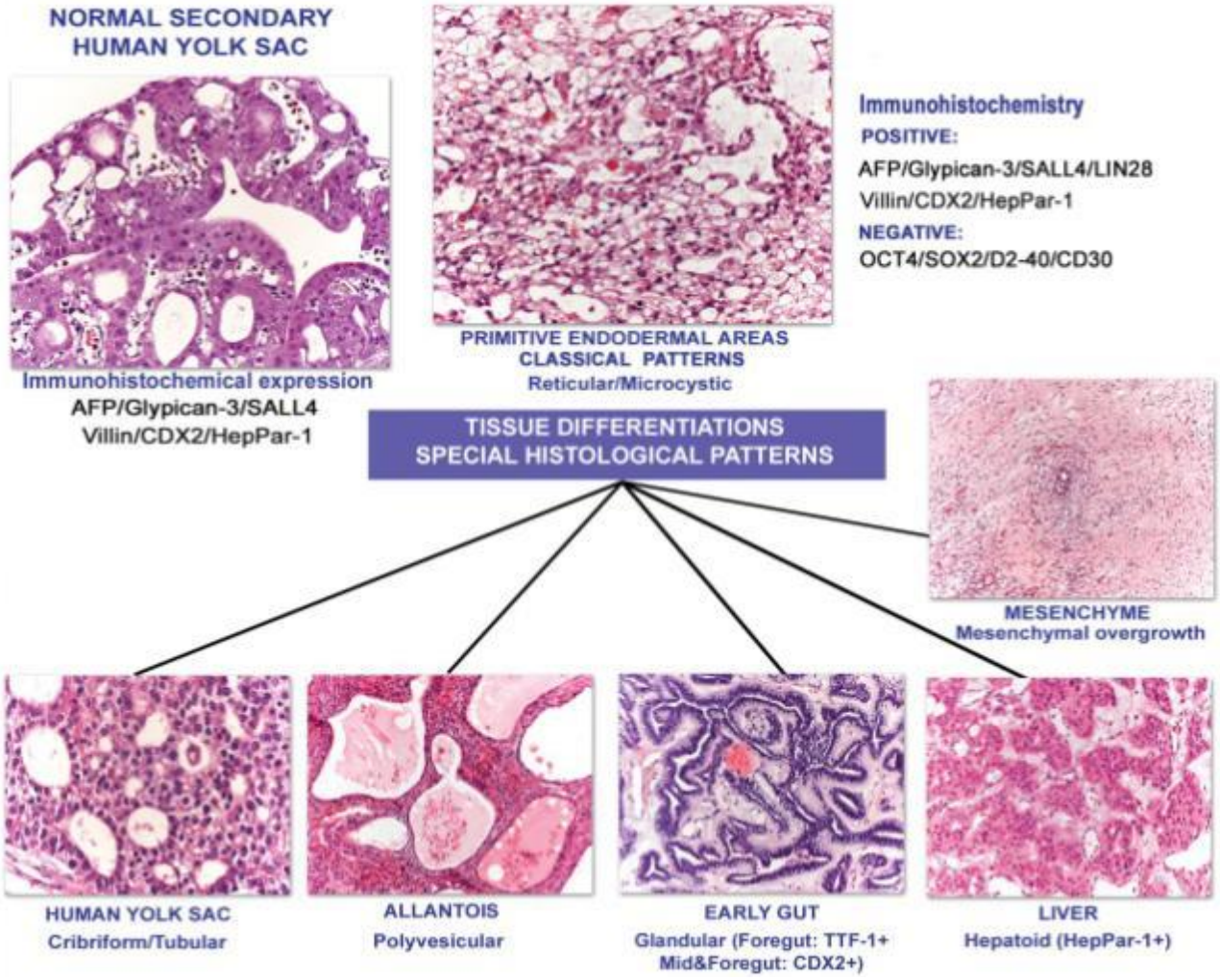
Definition

Yolk sac tumour is a primitive germ cell tumour with a variety of distinctive patterns and which may also exhibit differentiation into endodermal structures, ranging from the primitive gut and mesenchyme to the derivatives of extra-embryonal (secondary yolk sac and allantois) and embryonal somatic tissues (intestine, liver and mesenchyme) {1373}.

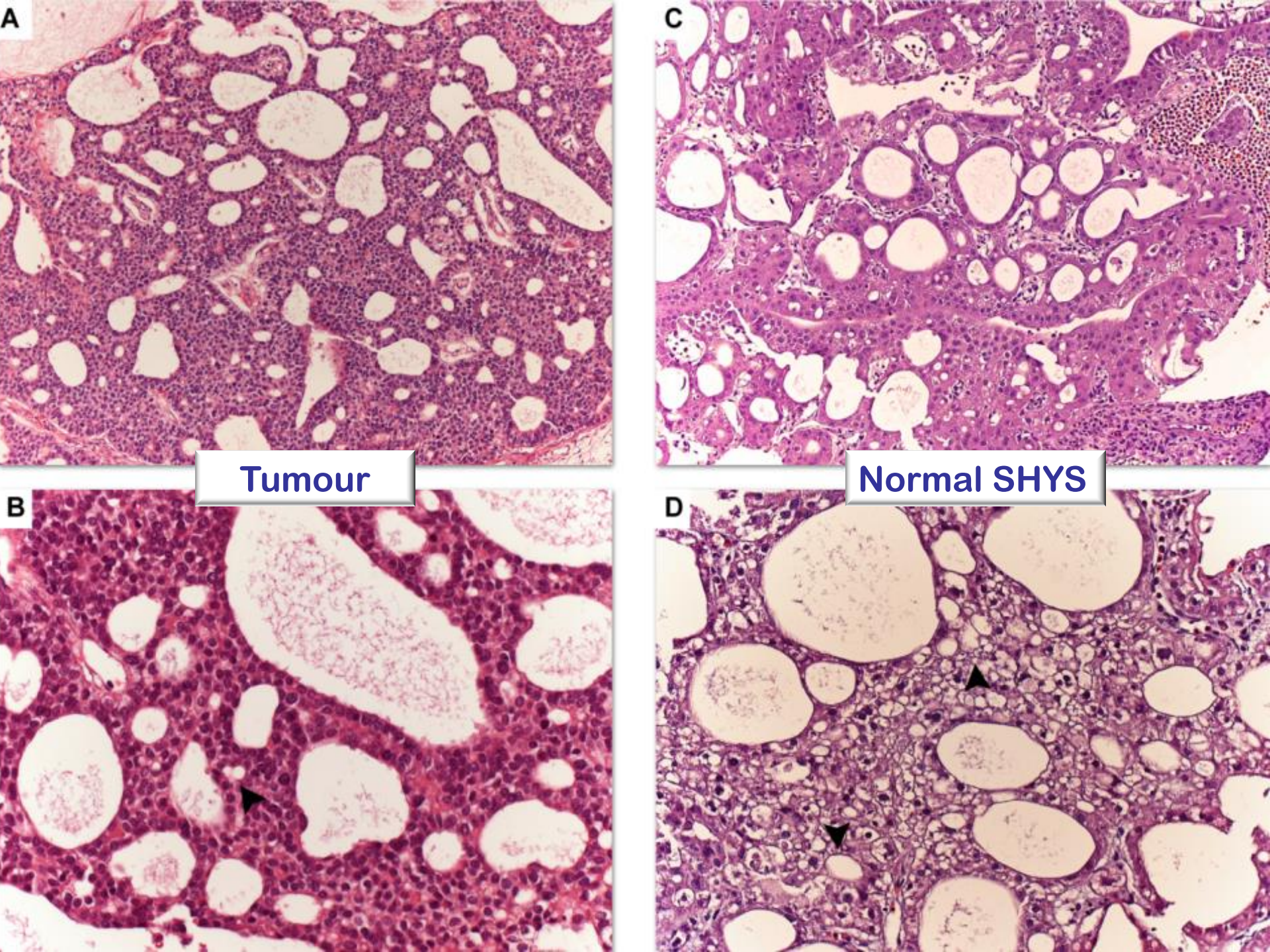
ICD-O code 9071/3

Macroscopy

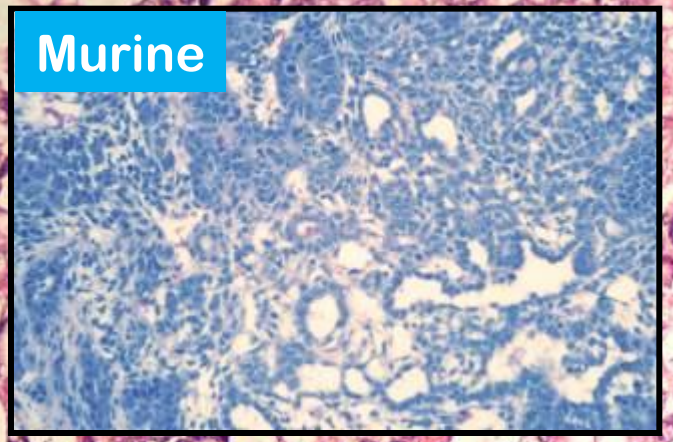
These tumours are large, soft and usually



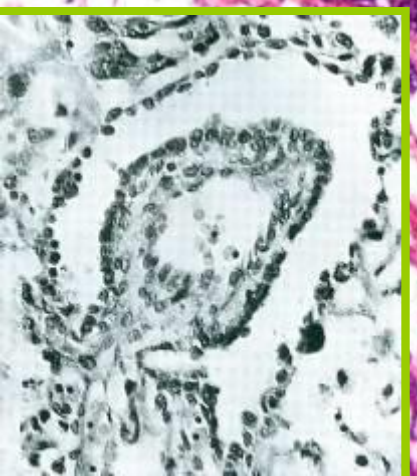
WHO 2014

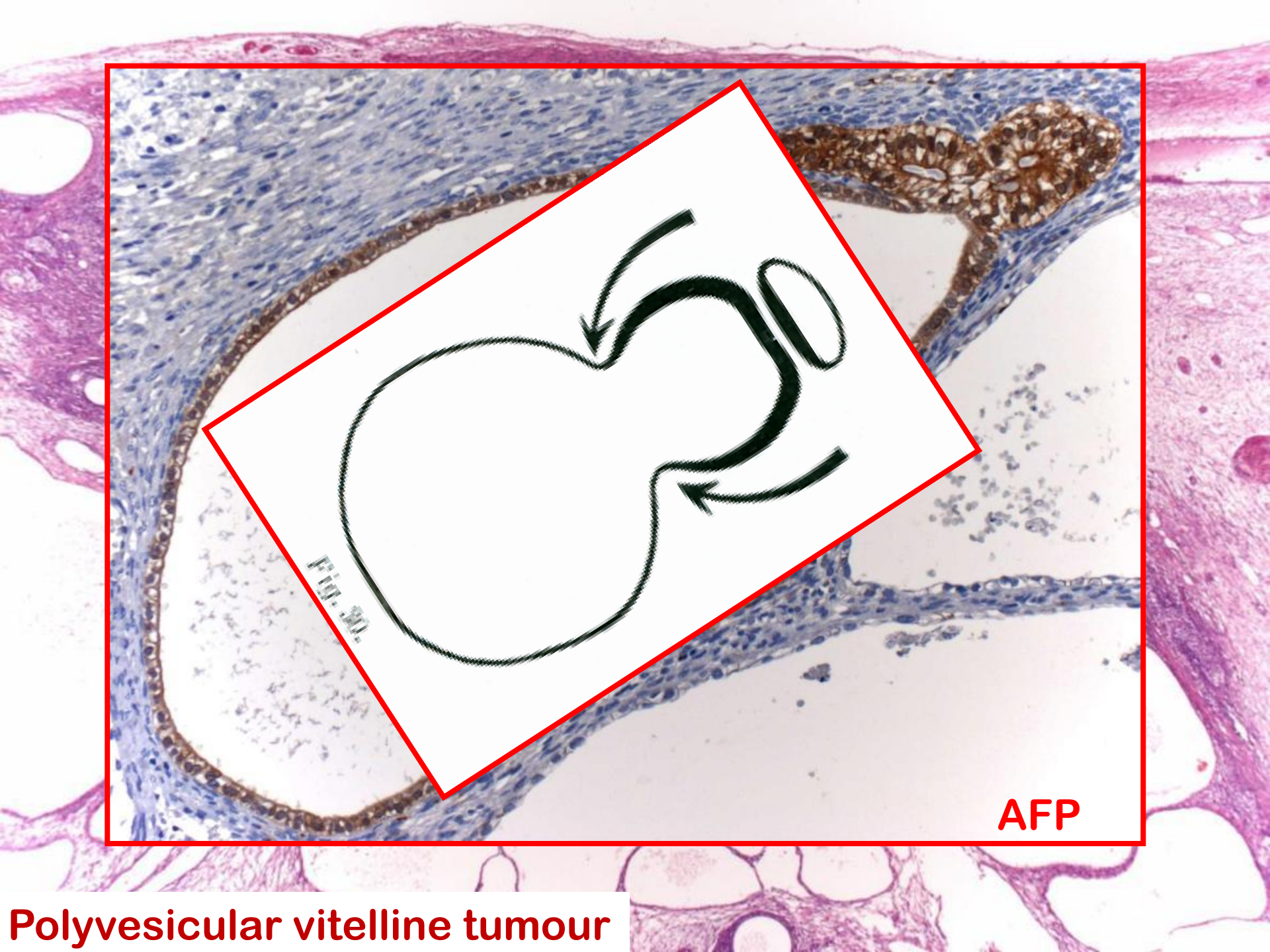

A
C
Tumour
Normal SHYS
B
D

Classic microcystic

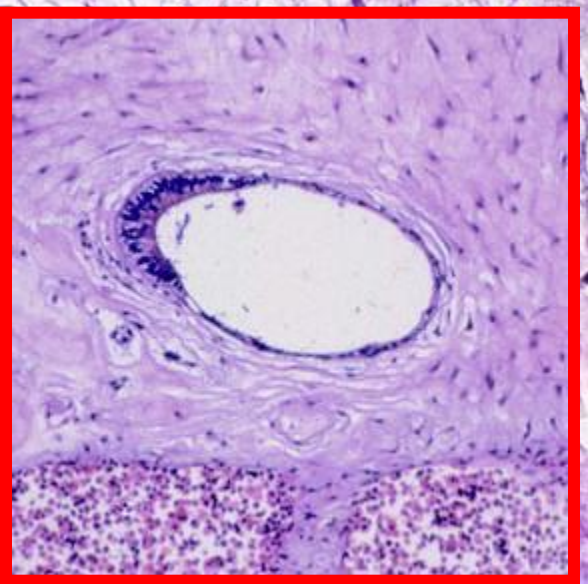


Endodermal sinus: a historical terminology NOT to be used



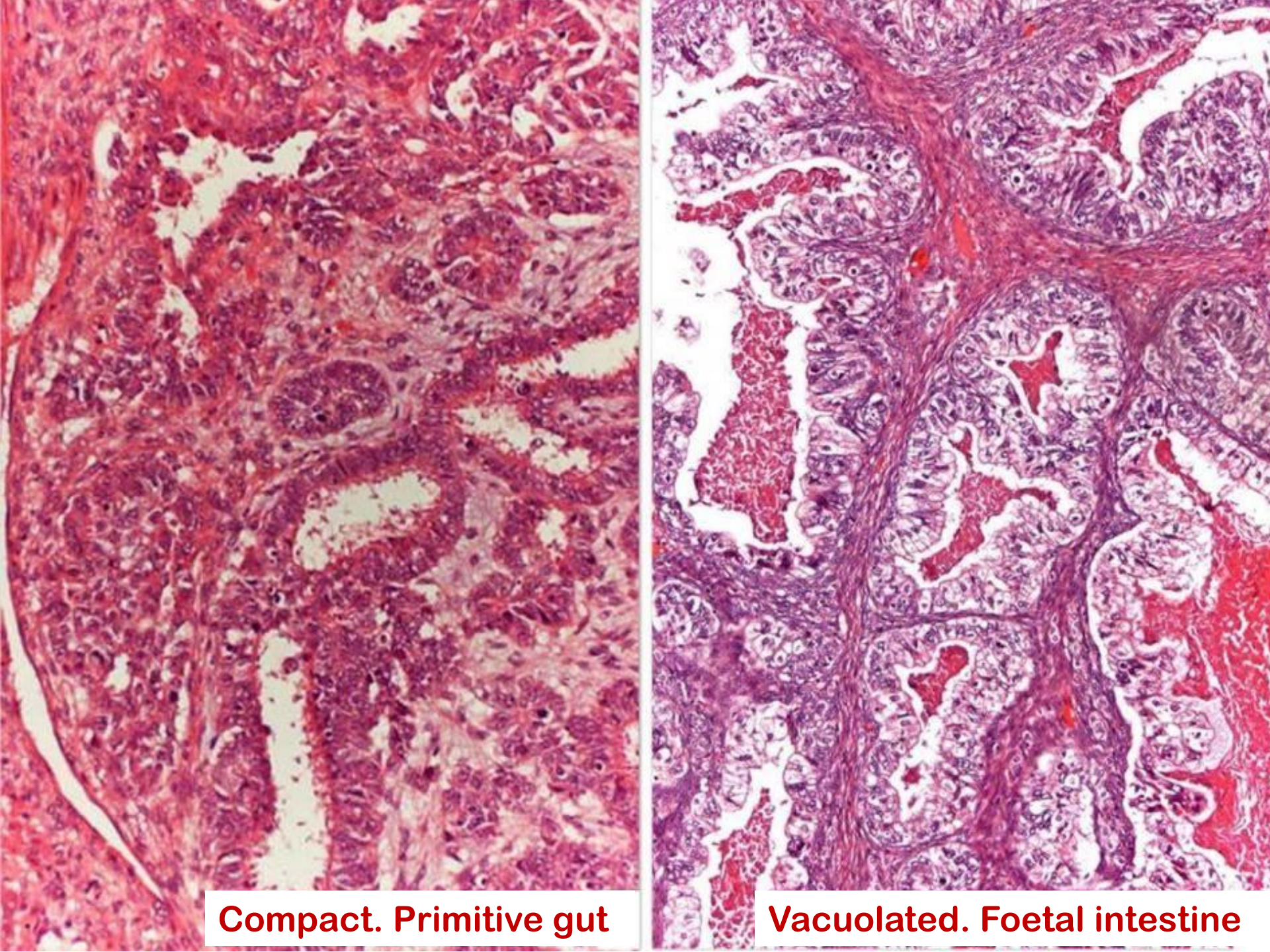


Polyvesicular vitelline tumour

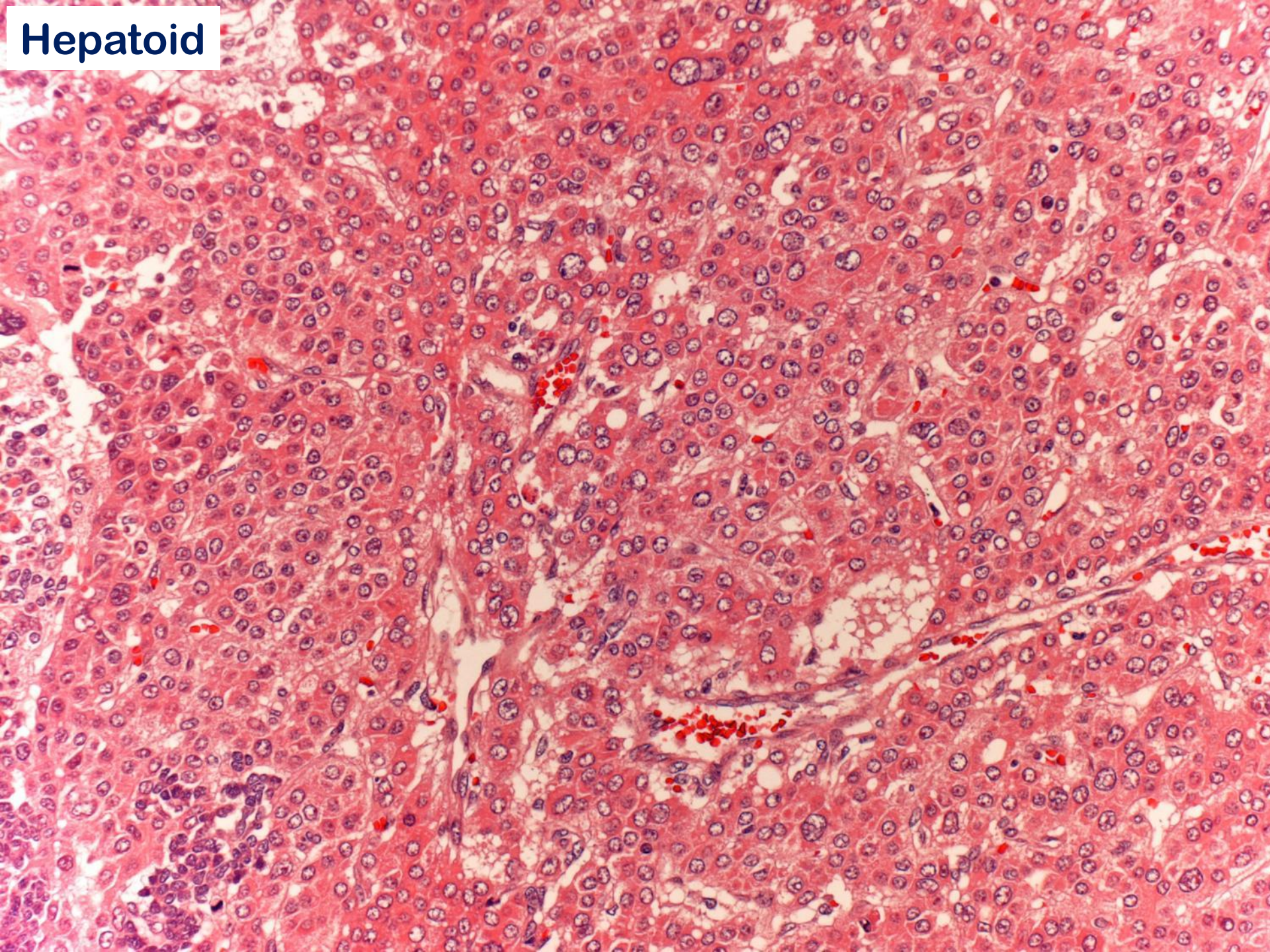


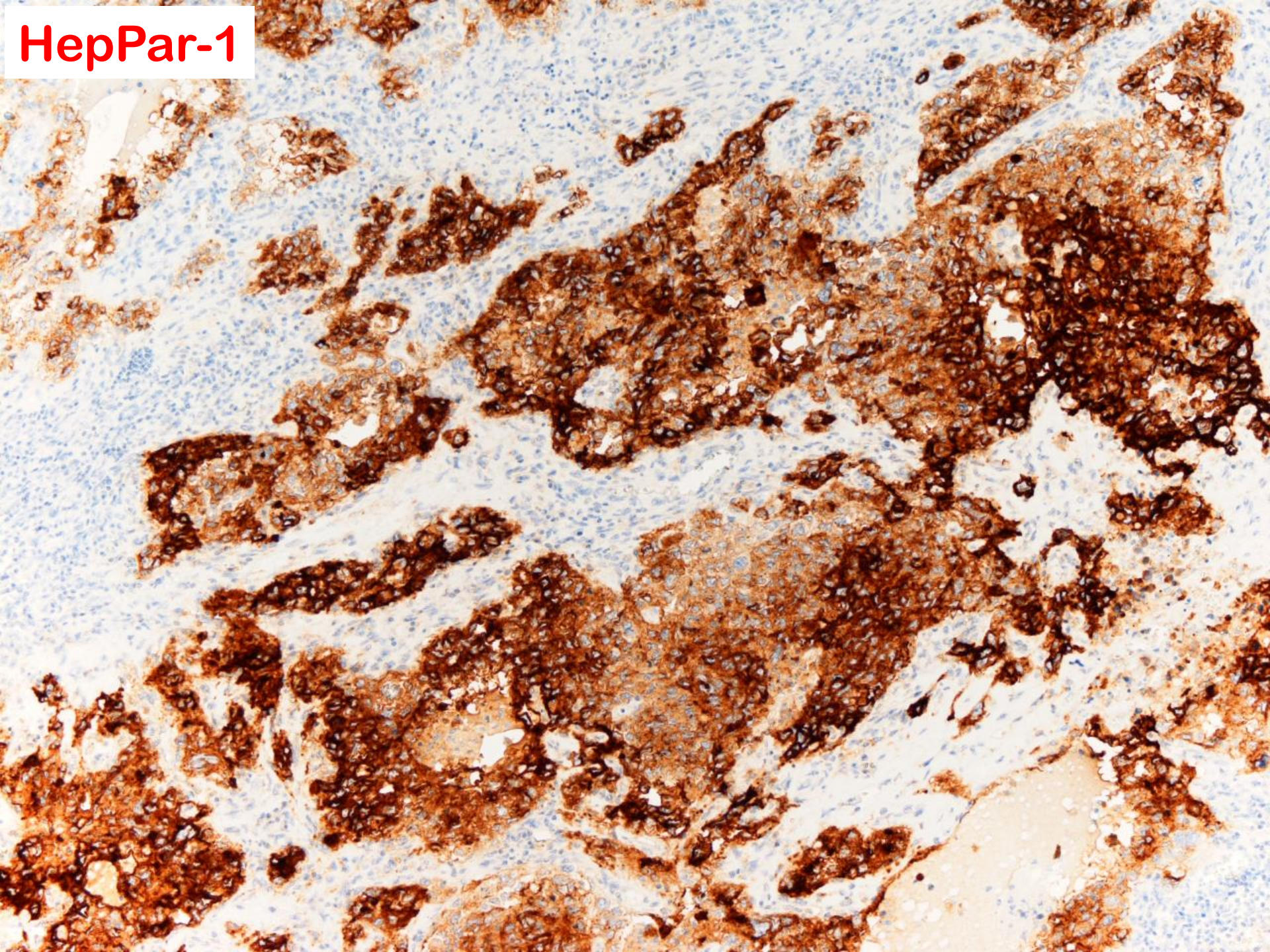
- 1: Heifetz et al. Immature teratomas in children: pathologic considerations: a report from the combined Pediatric Oncology Group/Children's Cancer Group. Am J Surg Pathol 1998;22:1115.

….morphologic diagnoses that were most frequently misinterpreted by contributing pathologists included the failure to recognize two well-differentiated patterns of YST (the **hepatoid** pattern resembling fetal liver and the **well-differentiated glandular** pattern resembling fetal lung or intestine).


Compact. Primitive gut
Vacuolated. Foetal intestine

Hepatoid




HepPar-1

Histopathology

Histopathology 2014 DOI: 10.1111/his.12373

A diagnostic immunohistochemical panel for yolk sac (primitive endodermal) tumours based on an immunohistochemical comparison with the human yolk sac

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[1]*Departments of Pathology, San Cecilio University Hospital, Granada, Spain,* [2]*Dr Abelardo Buch López Institute of Nephrology, Havana, Cuba, and* [3]*Master Diagnostica, Granada, Spain*

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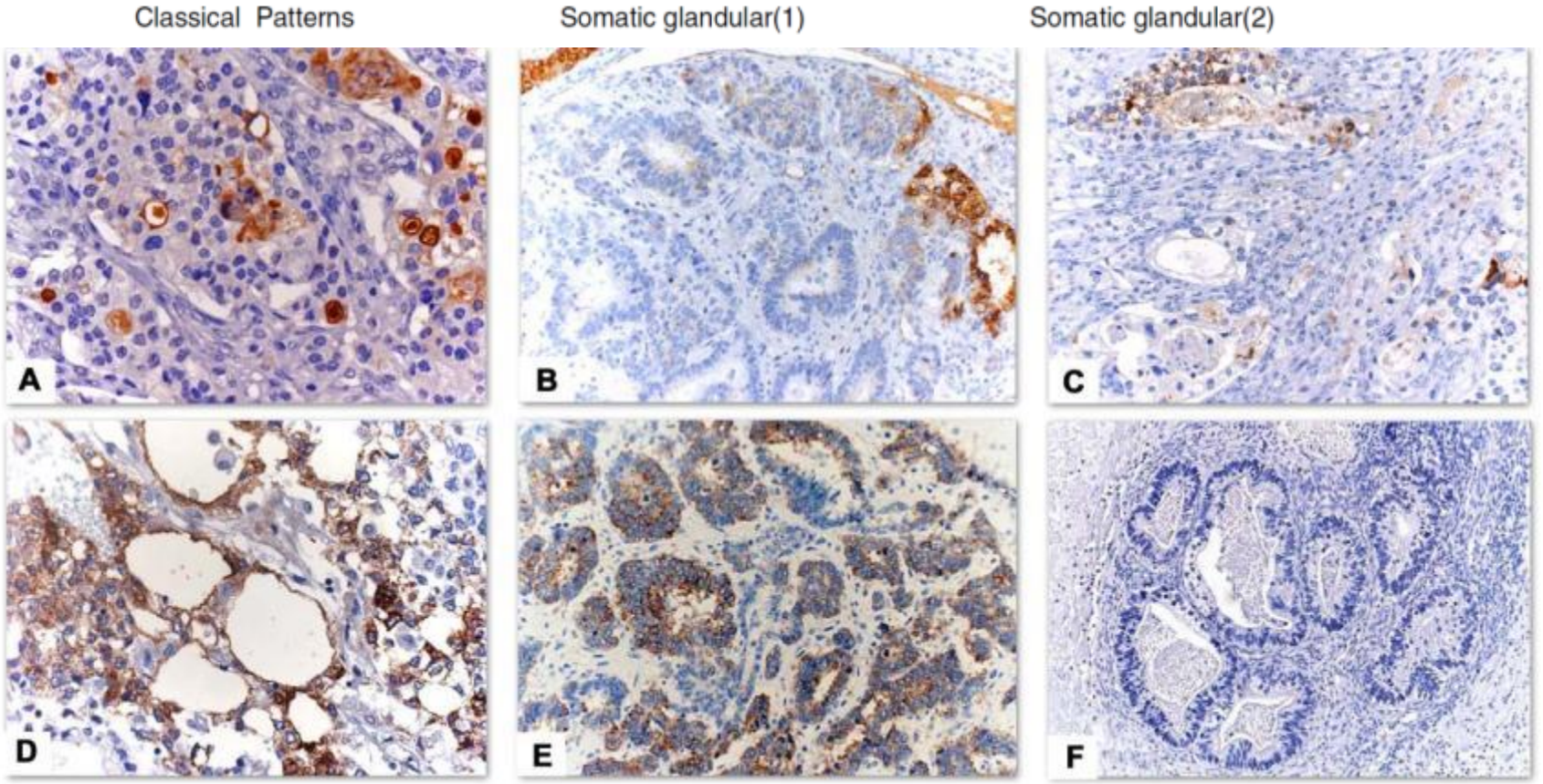
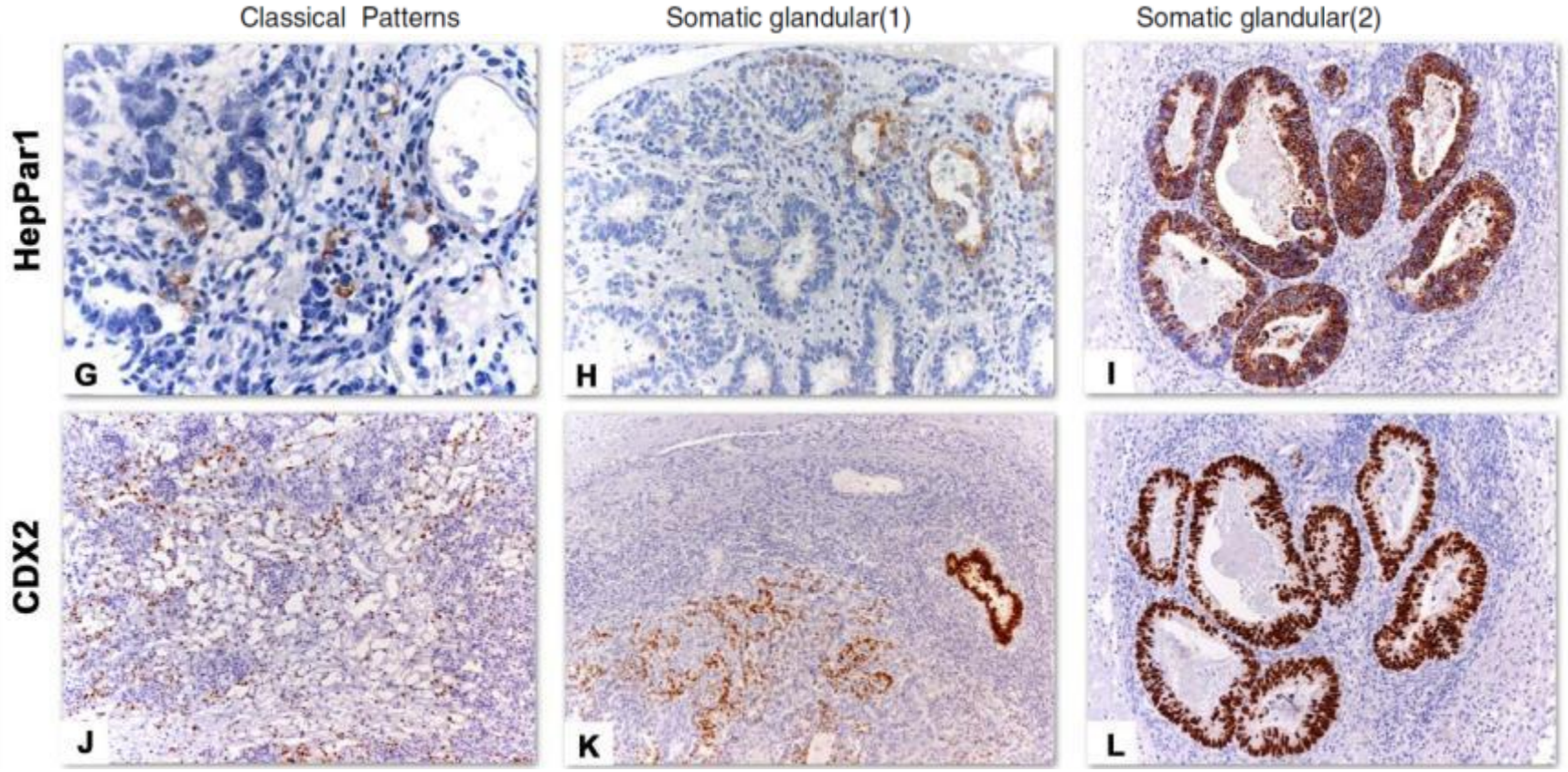
(2014) *Histopathology*



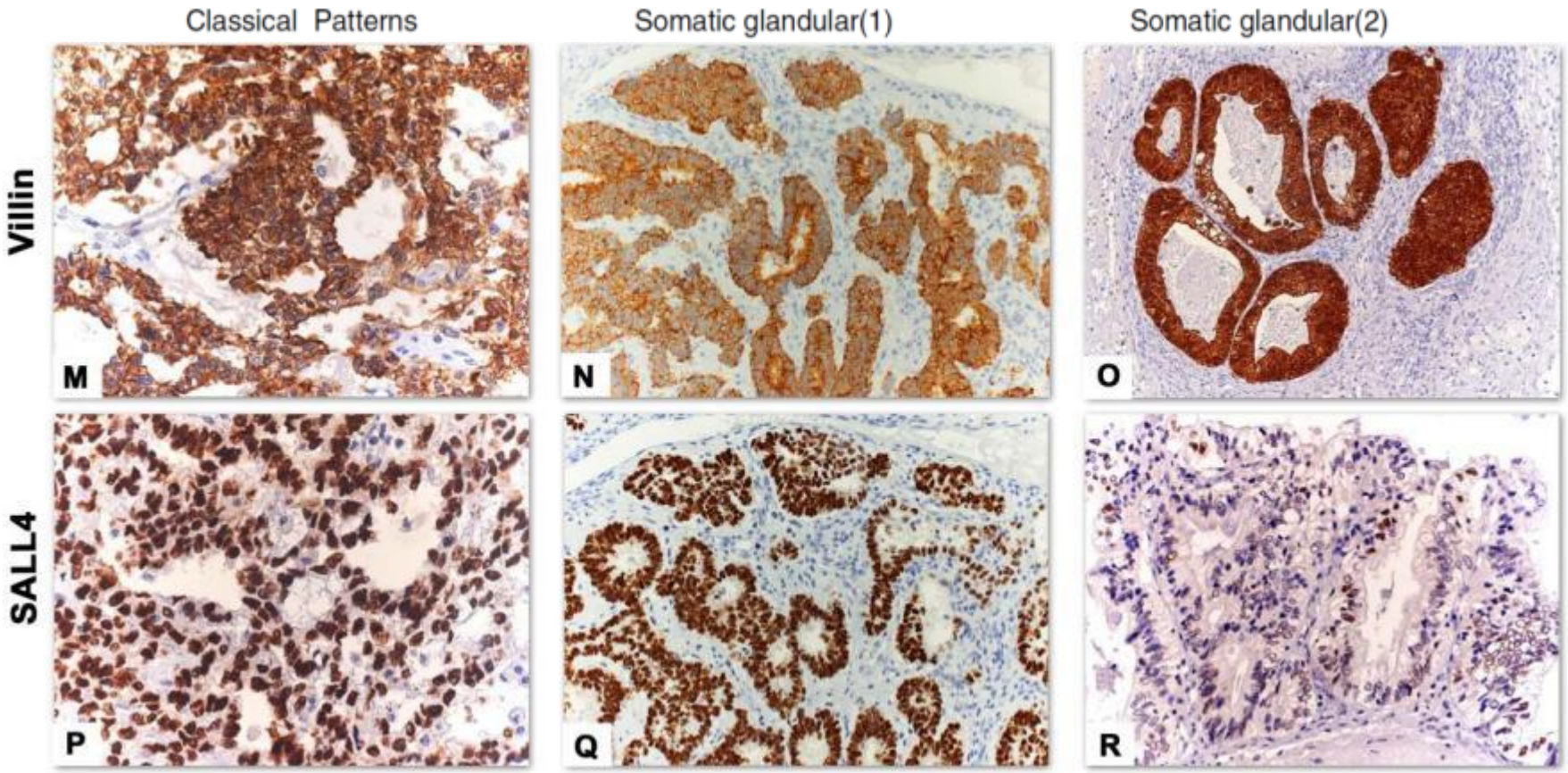
Histology	AFP	GPC3	HepPar–1	CDX2	Villin	TTF–1	SALL4	LIN28
Classical patterns								
Microcystic/reticular	14/14 H	14/14 D	14/14 F	14/14 F	14/14 D	–	13/13D	10/10 D
Polyvesicular	1/1 H	1/1 D	1/1 F	1/1 F	1/1 D	1/1	1/1 D	1/1 D
Hepatoid	1/1 H	1/1 D	1/1 D	1/1 H	1/1 D	–	1/1 D	1/1 H
Somatic glandular patterns	7/9 F	7/9 H	7/9 F	7/9 H	9/9D	3/5F	8/9 D	4/5 D
Normal human yolk sac[6]	D	D	D	D	D	ND	D	1/1 (5th week) 0/6 (7–8th weeks)

H, heterogeneous; D, diffuse; F, focal; ND, not done.



	Immunohistochemical staining results							
Histology	AFP	GPC3	HepPar–1	CDX2	Villin	TTF–1	SALL4	LIN28
Classical patterns								
Microcystic/reticular	14/14 H	14/14 D	14/14 F	14/14 F	14/14 D	–	13/13D	10/10 D
Polyvesicular	1/1 H	1/1 D	1/1 F	1/1 F	1/1 D	1/1	1/1 D	1/1 D
Hepatoid	1/1 H	1/1 D	1/1 D	1/1 H	1/1 D	–	1/1 D	1/1 H
Somatic glandular patterns	7/9 F	7/9 H	7/9 F	7/9 H	9/9D	3/5F	8/9 D	4/5 D
Normal human yolk sac[6]	D	D	D	D	D	ND	D	1/1 (5th week) 0/6 (7–8th weeks)

H, heterogeneous; D, diffuse; F, focal; ND, not done.



Immunohistochemical staining results

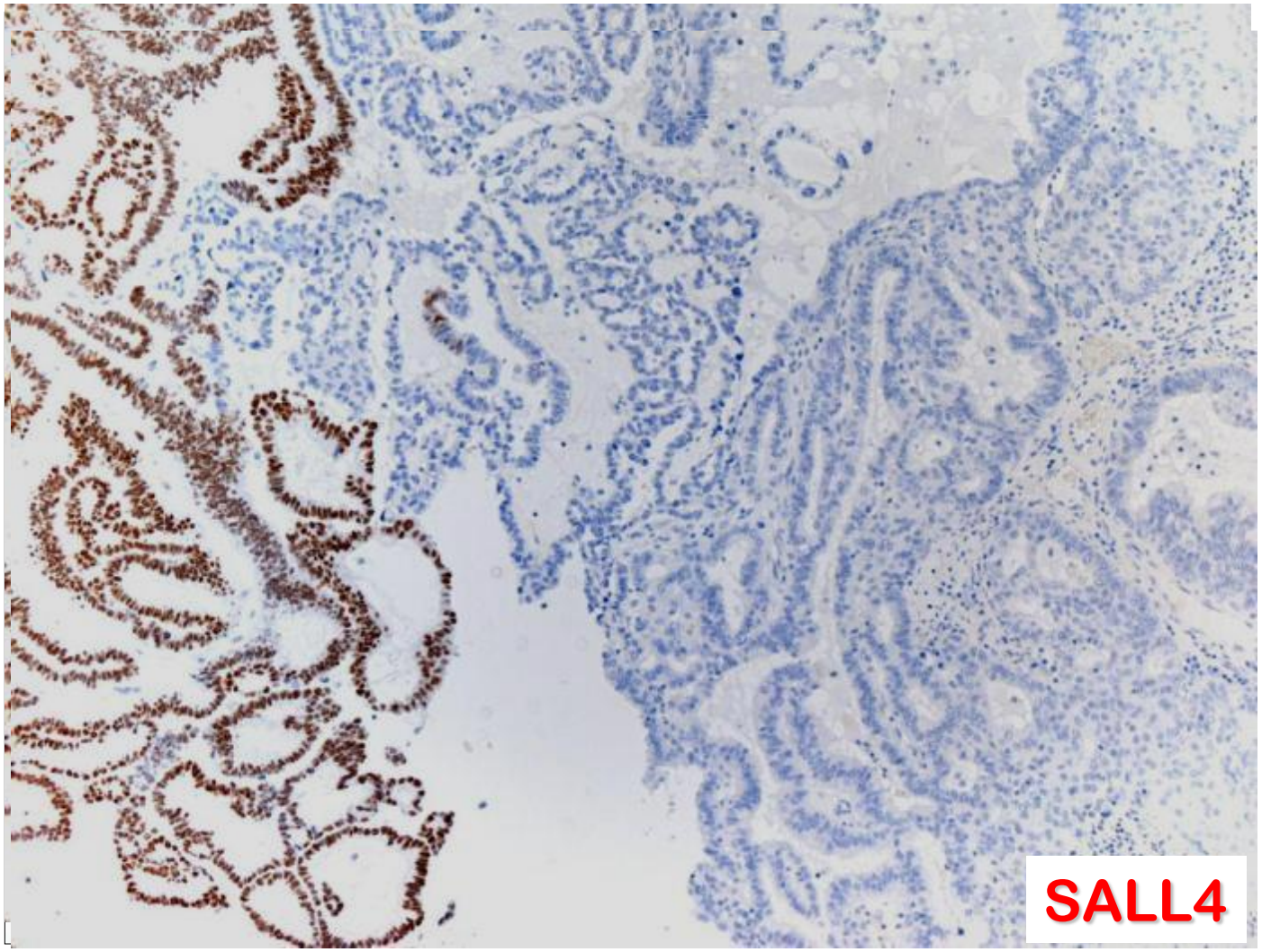
Histology	AFP	GPC3	HepPar–1	CDX2	Villin	TTF–1	SALL4	LIN28
Classical patterns								
Microcystic/reticular	14/14 H	14/14 D	14/14 F	14/14 F	14/14 D	–	13/13D	10/10 D
Polyvesicular	1/1 H	1/1 D	1/1 F	1/1 F	1/1 D	1/1	1/1 D	1/1 D
Hepatoid	1/1 H	1/1 D	1/1 D	1/1 H	1/1 D	–	1/1 D	1/1 H
Somatic glandular patterns	7/9 F	7/9 H	7/9 F	7/9 H	9/9D	3/5F	8/9 D	4/5 D
Normal human yolk sac[6]	D	D	D	D	D	ND	D	1/1 (5th week) 0/6 (7–8th weeks)

H, heterogeneous; D, diffuse; F, focal; ND, not done.

Interpretation problems in special patterns.

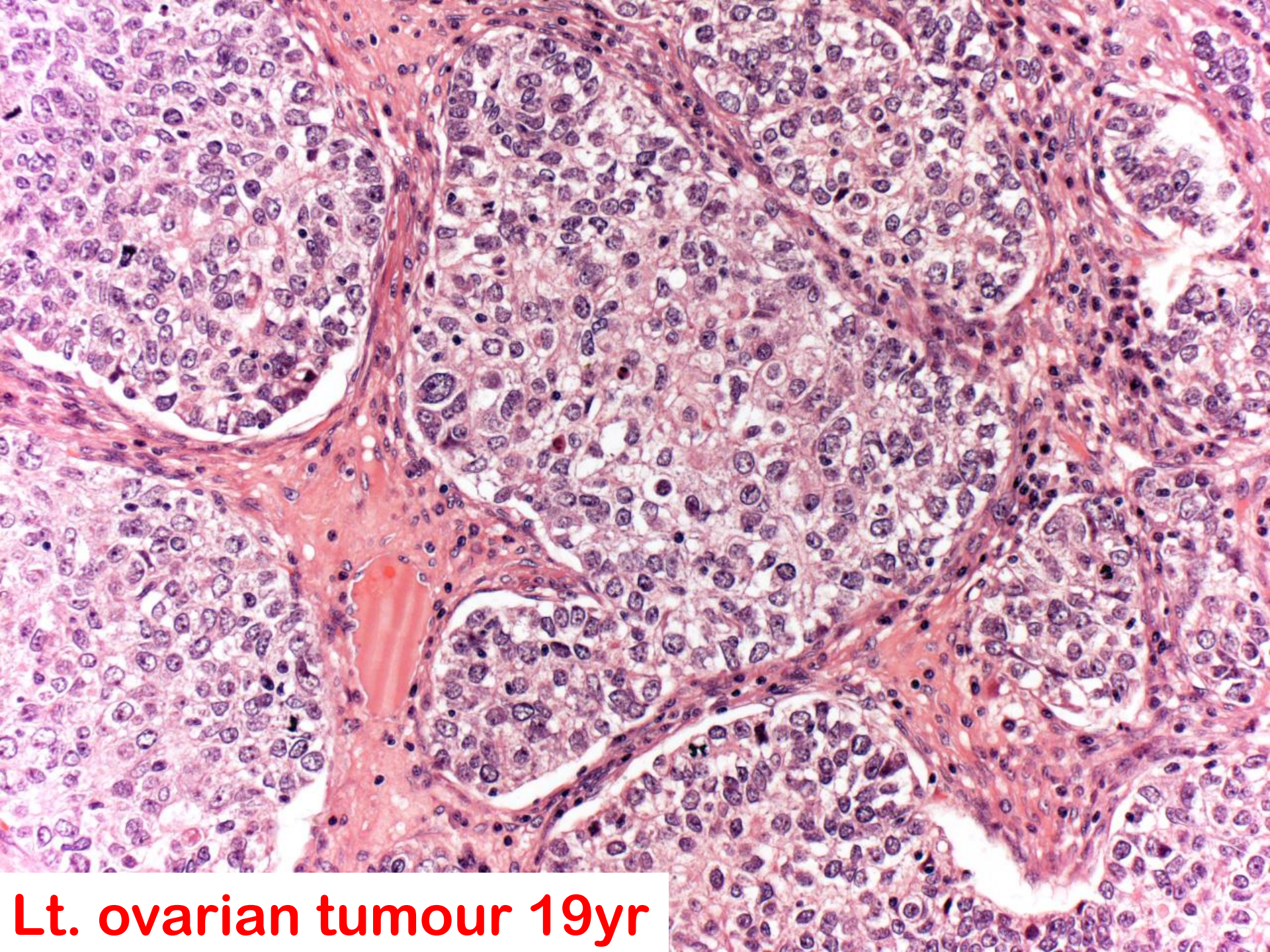
- In absence of classical patterns
- In older age groups
  - Associated to somatic tumours

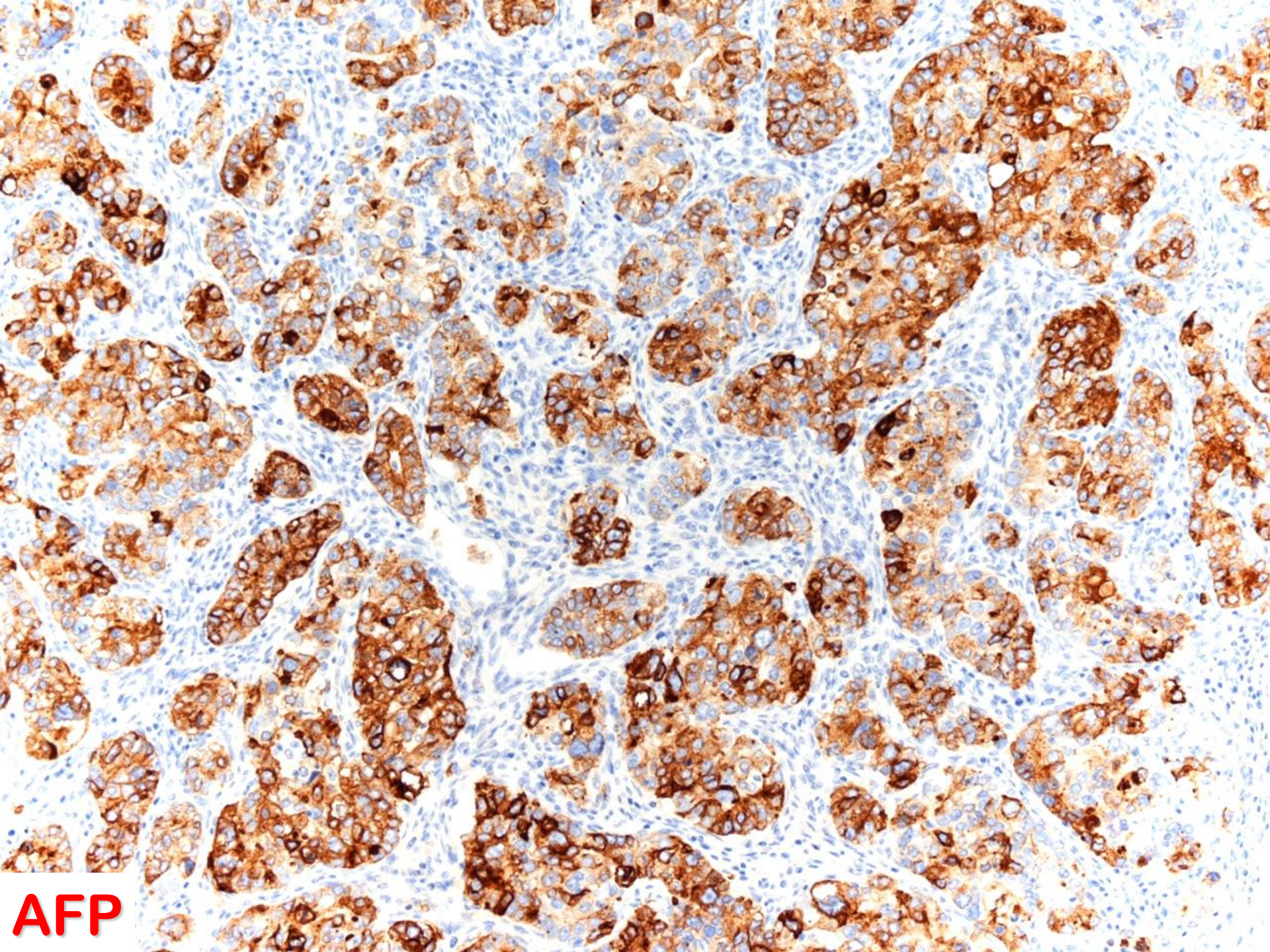
Markers differentiate YST from somatic tumours

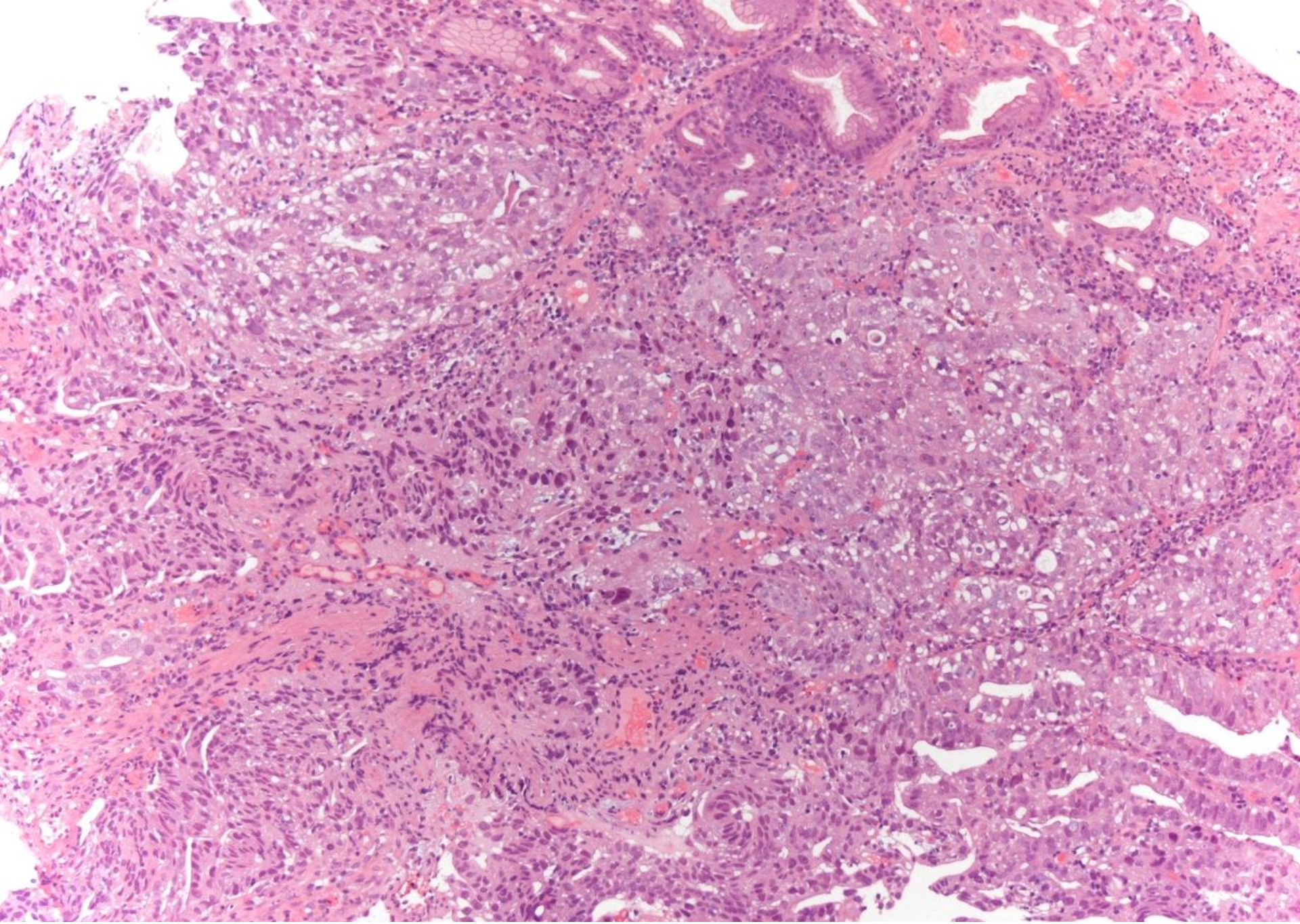


Interpretation problems

- In absence of classical patterns
- In older age groups
  - Associated to somatic tumours
  - Gastric carcinoma metastases


Lt. ovarian tumour 19yr

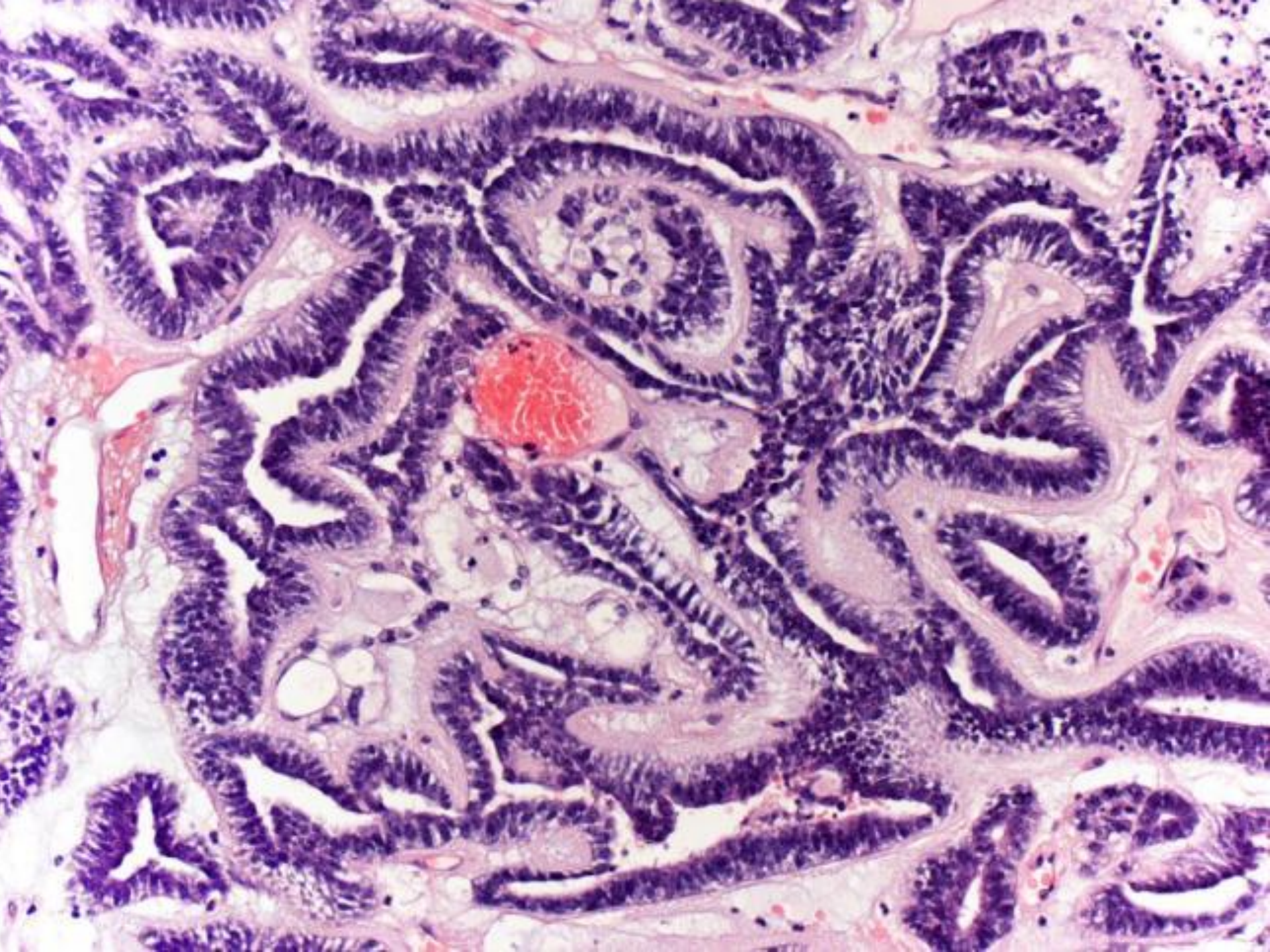

AFP

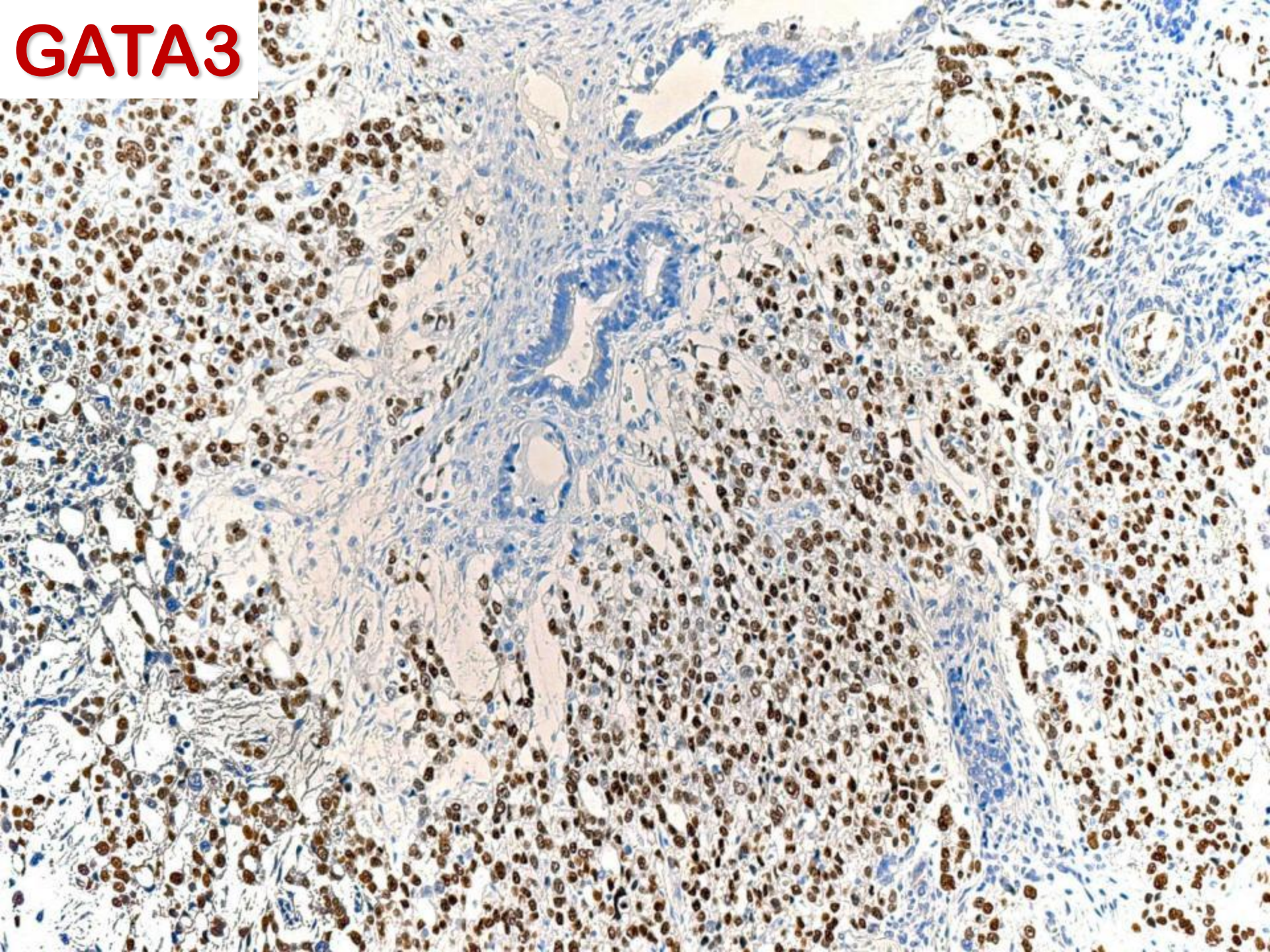


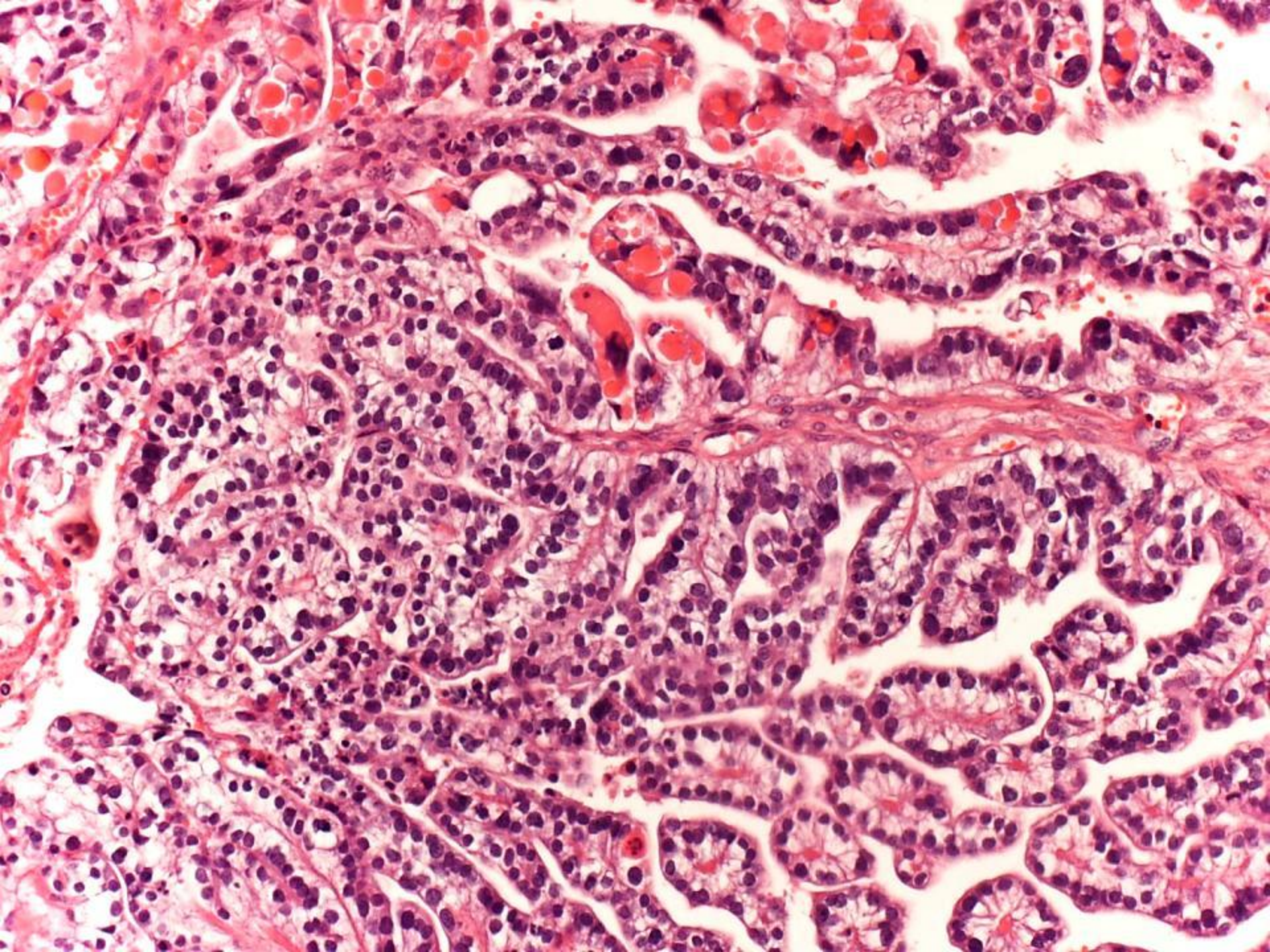
Clear-cell, alpha-foetoprotein-producing gastric carcinoma with hepatoid differentiation.

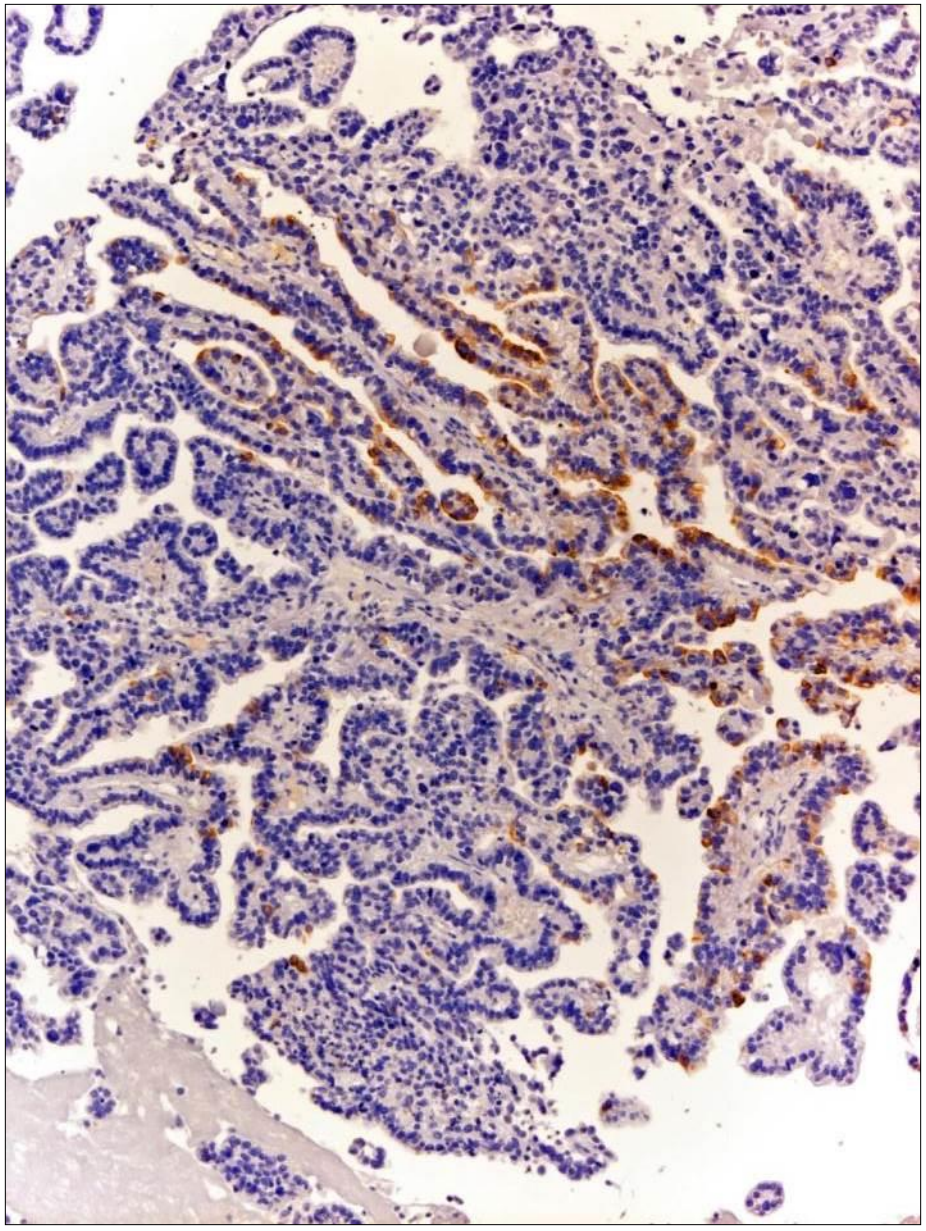
Interpretation problems

- Glandular patterns
  - Compact glands
  - Vacuolated (intestinal)
  - Papillary

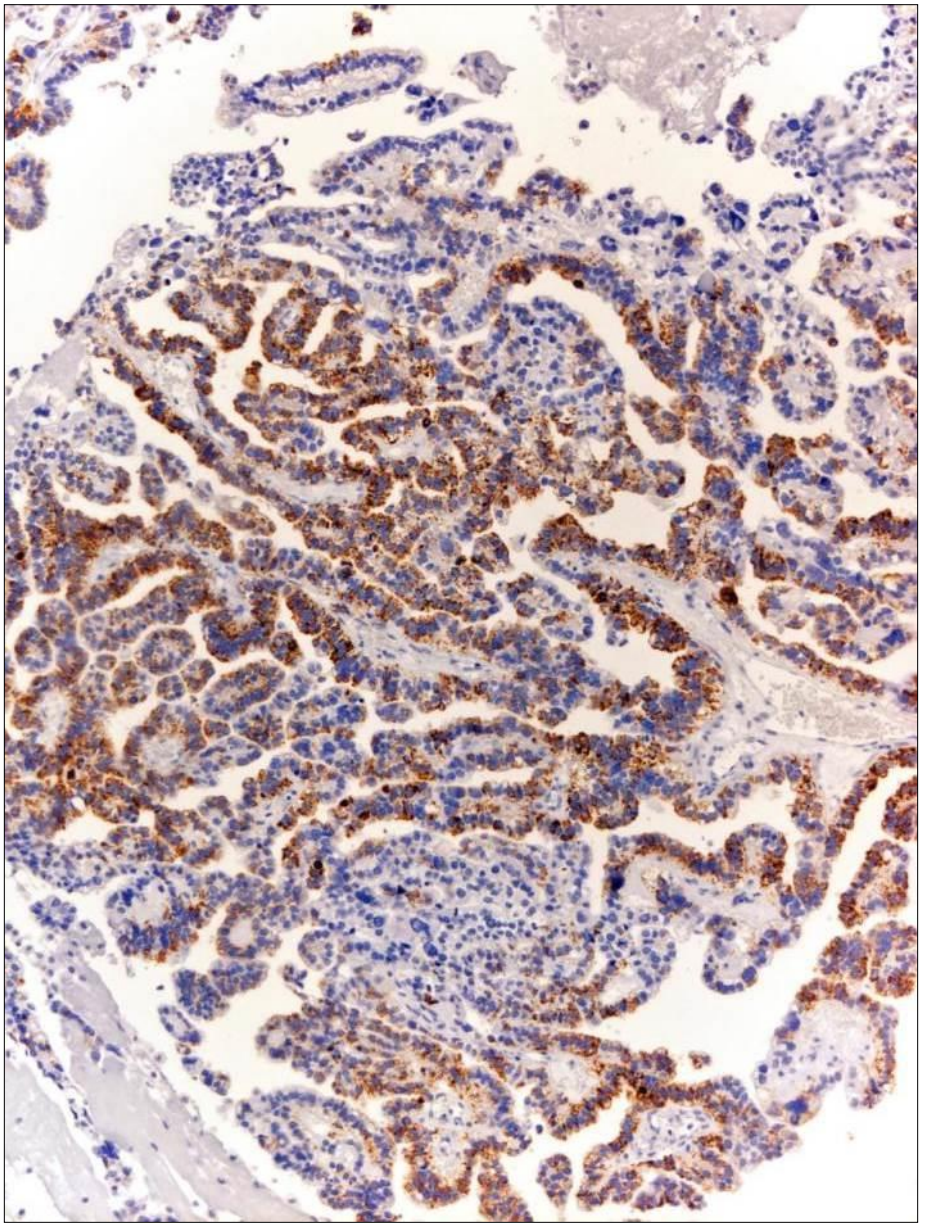



GATA3





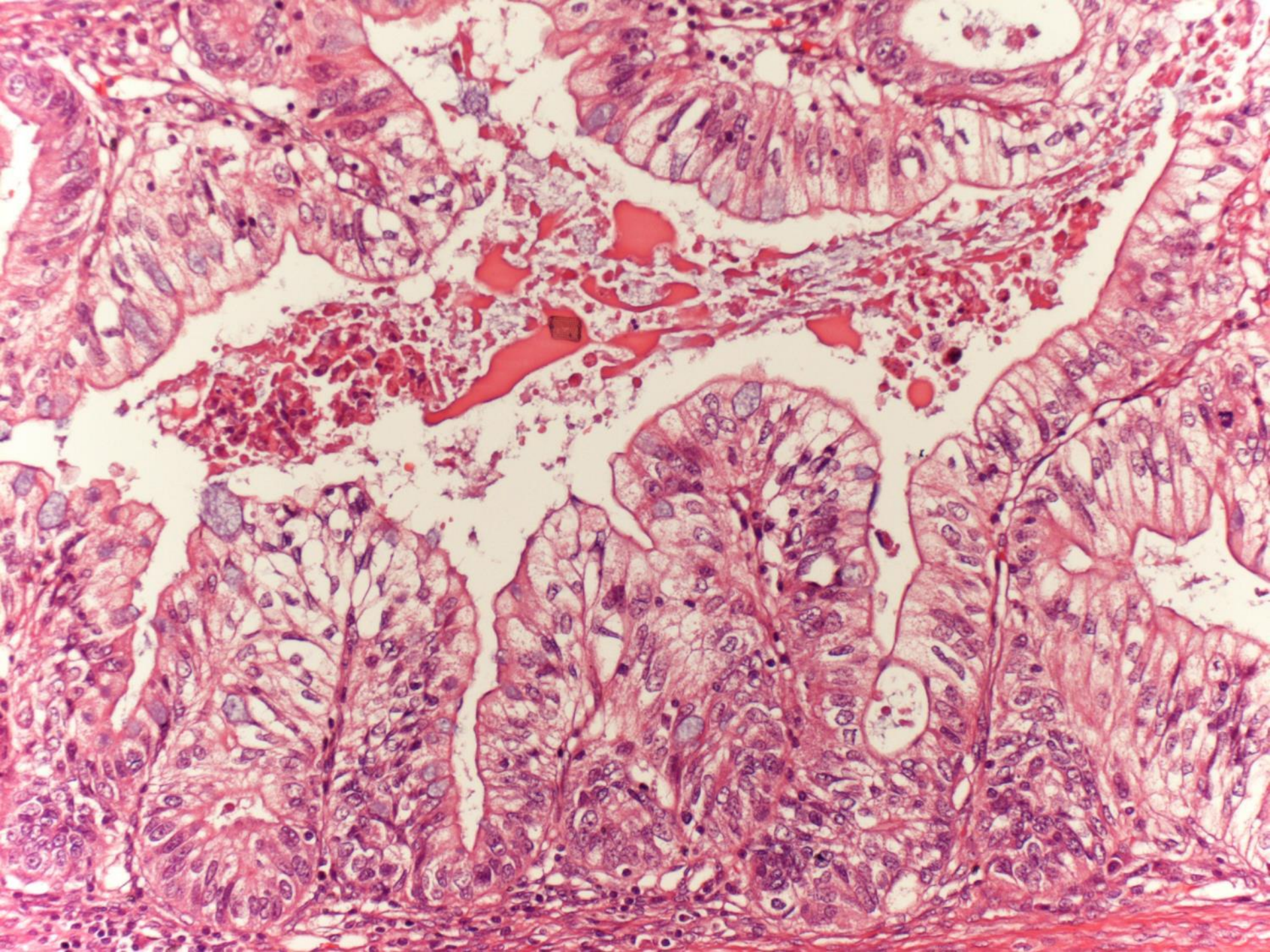
AFP

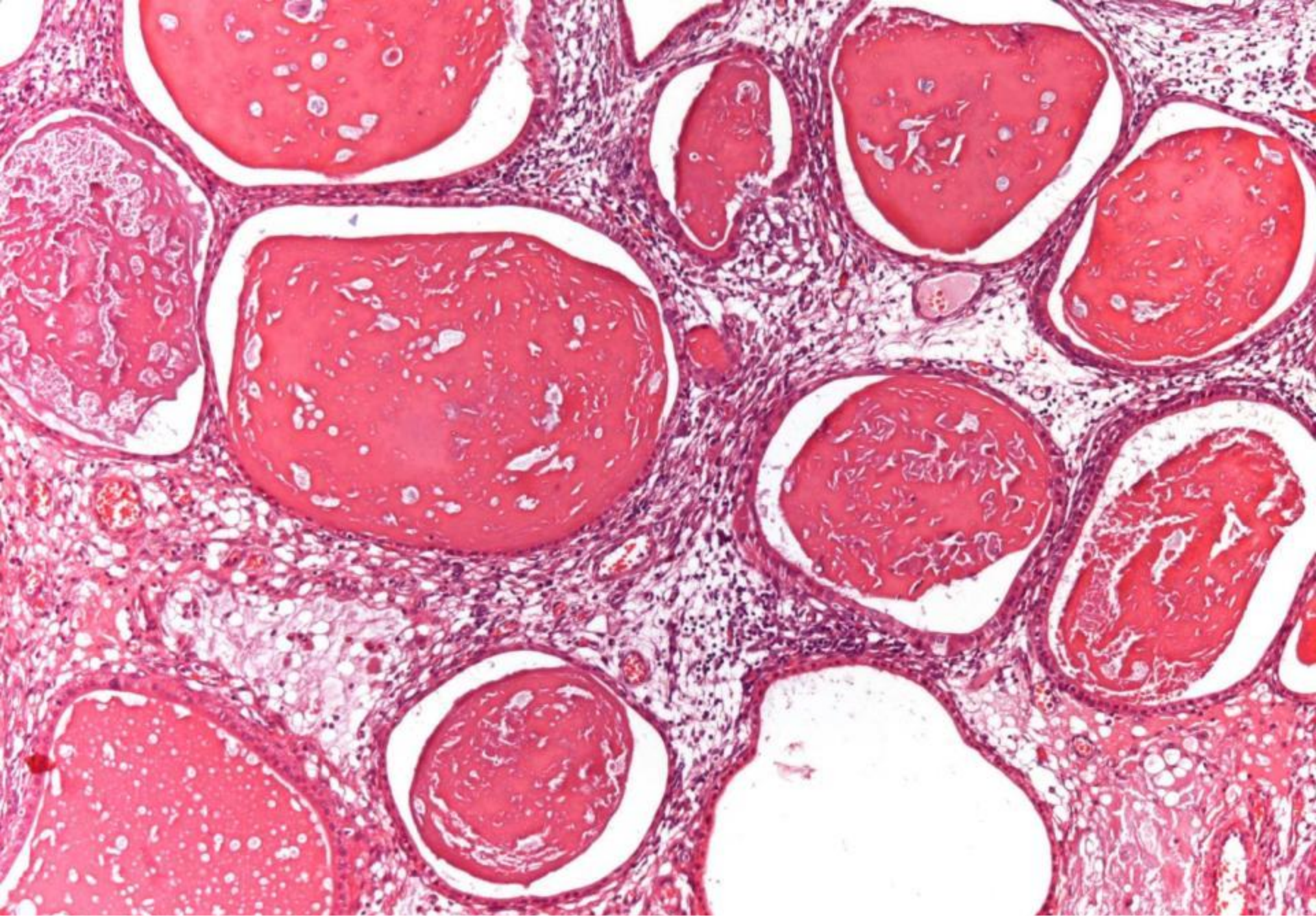


HepPar1

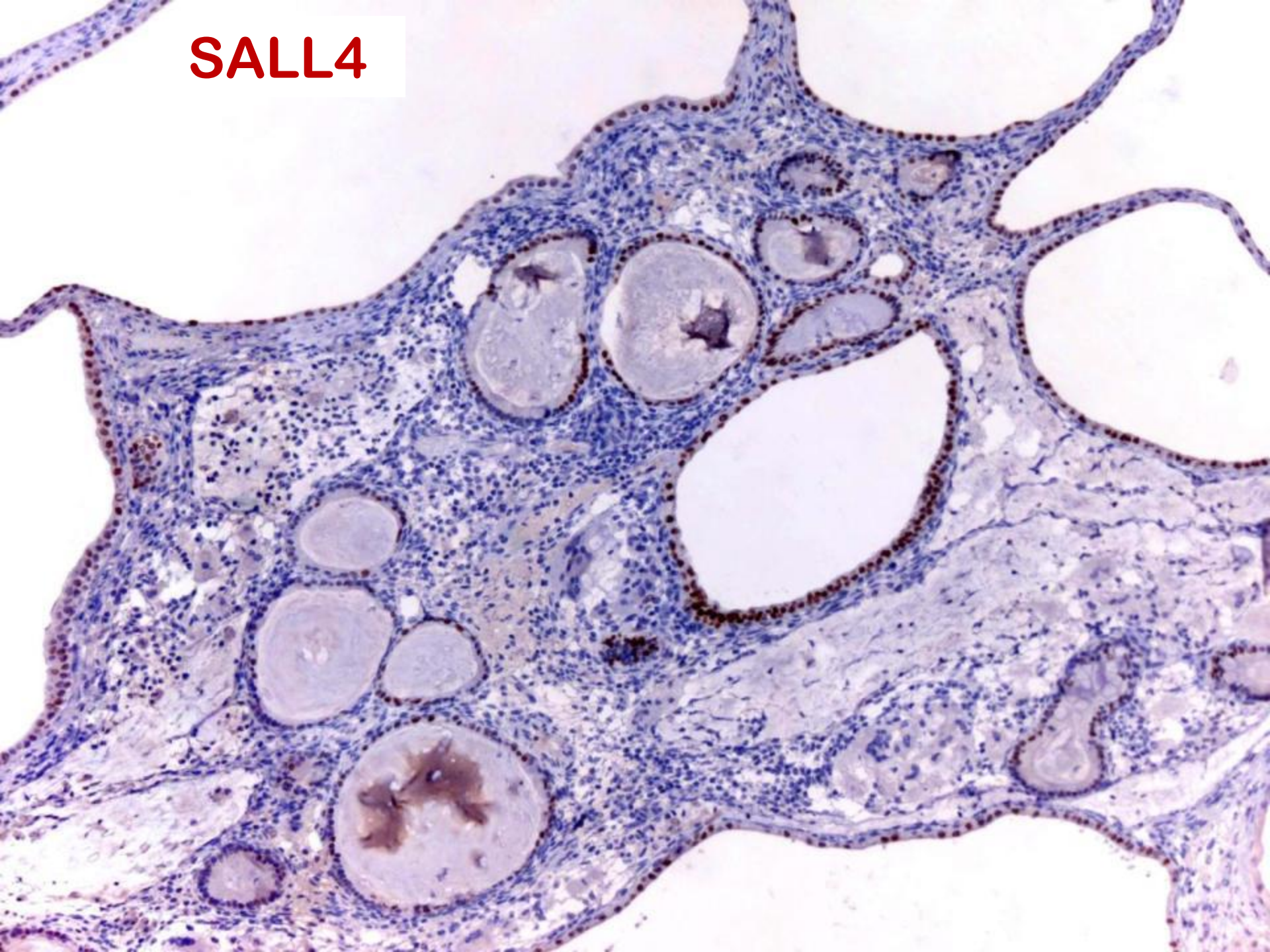
Interpretation problems

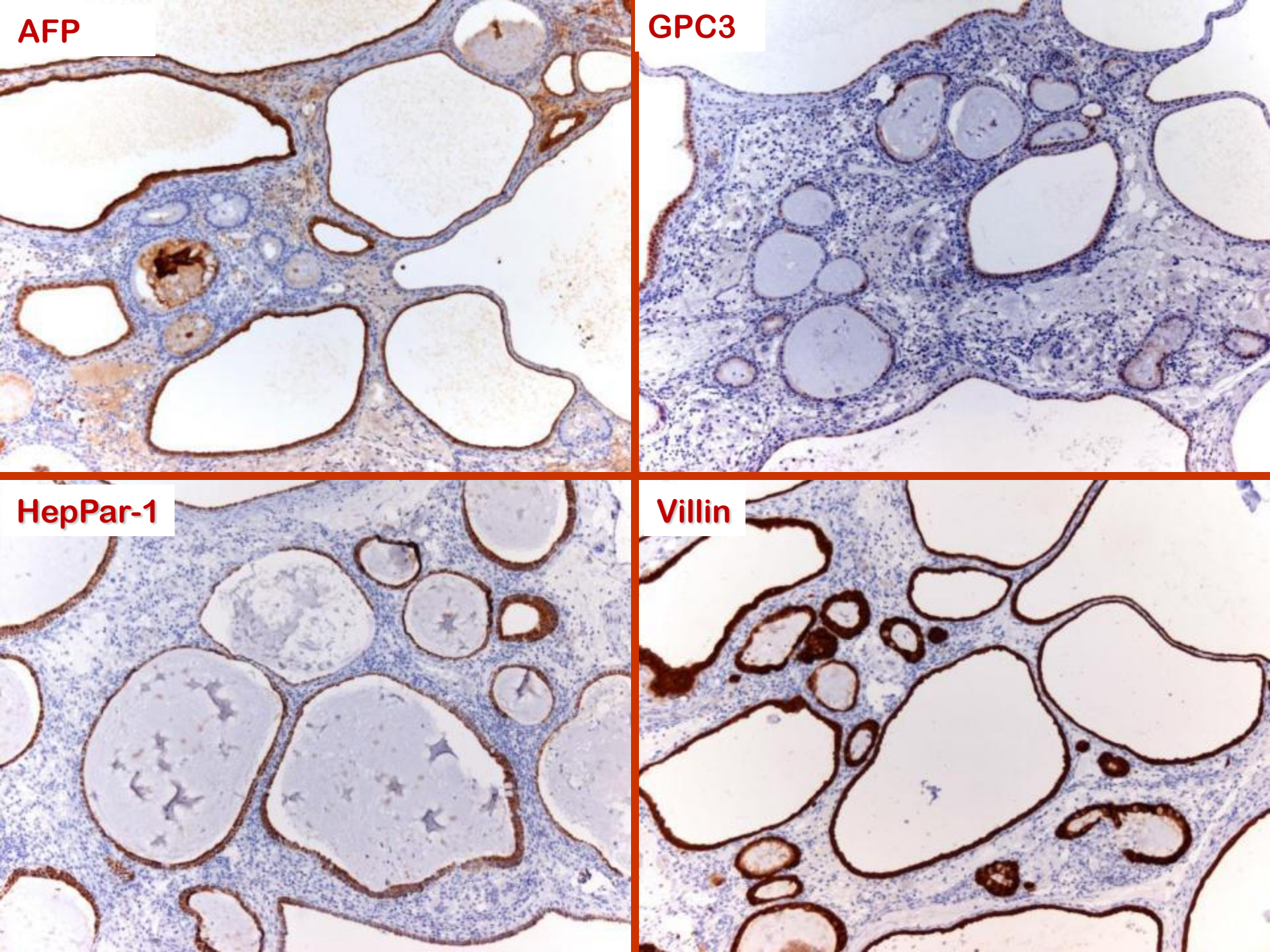
- Glandular patterns
  - Compact glands
  - Vacuolated (intestinal)
  - Papillary
- Mimicking intestinal-type mucinous tumours





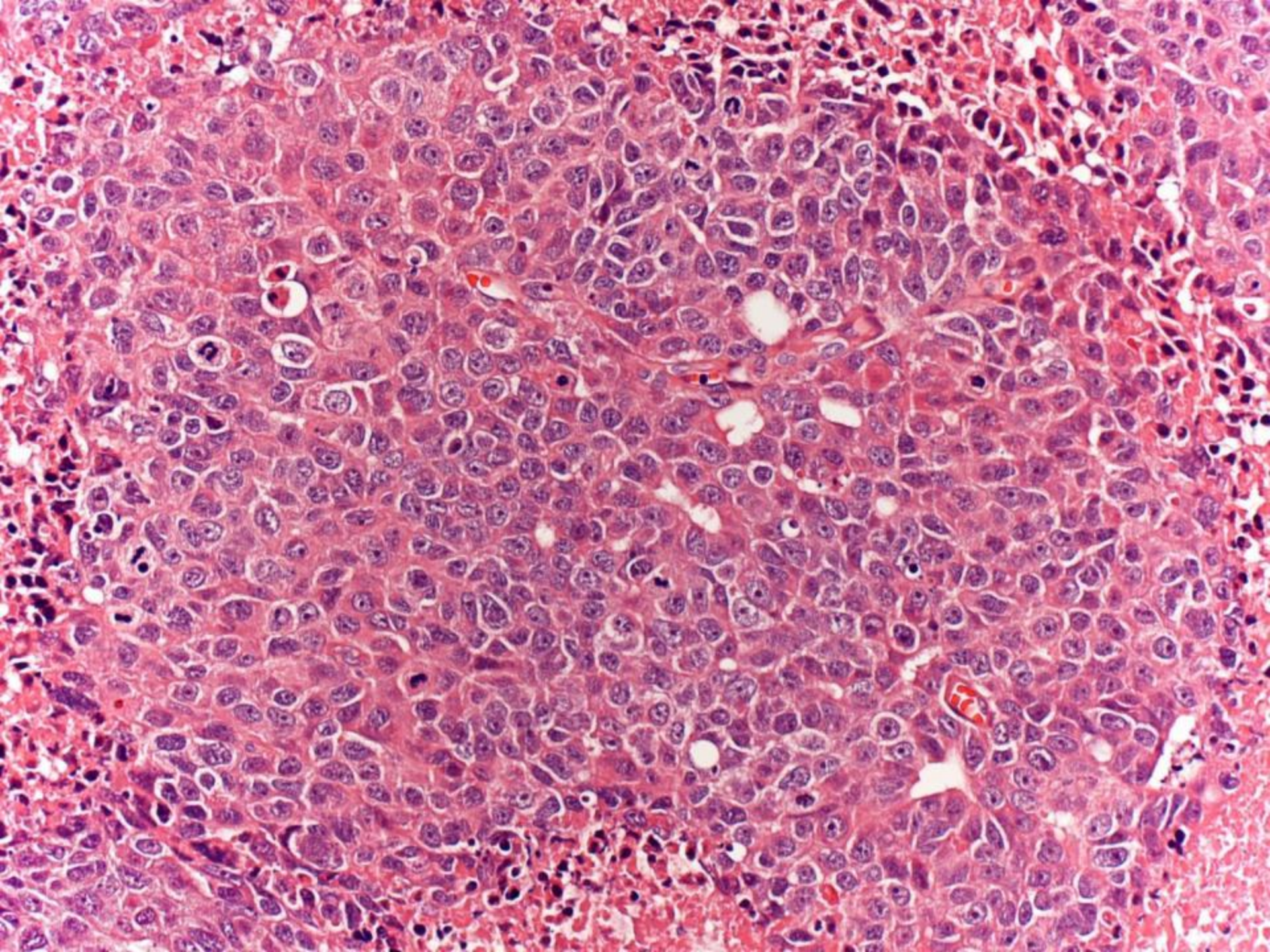
20cm ovarian tumour in a 24 yr old


SALL4


AFP
GPC3
HepPar-1
Villin

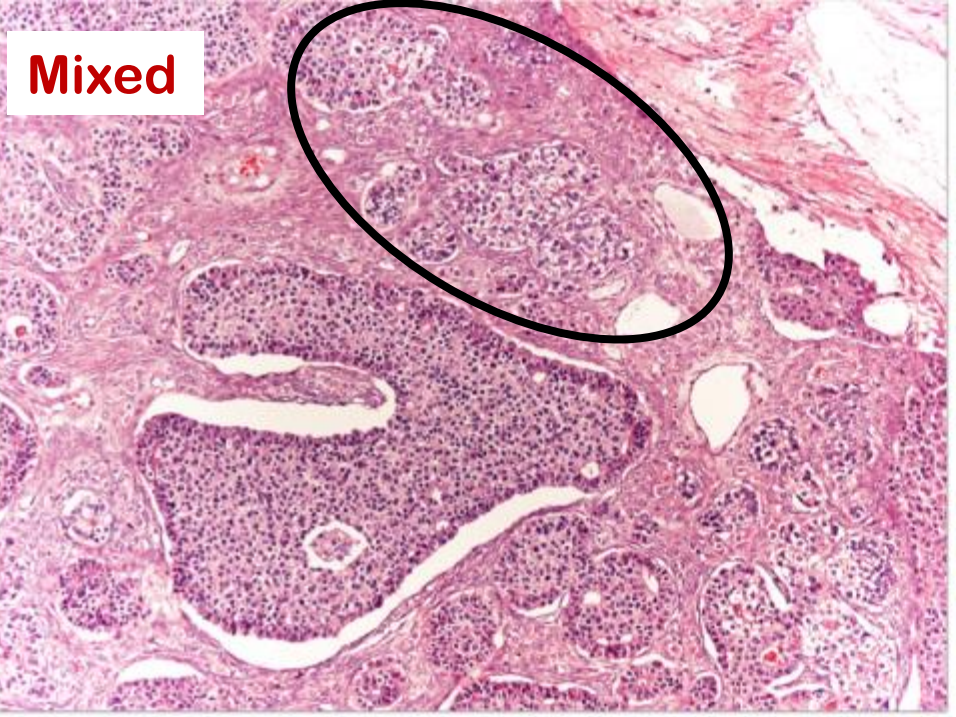
Interpretation problems

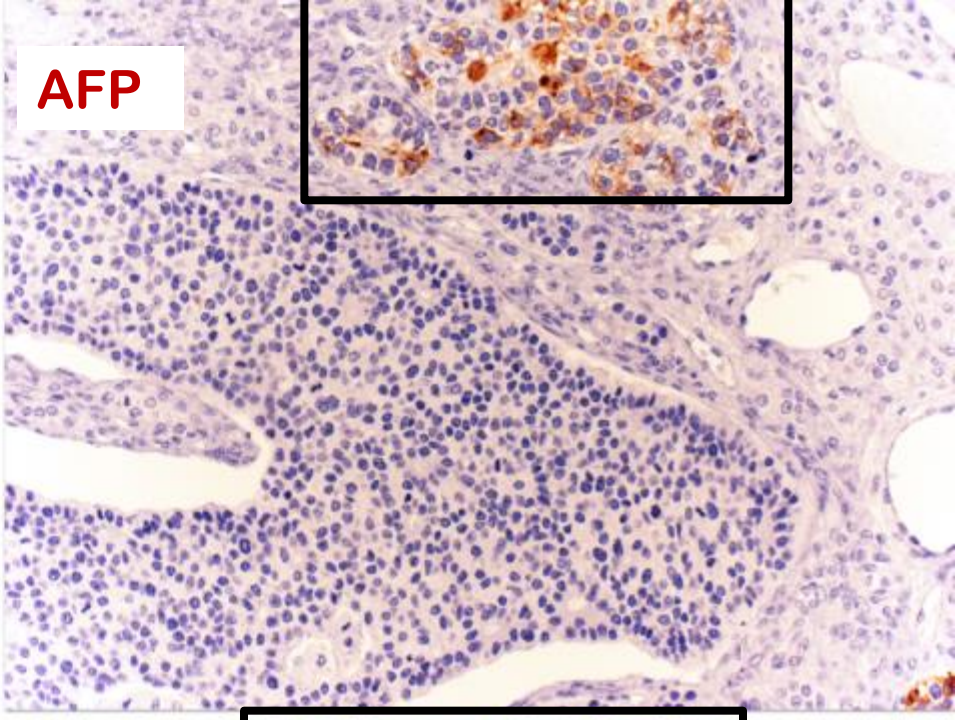
- Glandular patterns
  - Compact glands
  - Vacuolated (intestinal)
  - Papillary
- Mimicking intestinal-type mucinous tumours
- Solid

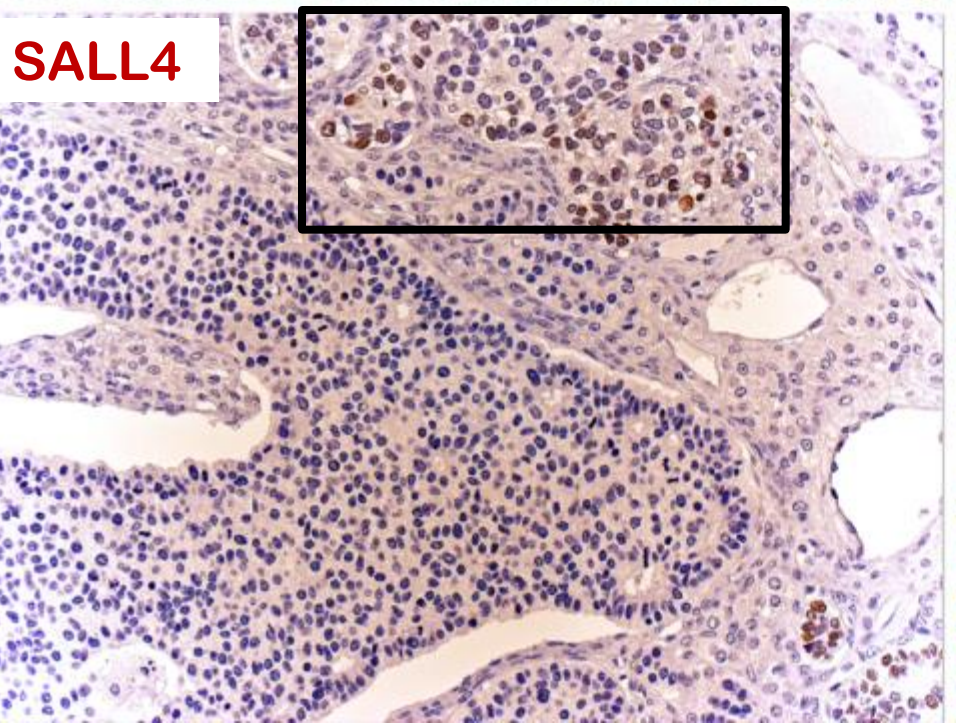


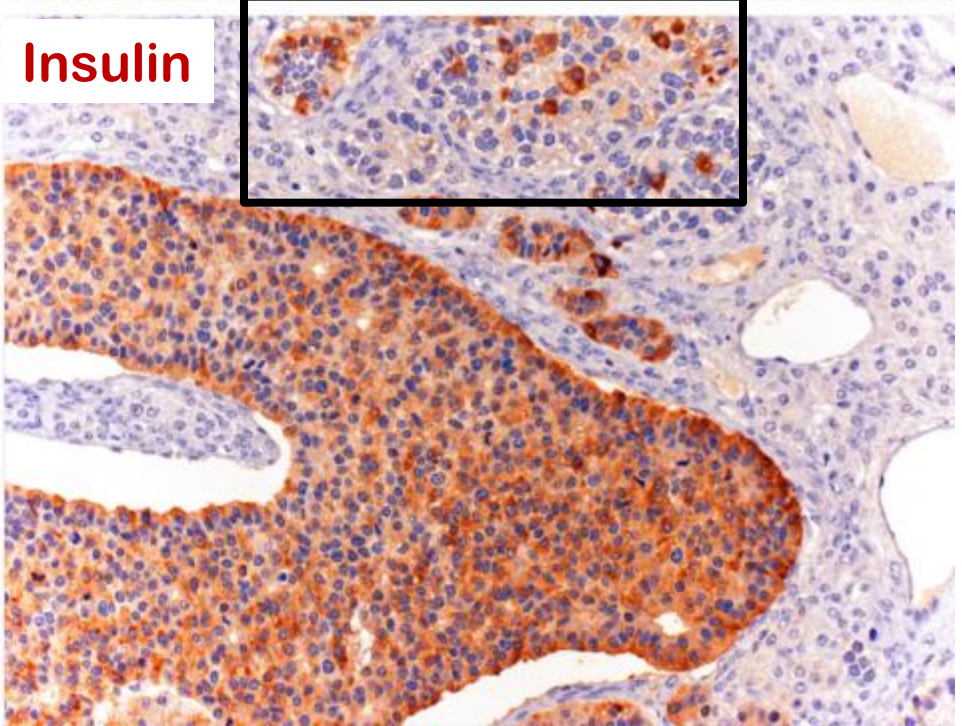
Interpretation problems

- Glandular patterns
  - Compact glands
  - Vacuolated (intestinal)
- Mimicking intestinal-type mucinous tumours
- Solid
- Carcinoid-associated

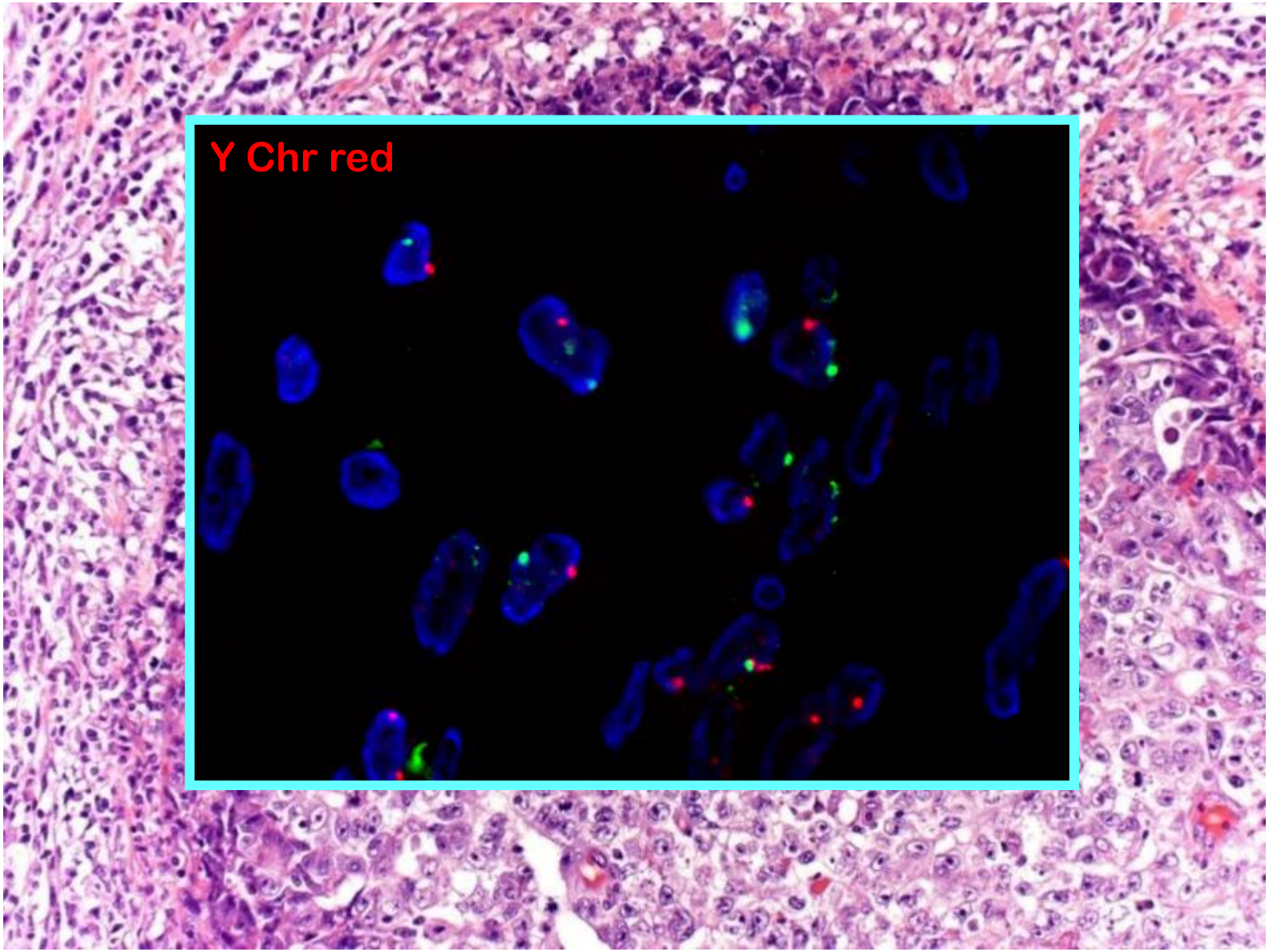

Mixed


AFP

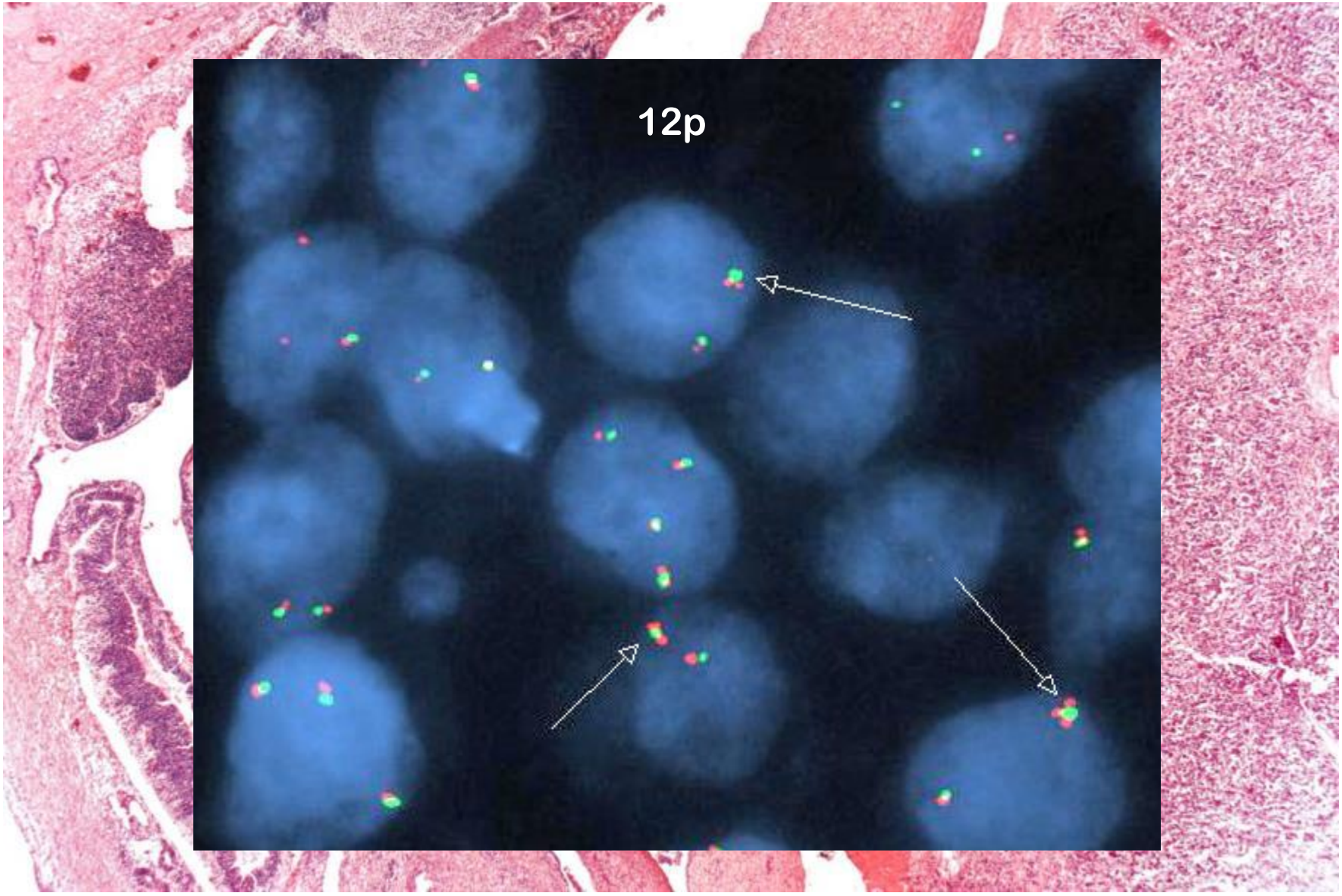

SALL4


Insulin

Embryonal Carcinoma

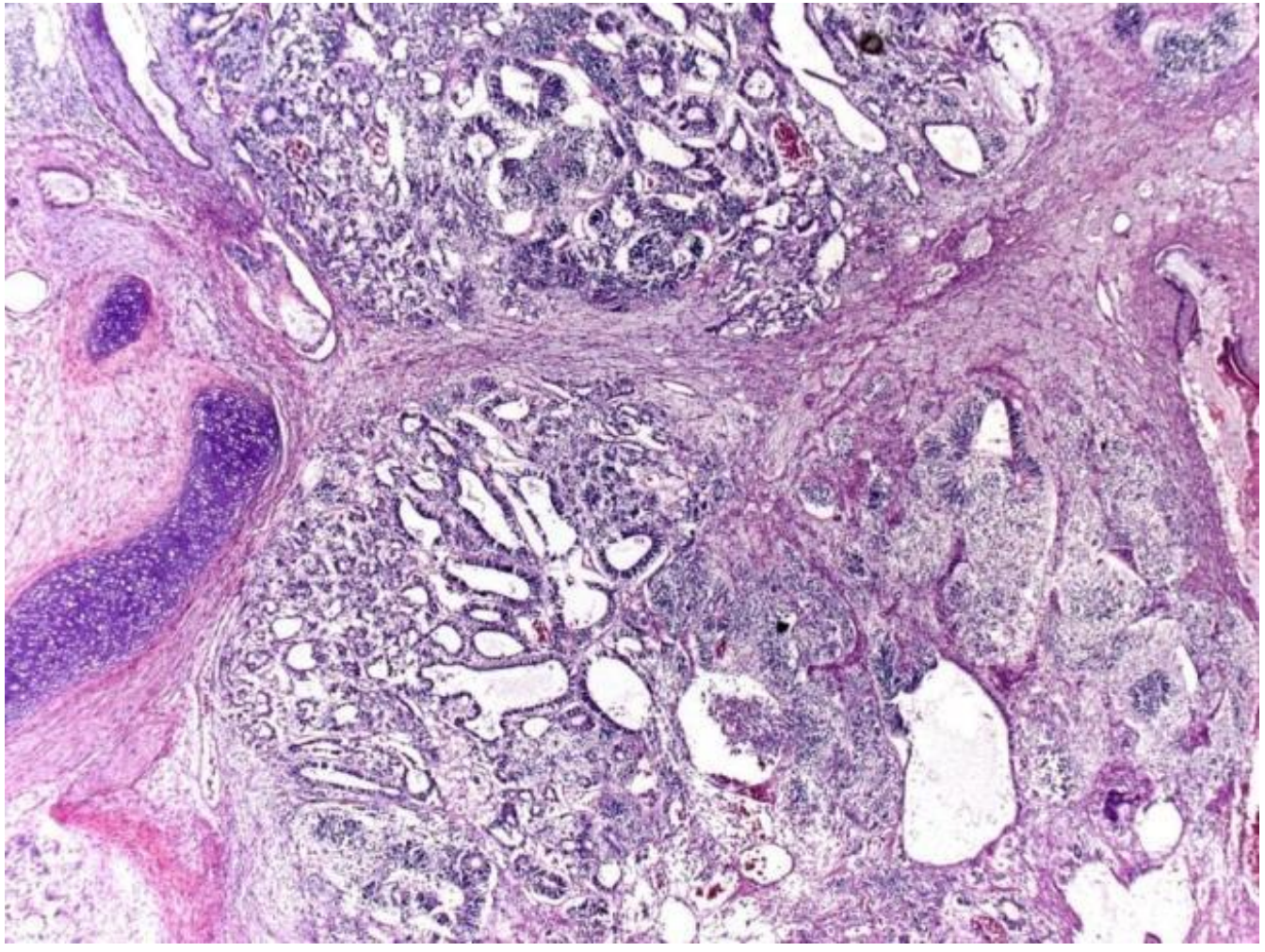


Mixed germ cell tumour



Immature teratomas

Grade 1	Immature neuroectoderm ≤ 1lpf (4x)
Grade 2	Immature neuroectoderm > 1lpf ≤ 3cba (4x)
Grade 3	Immature neuroectoderm > 3lpf (4x)



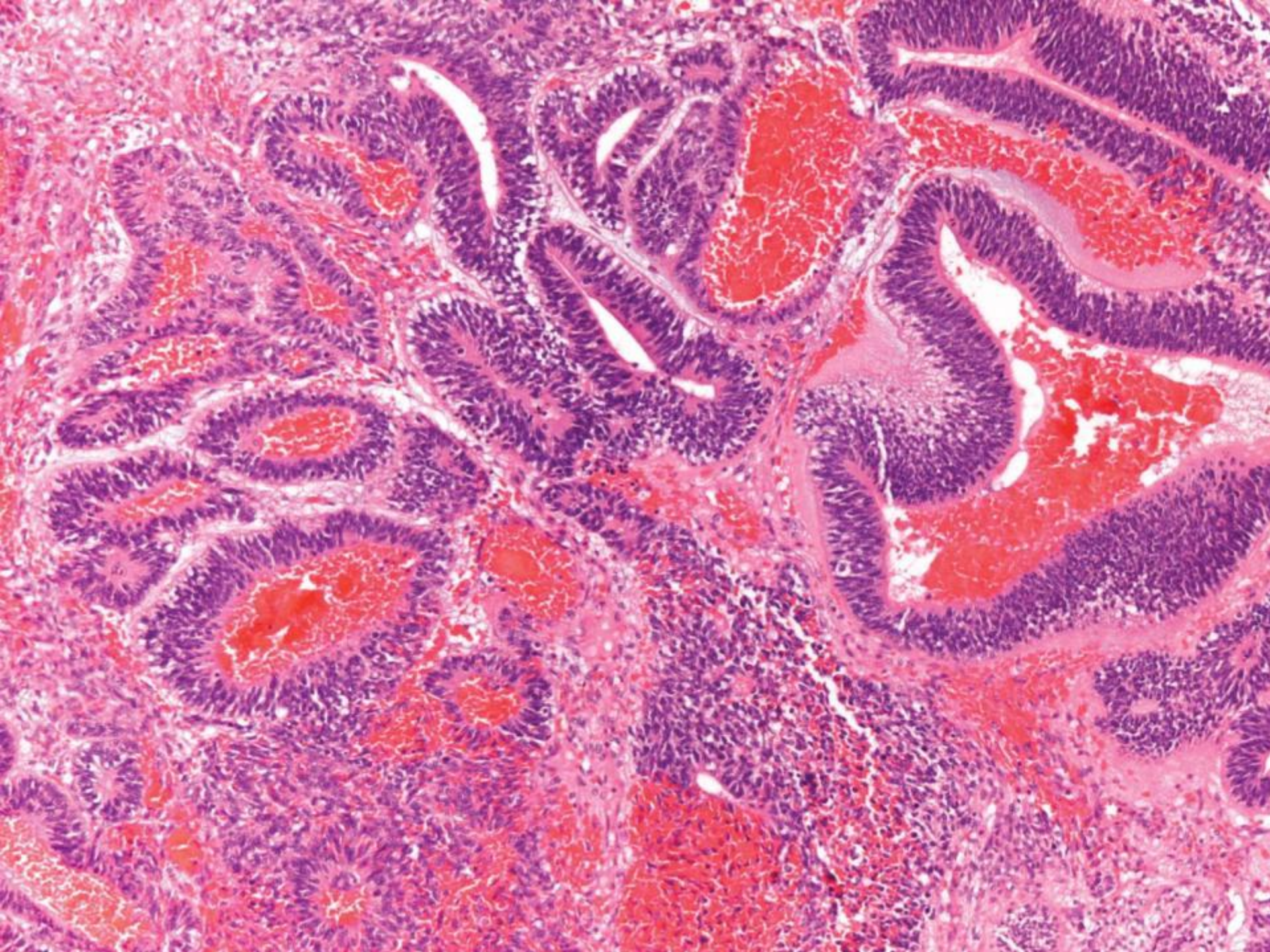
Immature teratoma

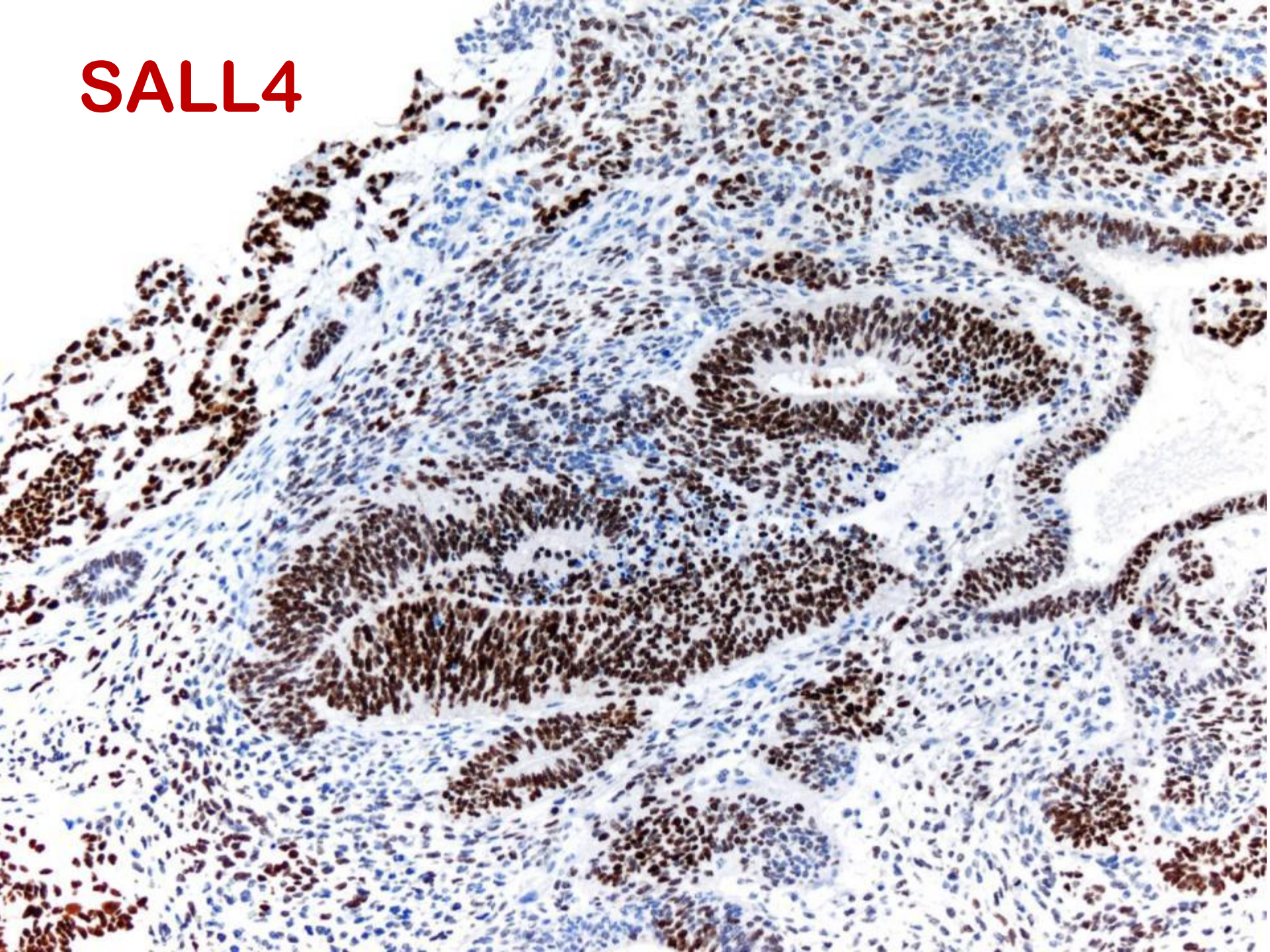
Immature teratomas usually present with non-specific mass related symptoms but occasionally the history is noteworthy because an ipsilateral dermoid cyst has been resected previously.[46] The risk of an immature teratoma in such patients may be increased if the dermoid cysts are bilateral, multiple, or associated with rupture.[47] The median diameter is over 15 cm and the predominantly solid cut surface is fleshy, gray to pink, often with associated variably sized cysts, focal haemorrhage and necrosis (Figure 14). Although an associated dermoid cyst is grossly evident in 25% of tumours, the overall features are in most cases in marked contrast to those of dermoid cysts.

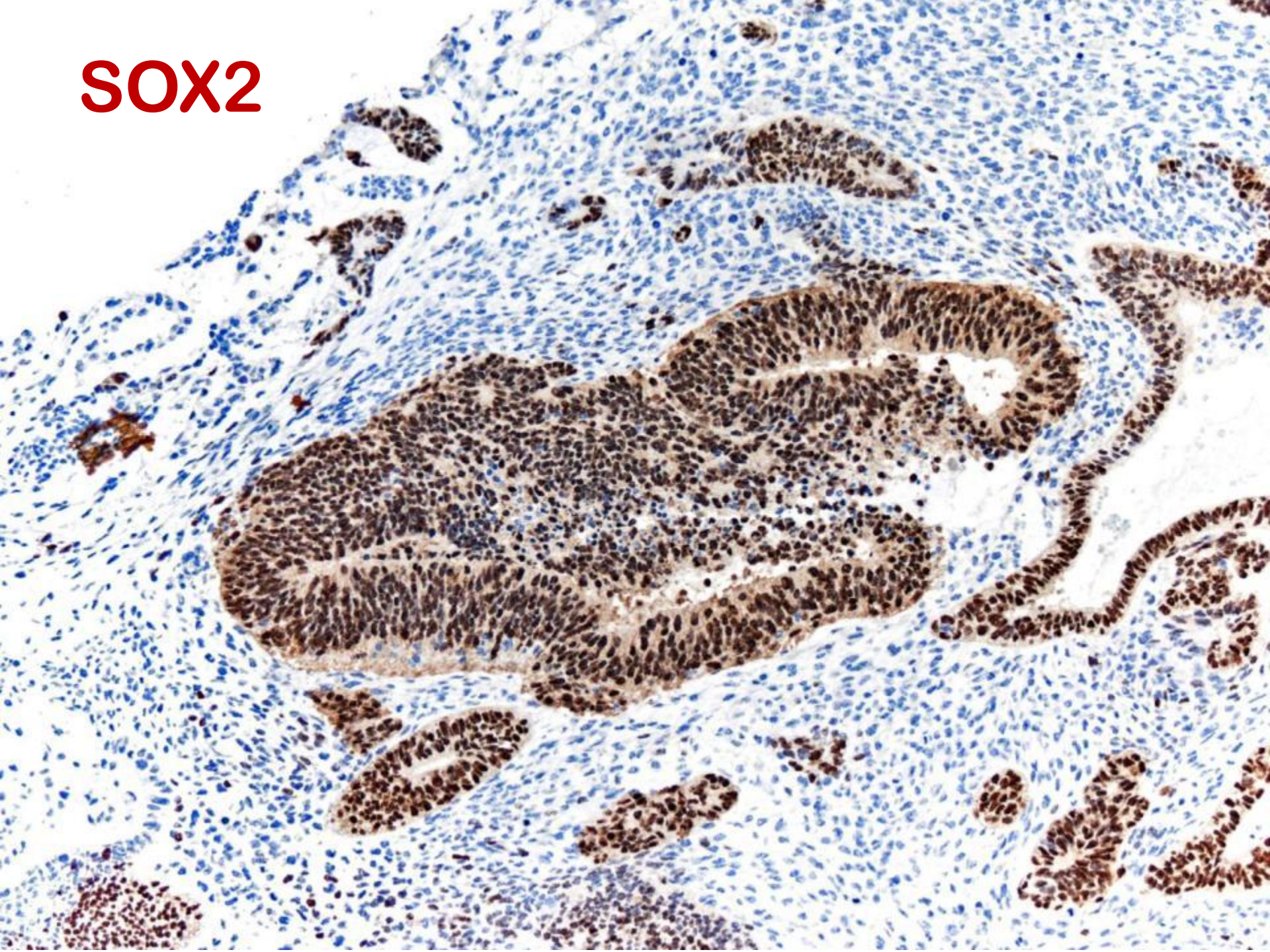
The tumours are graded based on the degree of immaturity of the neural tissue (Figure 15). Grade 1 tumours contain rare foci of immature neural tissue (<1 low-power-field [LPF] in any one slide), while grade 2 and grade 3 tumours contain 2–3 LPFs or 4 or more LPFs of immature neural tissue in any one slide respectively. A 2-grade system has been proposed: low-grade (grade 1) and high-grade (grades 2 and 3) based on outcome, as patients with grade 1 immature teratomas do not need adjuvant treatment and have a good outcome.[48] Embryoid bodies may be present in immature teratoma, and in fact they are not an uncommon finding (Figure 16). They reflect high-grade imma-

Immature tubular structures in IT

- Neural tubules

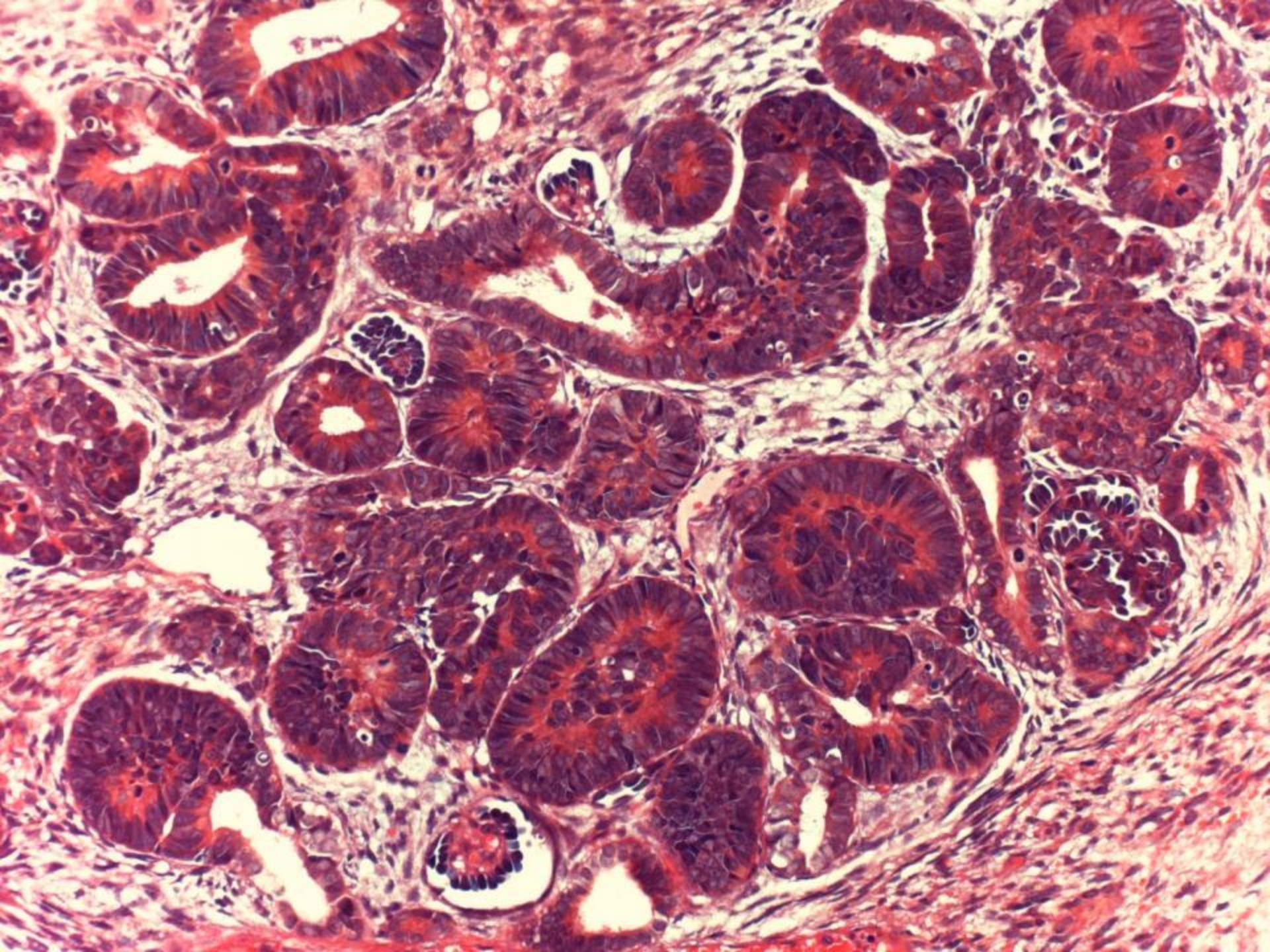



SALL4


SOX2

Immature tubular structures in IT

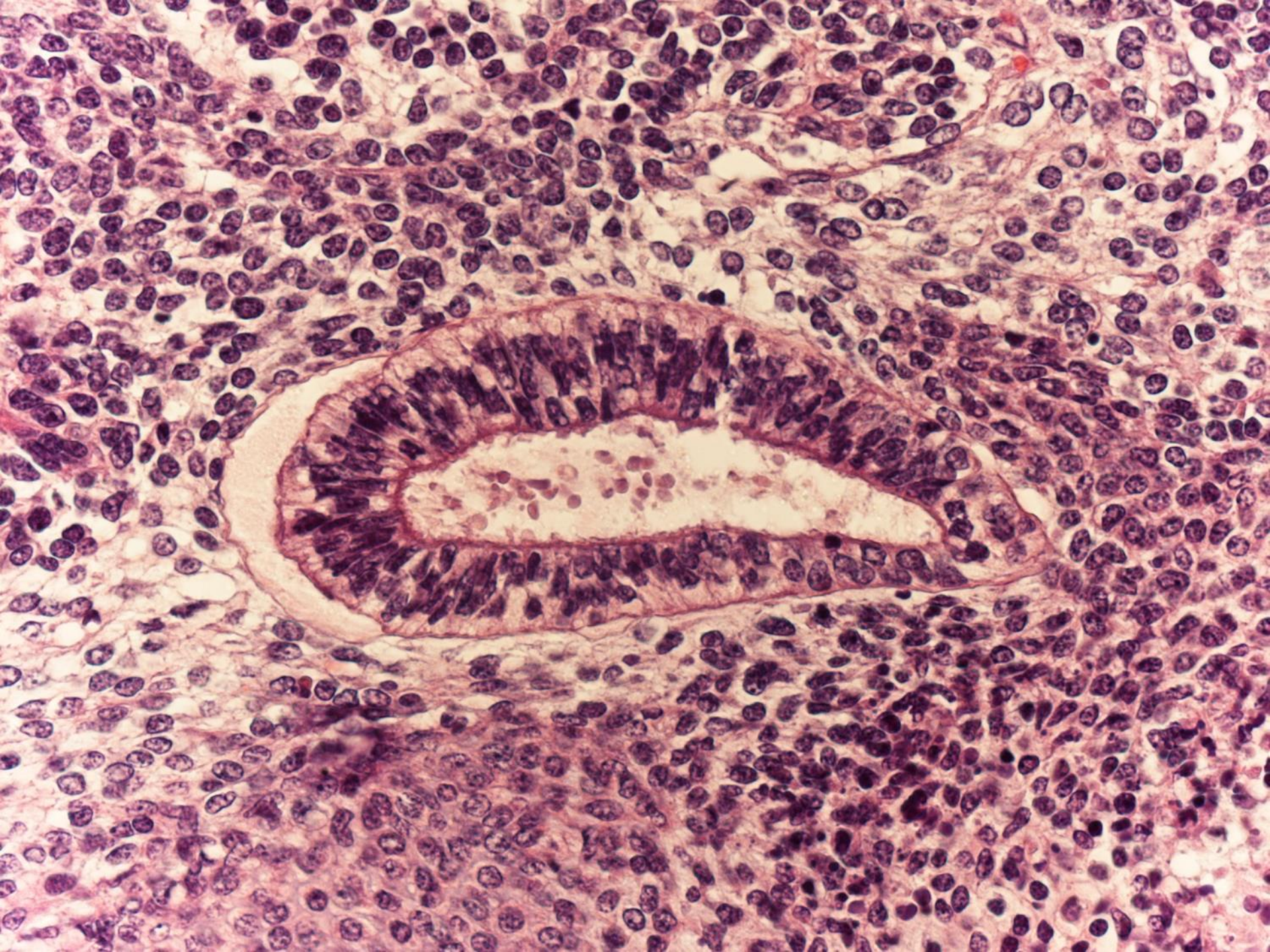
- Neural tubules
- Nephrogenic tubules



Immature tubular structures in IT

- Neural tubules
- Nephrogenic tubules
- Endodermal tubules

Immature endodermal areas are also present in high grade immature teratoma and its presence may imply aggressive behaviour

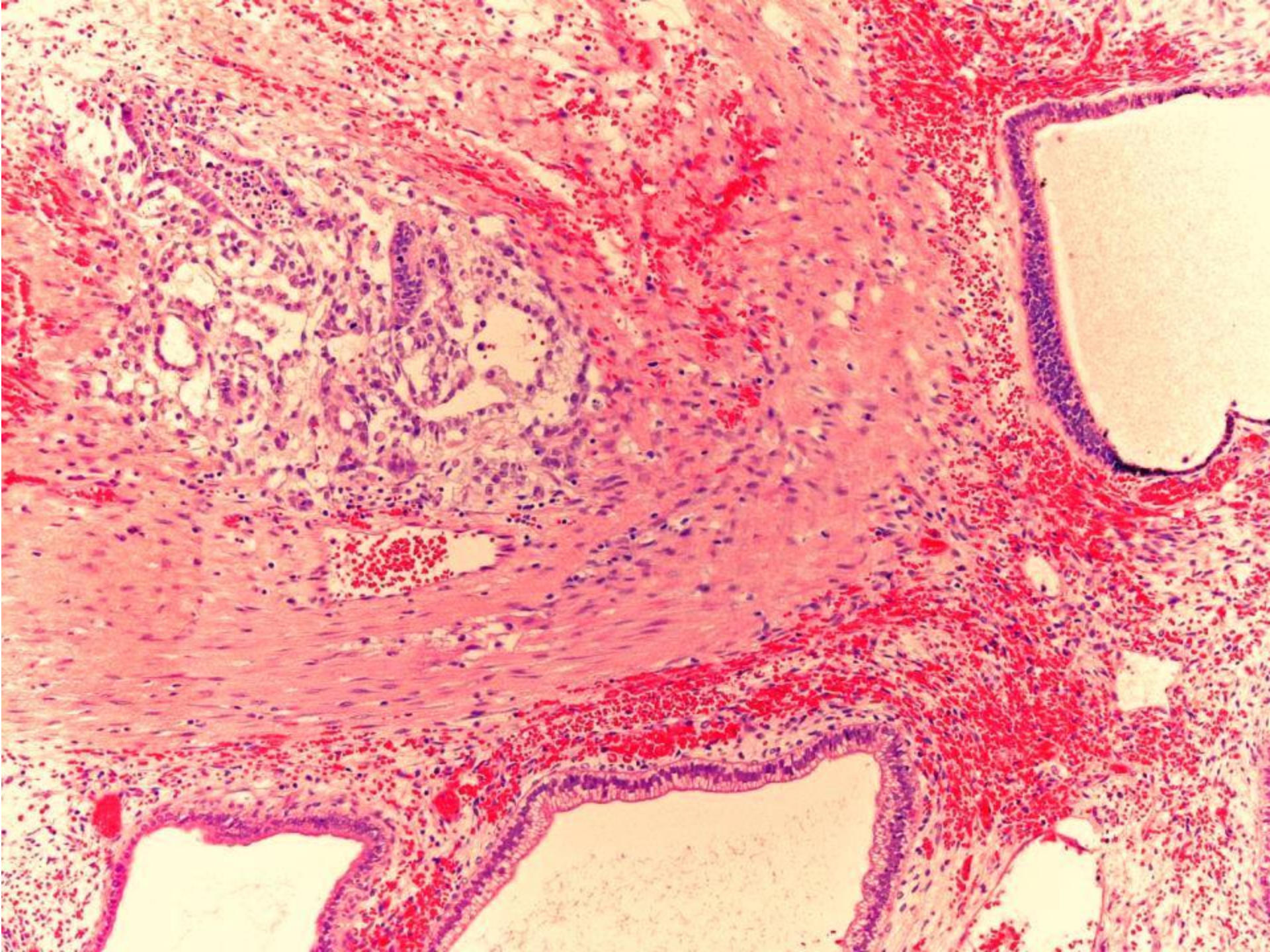


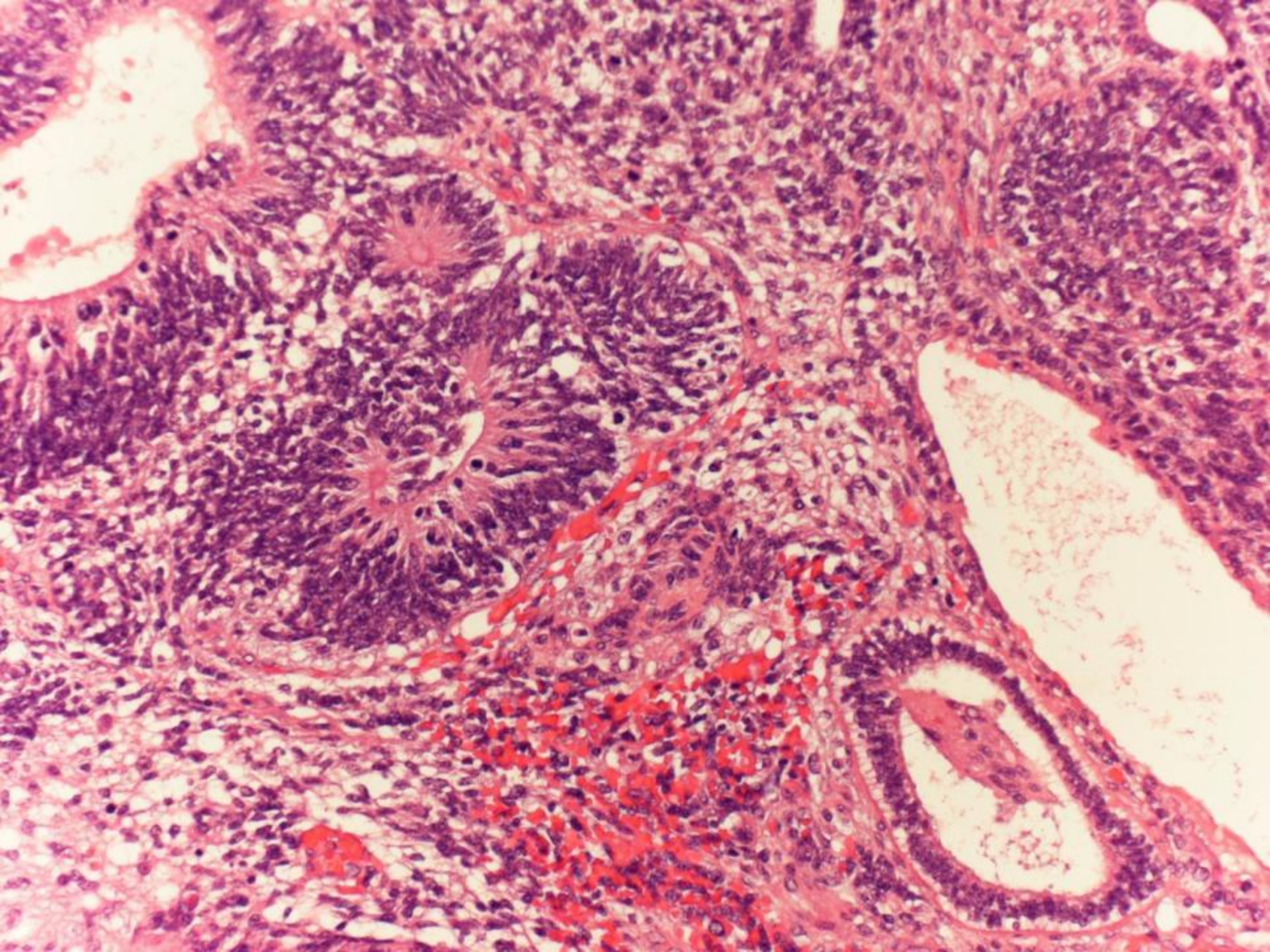
Immature teratoma and endodermal areas

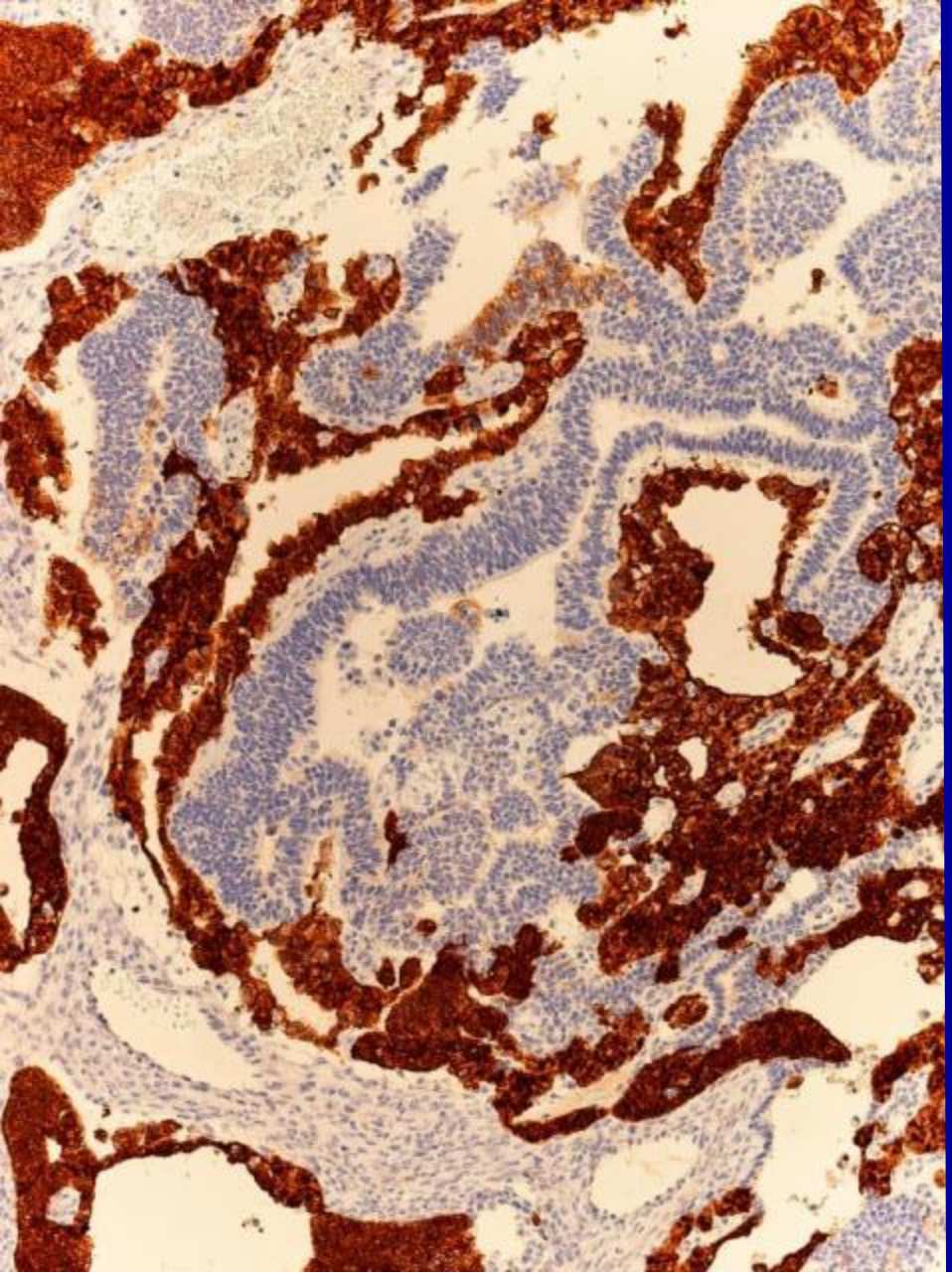
- 1: Heifetz et al. Immature teratomas in children: pathologic considerations: a report from the combined Pediatric Oncology Group/Children's Cancer Group. Am J Surg Pathol 1998;22:1115.

Overall 2- to 6-year survival rate was 96% and was related to the presence of YST….

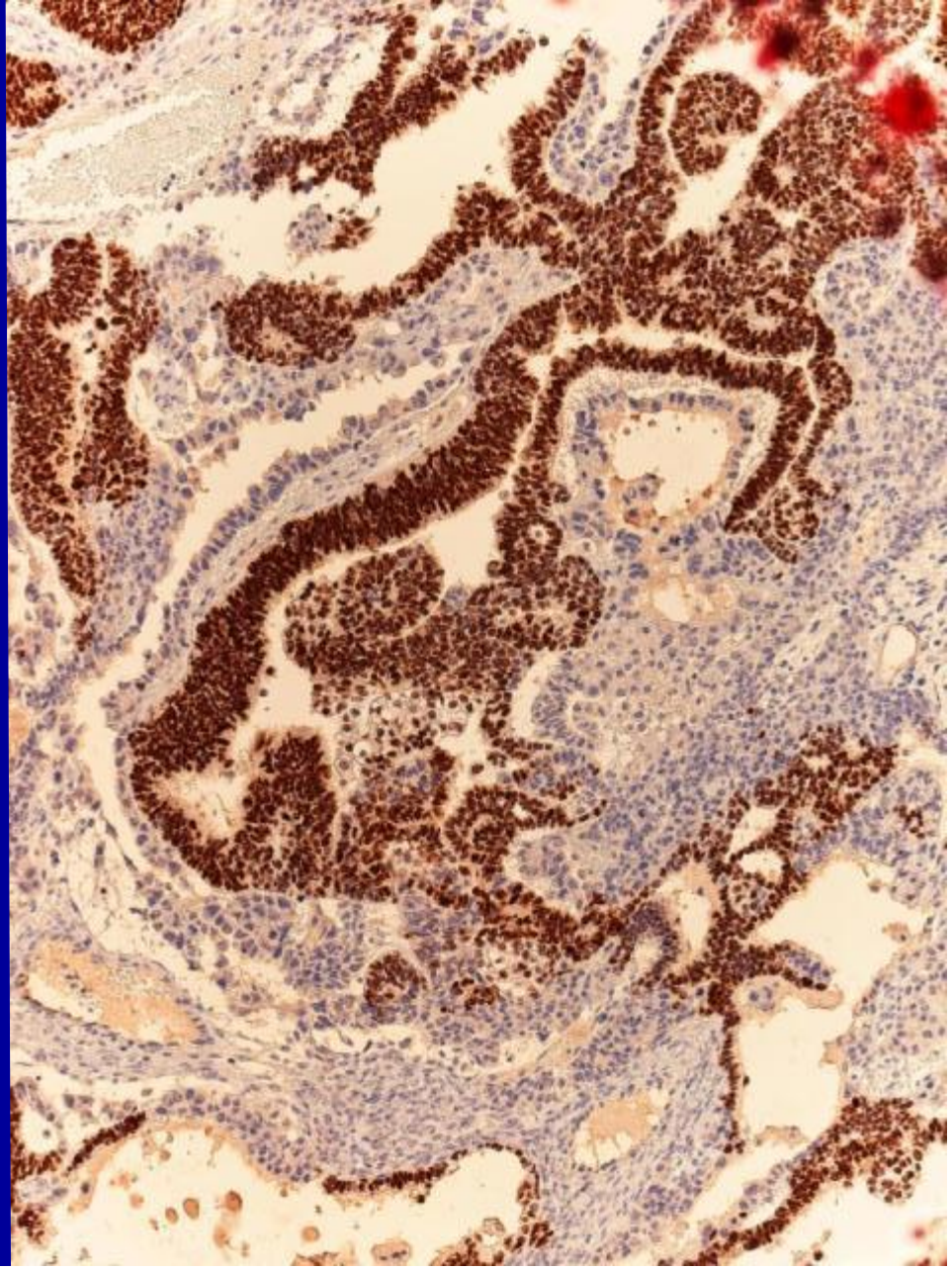
….the presence of microscopic foci of YST, rather than the grade of IT, *per se*, is the only valid predictor of recurrence in pediatric IT at any site.





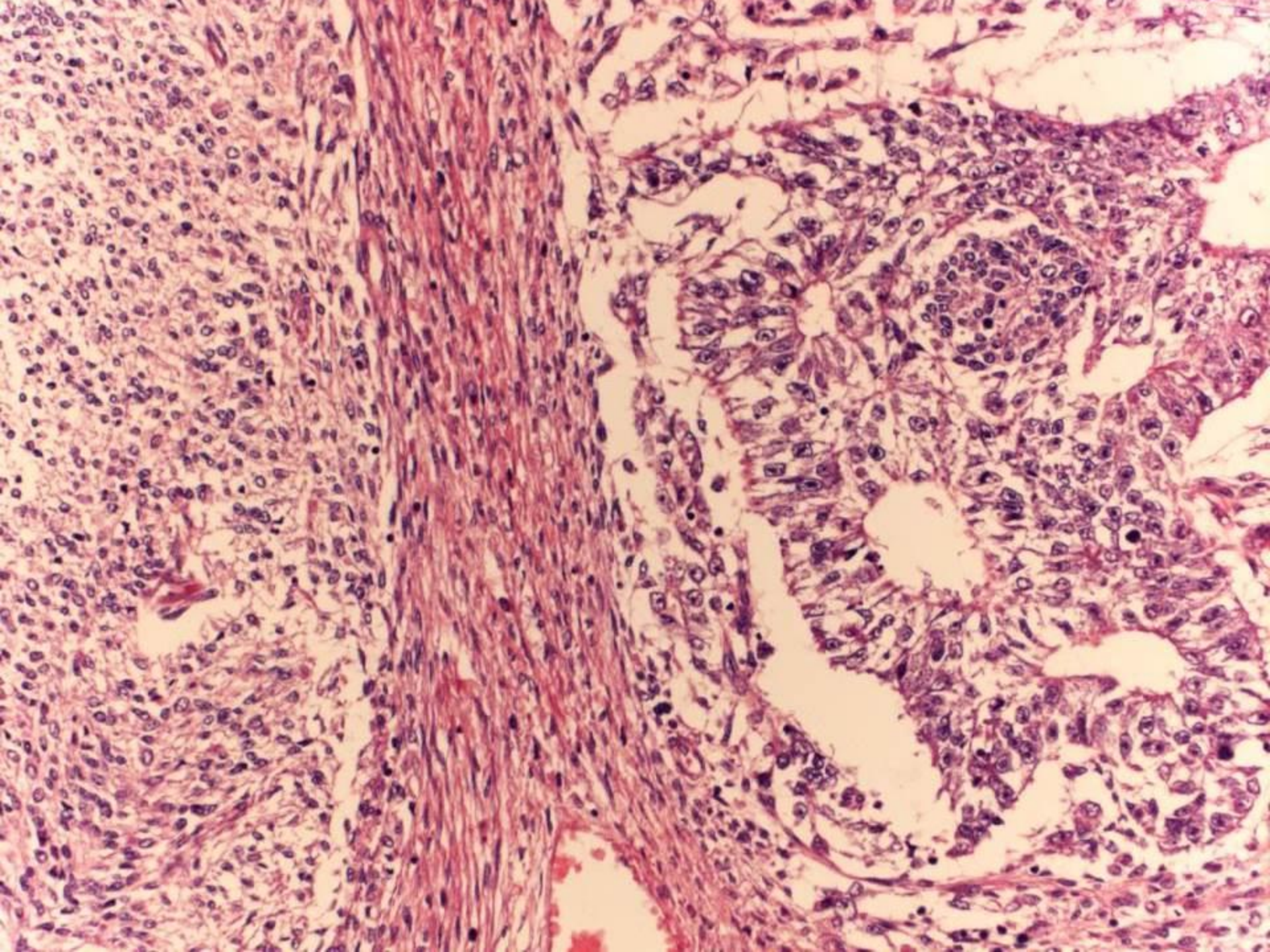


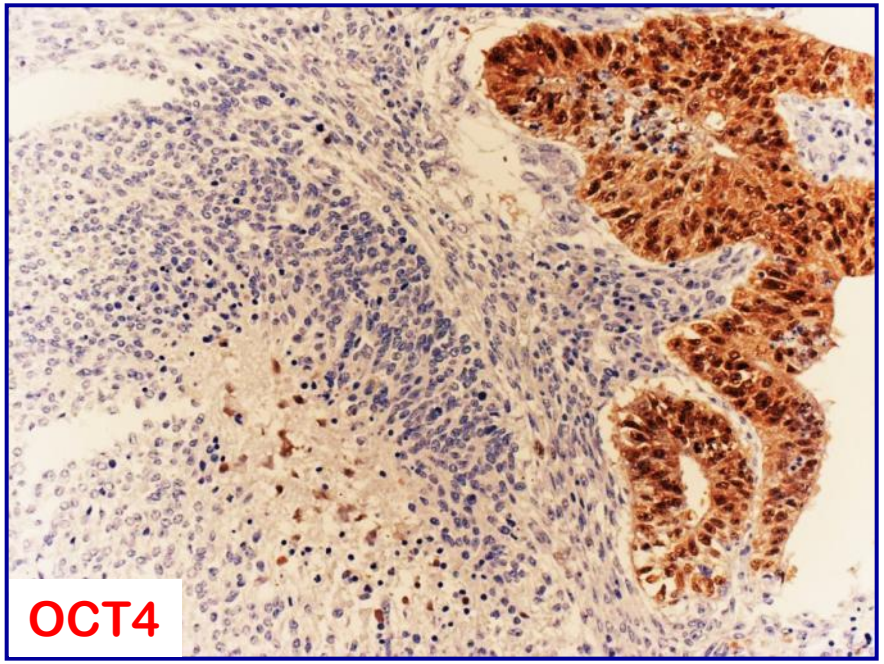
Villin

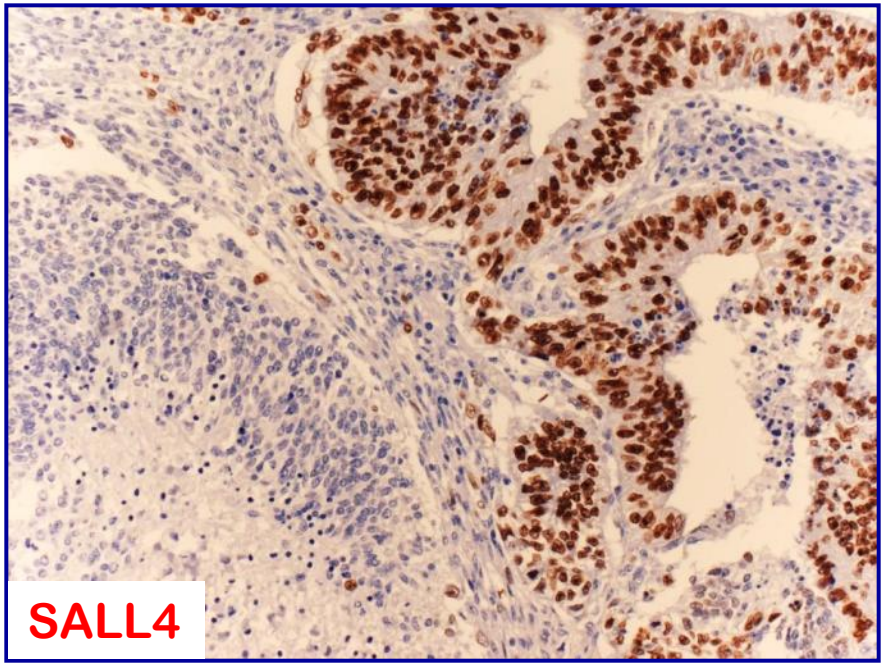


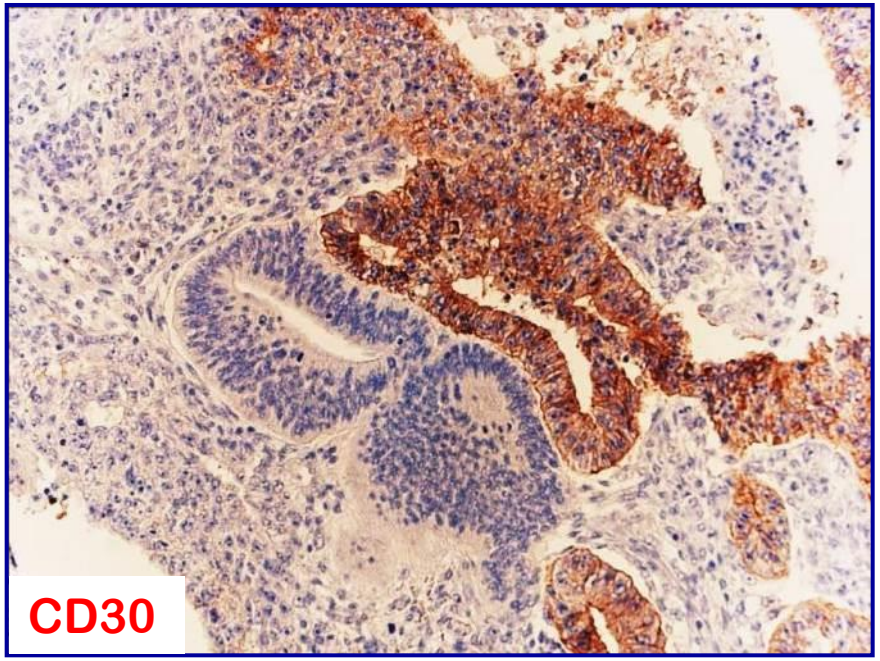
SOX2

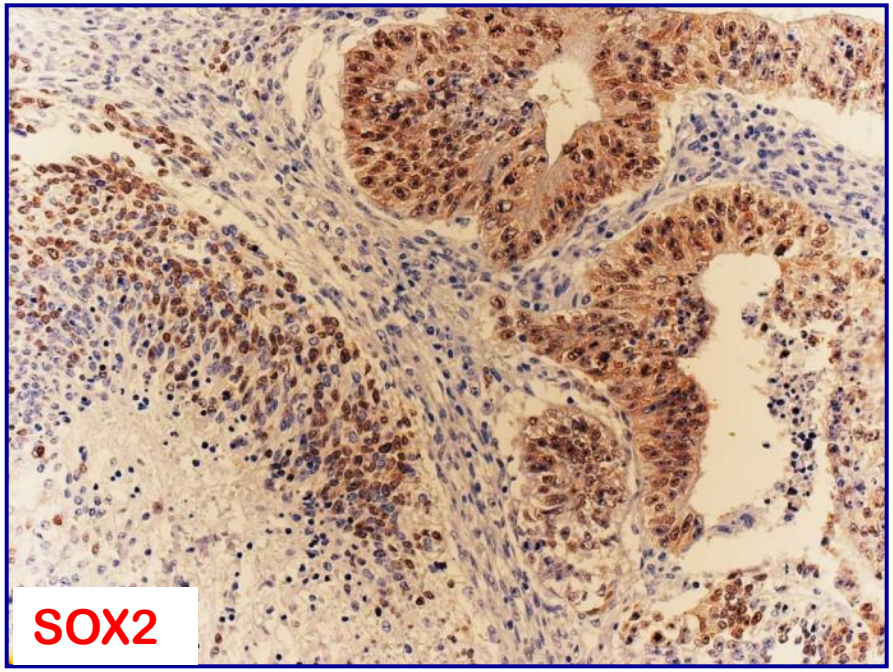
Embryonal Carcinoma-like areas can be present in high grade immature teratomas



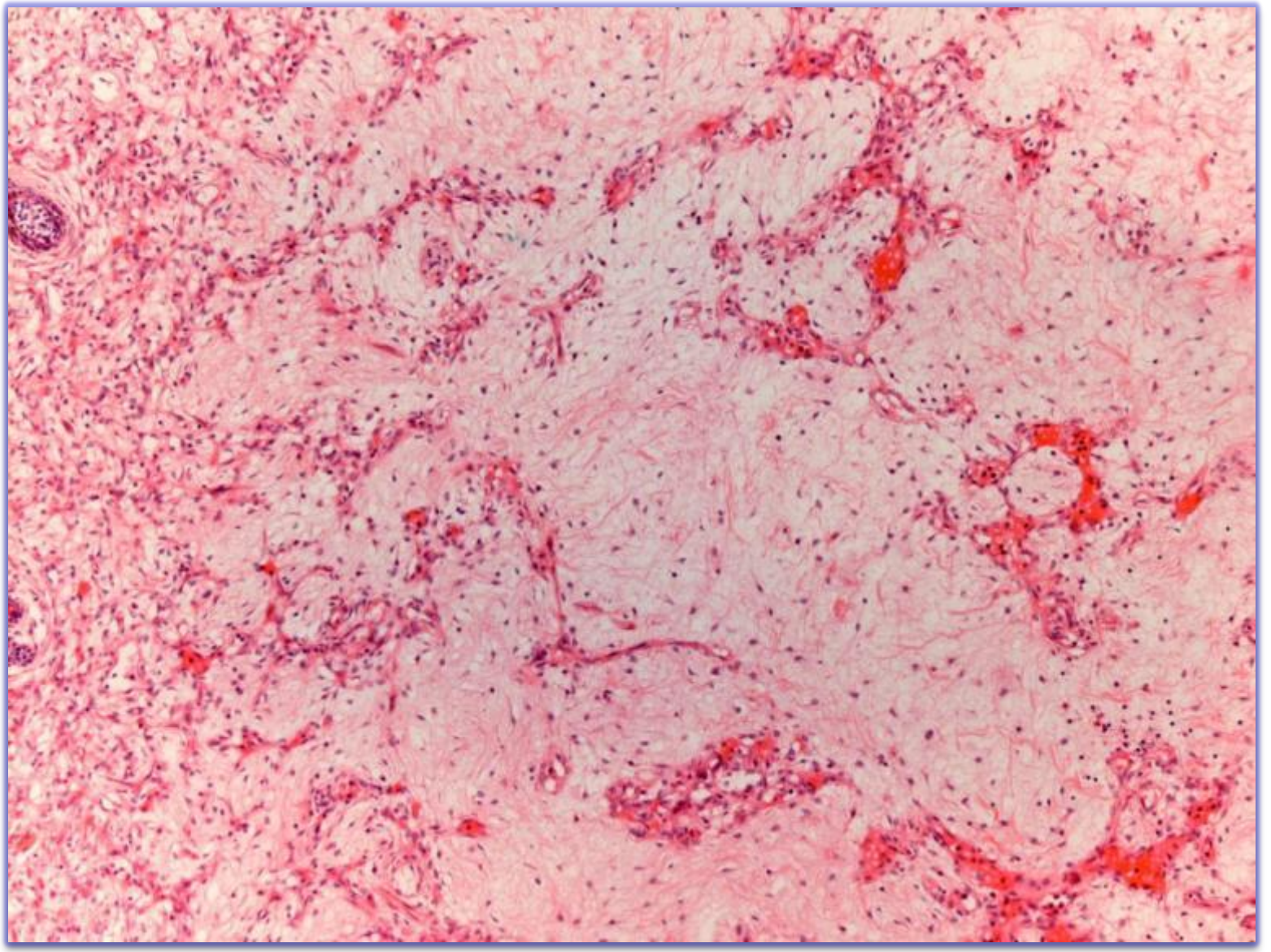

OCT4


SALL4


CD30


SOX2

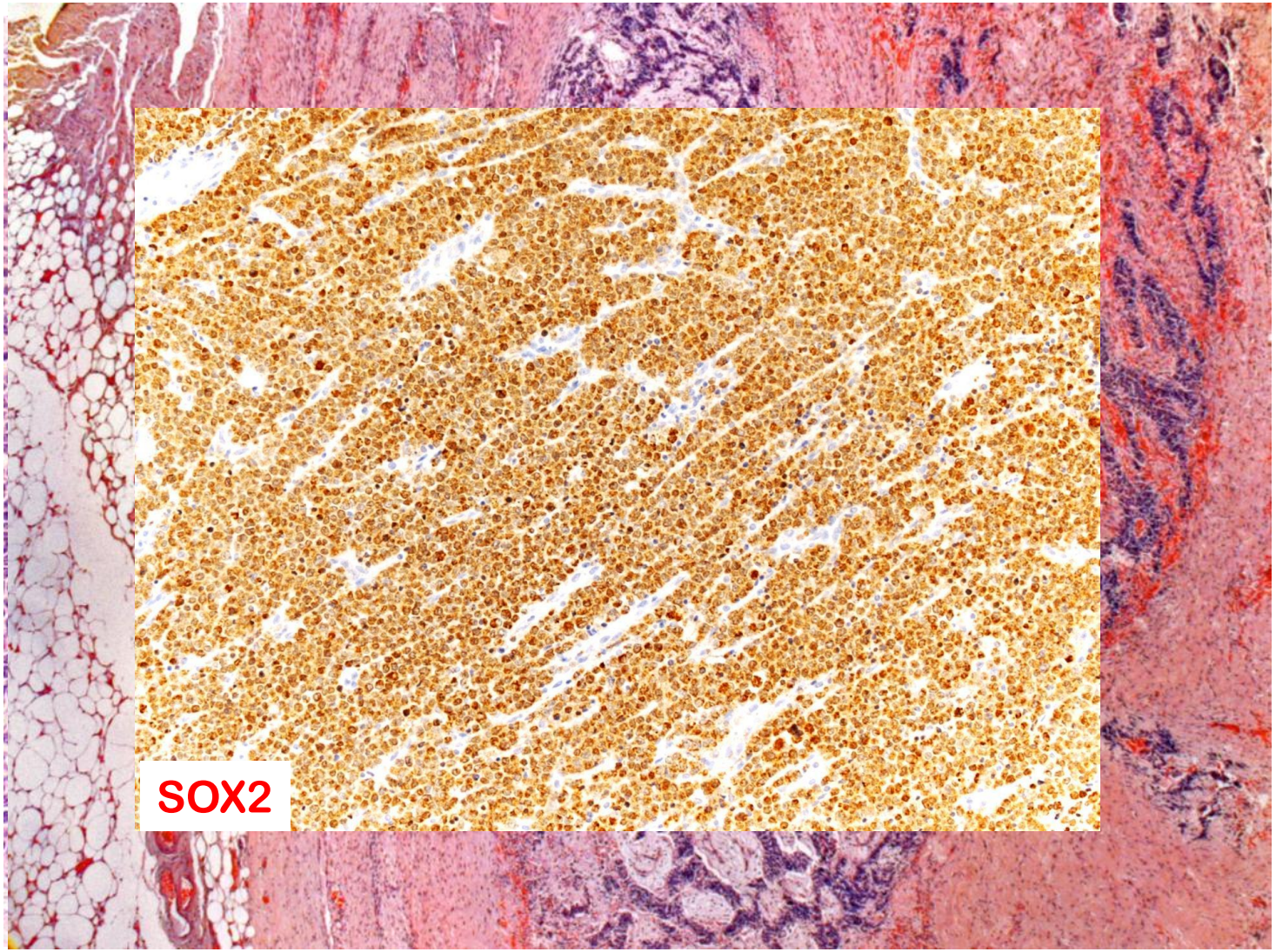
Immature mesenchyme in IT



Immature teratoma grading

- Should be comprehensive of neural/endodermal/mesenchymal immature areas
- Grading facilitated by PPM expression analysis (SALL4/SOX2/OCT4)
- General assessment of tissue immaturity rather than mixed GCT

PNET and IT (MT)



Classification conundrums

PRIMORDIAL GERM CELLS

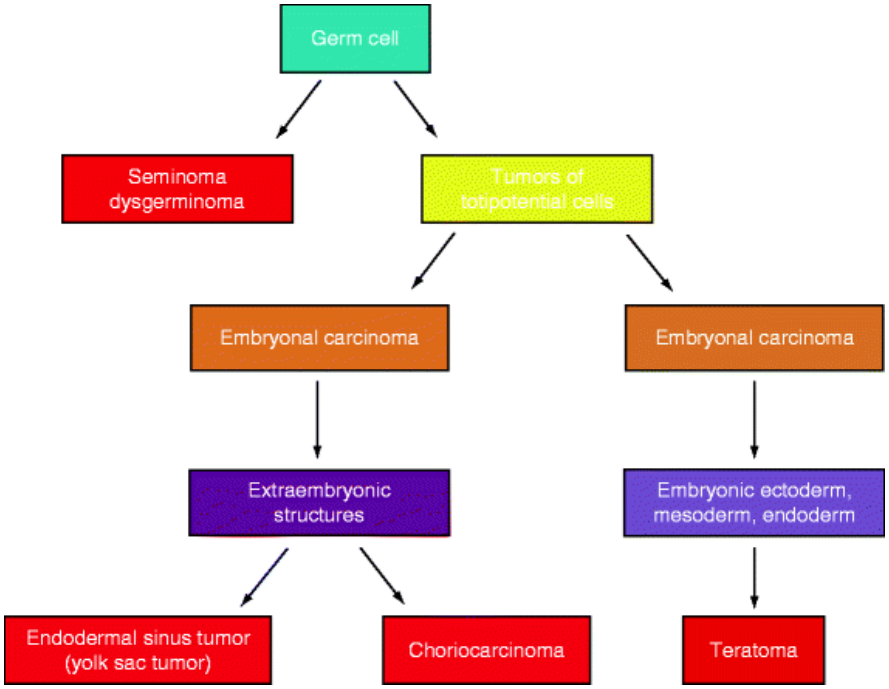
SEMINOMA

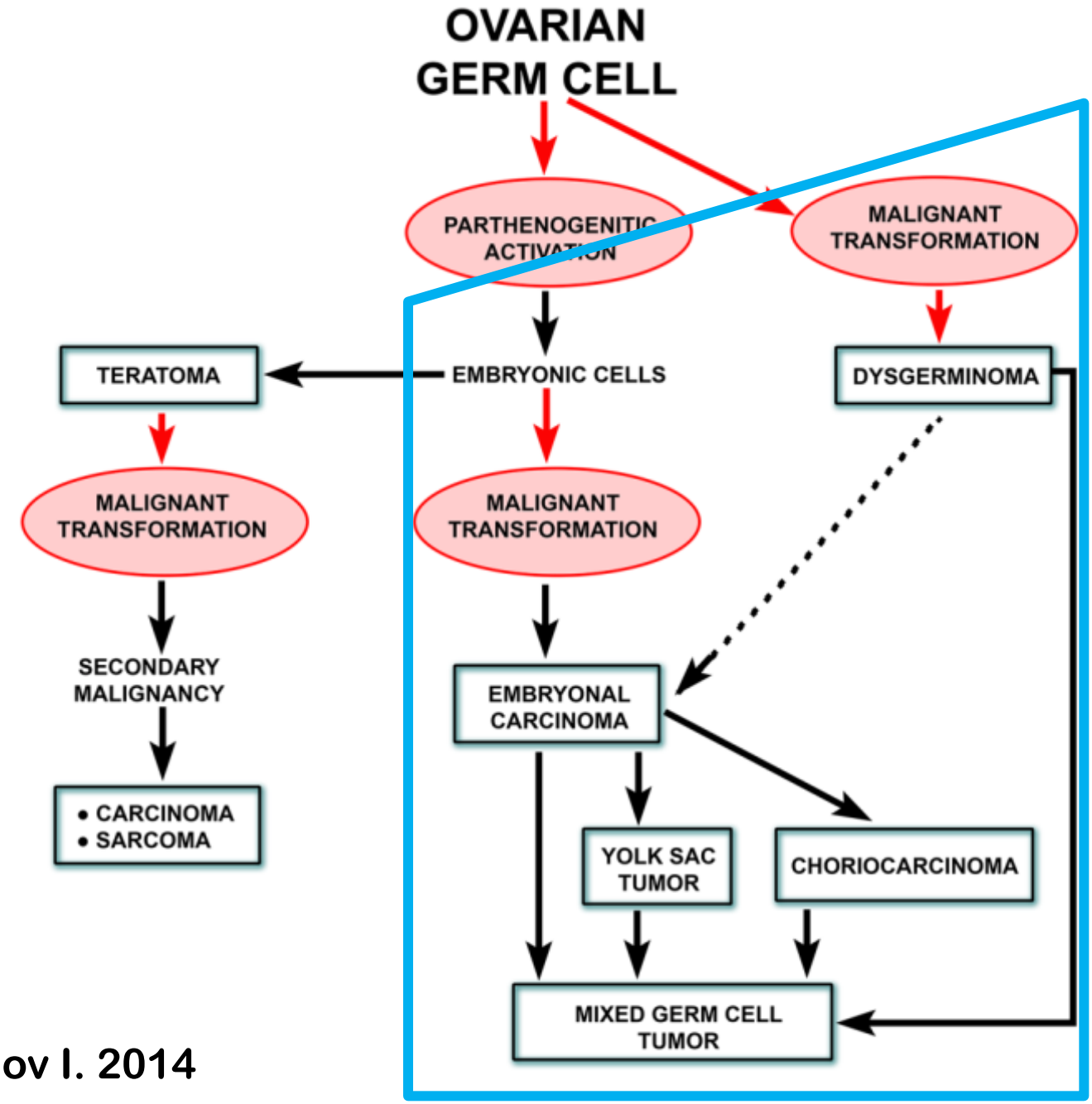
EMBRYONAL CARCINOMA

YOLK SAC TUMOUR

CHORIOCARCINOMA

TERATOMA



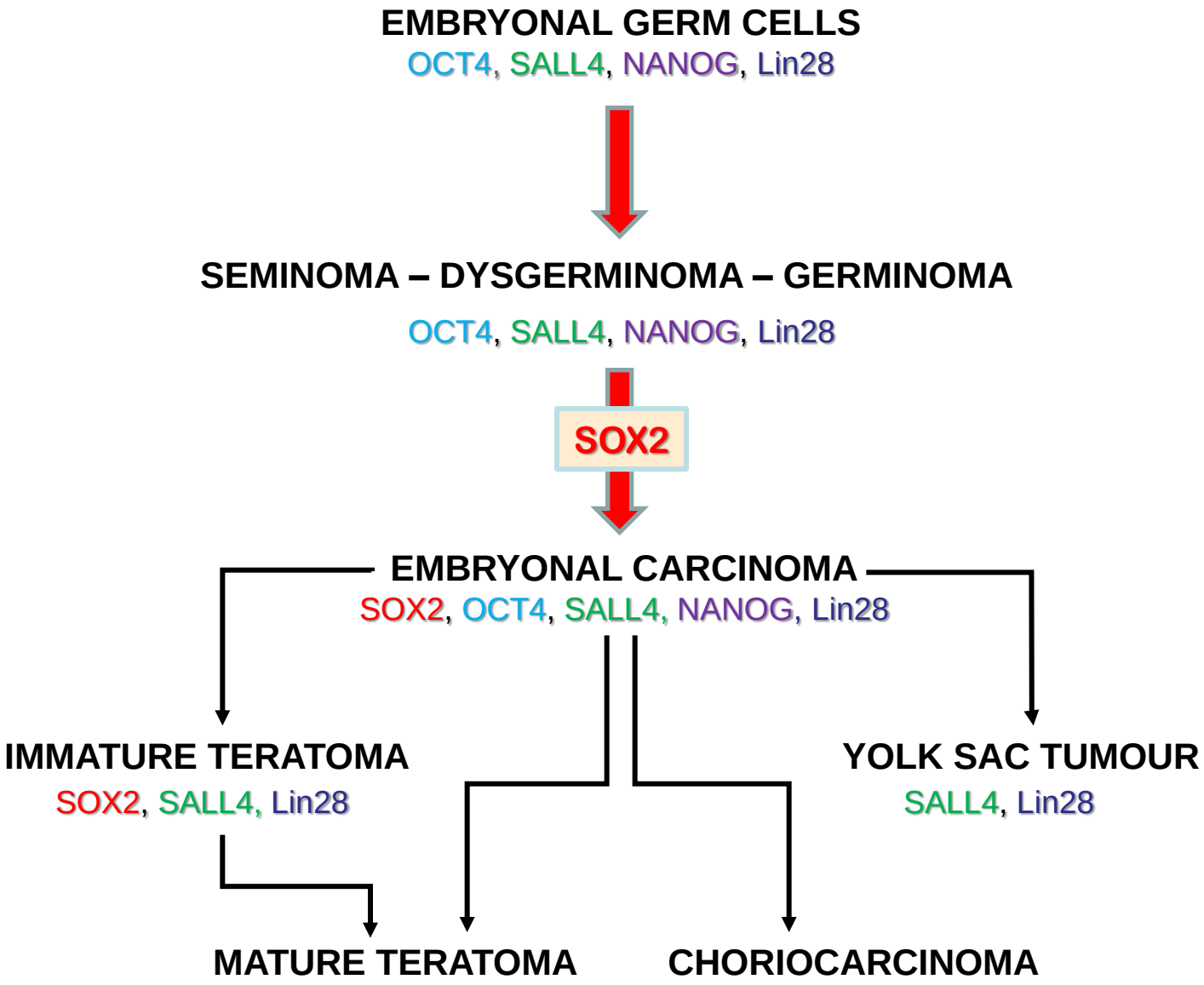


Damjanov I. 2014

Comparative Immunohistochemical Expression in Malignant Ovarian Germ Cell Tumors of Classic, Pluripotency, and Somatic Differentiation Markers

	Immunohistochemical Markers											
	Classic					Pluripotency			Somatic Differentiation			
Tumor	PLAP	CD30	AFP	GLP3	D2-40	OCT3/4	SOX2	SALL4	Villin	CDX2	HepPar-1	TTF1
Dysgerminoma	+	−	−	−	+	+	−	+	−	−	−	−
Yolk sac tumor	+/−	−	+	+	+/−	−	−	+	+ INT	+ INT	+ HEP	+ FRG
Immature teratoma	−	−	−	−	−	−	−	+	−	−	−	−
	−		+ END	+ NEP	+ STR		+ NEP		+ INT	+ END		
Embryonal carcinoma	+	+	−	+ Focal	+/− Apical	+	+	+	NA	−	−	−
Choriocarcinoma	−	−	−	−	−	−	−	−	−	−	−	−
	+SYNC			+SYNC								

Abbreviations: AFP, α-fetoprotein; END, endodermal; FRG, foregut; GLP3, glypican3; HEP, hepatic; INT, intestinal; NA, not available; NEP, neuroepithelium; PLAP, placental alkaline phosphatase; STR, stroma; SYNC, syncytiotrophoblast; TTF1, thyroid transcription factor 1.


EMBRYONAL GERM CELLS
OCT4, SALL4, NANOG, Lin28
SEMINOMA – DYSGERMINOMA – GERMINOMA
OCT4, SALL4, NANOG, Lin28
SOX2
EMBRYONAL CARCINOMA
SOX2, OCT4, SALL4, NANOG, Lin28
IMMATURE TERATOMA
SOX2, SALL4, Lin28
YOLK SAC TUMOUR
SALL4, Lin28
MATURE TERATOMA
CHORIOCARCINOMA

FIGO staging, cancer datasets and the ICCR

Dr Lynn Hirschowitz

Birmingham Women's NHS
NHS Foundation Trust

1. Cancer staging (including FIGO)
2. Specific points about FIGO staging
3. International Collaboration on Cancer Reporting (ICCR)
4. New ICCR ovarian/fallopian tube/ primary peritoneal carcinoma dataset

1. General principal for cancer staging systems

- Stage I: tumour that is strictly confined to the organ of origin
- Stage II: tumour that has extended locally beyond the site of origin to involve adjacent organs or structures
- Stage III: more extensive local involvement or infiltration of neighbouring organs
- Stage IV: tumour with distant metastases

General principal for all staging systems

- 4 basic stages divided into substages to reflect tumour-specific clinical, pathological or biological prognostic factors within a given stage.
- Most staging systems have moved from clinical staging to ‘surgico-pathological’ staging (apart from cervical cancer and gestational trophoblastic disease).

FIGO staging system

- Internationally agreed system for gynaecological cancers
- FIGO staging predates other systems
- Annual reports and ‘horizon scanning’ to provide evidence for revisions
- FIGO Committee for Gynecologic Oncology

Members FIGO Gynaecological Oncology Committee 2012-2015

- Professor Lynette Denny (Chair), South Africa
- Professor Michael Quinn (Co-Chair), Australia
- Professor Sergio Pecorelli, Italy
- Dr Adriana Bermudez, Argentina
- Dr David Mutch, USA
- Professor Neville Hacker, Australia
- Professor Jaime Prat, Spain
- Professor Elisabeth Åvall Lundqvist, Sweden
- Professor Joanna Cain, USA
- Professor Keiichi Fujiwara, Japan
- Dr Shyam Kishore Shrivastava, India
- Professor Muhieddine A-F Seoud, Lebanon
- Dr Neerja Bhatla, India

FIGO, AJCC, TNM/UICC

- Reciprocal representation
- Collaboration but no agreed co-ordination of timing of revisions
- TNM staging focus remains ‘anatomic’
- AJCC staging – moves to include ‘non-anatomic’ data
- FIGO position; dictated by prognosis

On the FIGO radar -

Possible issues:

- Stage III vulval cancer
- LVI in cervical cancer
- Extracapsular invasion and LN metastases in cervical cancer
- Stage I endometrial cancer

2. Specific points about FIGO staging - vulva

- Poor spread of prognostic groupings with1988 surgical staging system for stage III.
- Importance of lymph node status, number of positive nodes, size of deposits, extracapsular extension recognised in 2009 revision.
- Tumour size: node negative IB and II combined (IB).

Specific points about FIGO staging - cervix

- Clinically staged but FIGO recognises importance of pre-treatment clinical staging.
- Use of COSD in UK.
- Stage IIA subdivided to take account tumour size (4 cm or > 4cm).
- Recording of lymph node involvement.

Specific points about FIGO staging - uterus

Clinical scenario:

60 mm uterine tumour; outer half myometrial invasion; cervical stromal infiltration; parametrial lymphovascular invasion.

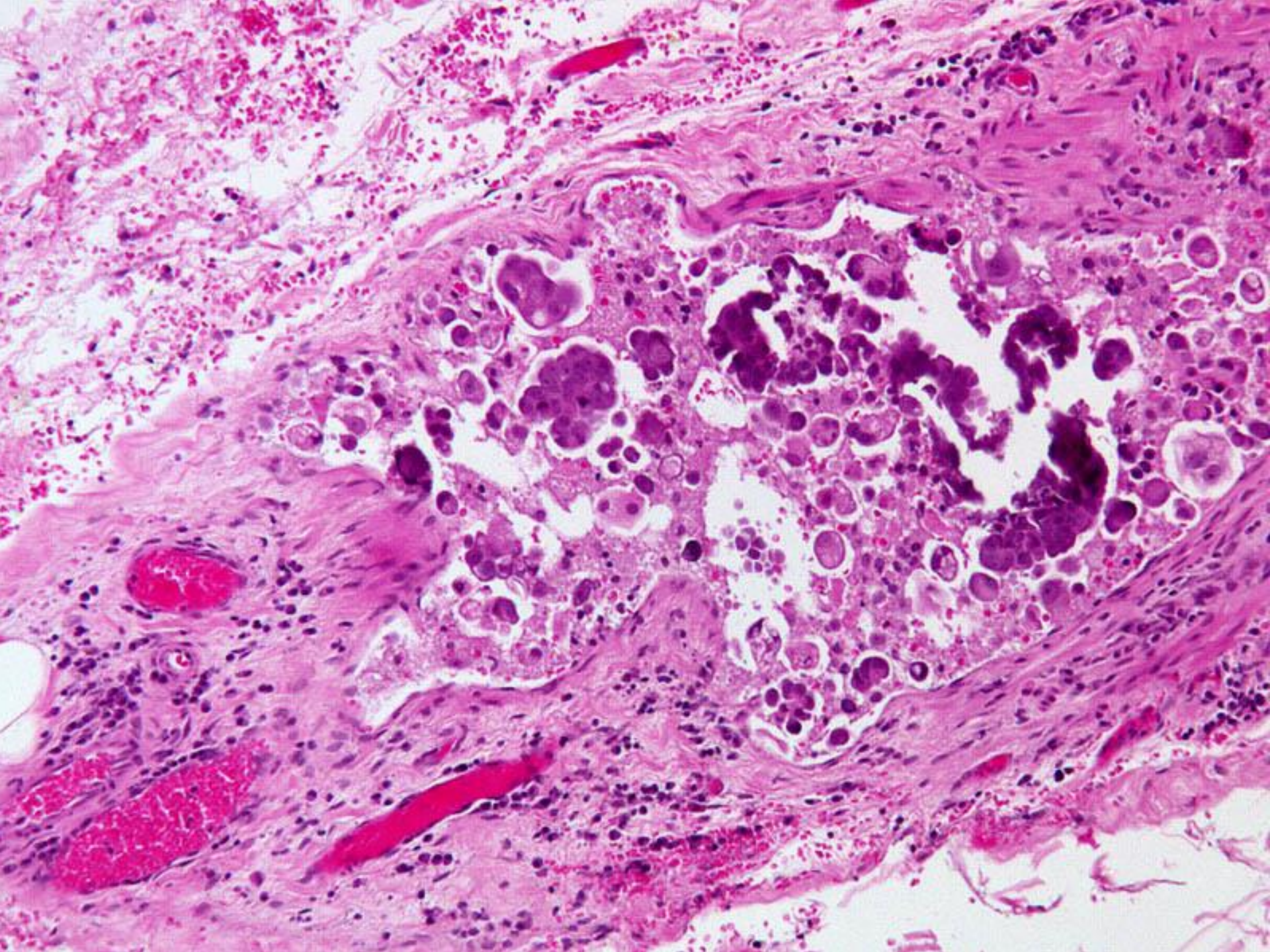
What is the FIGO stage if this is:

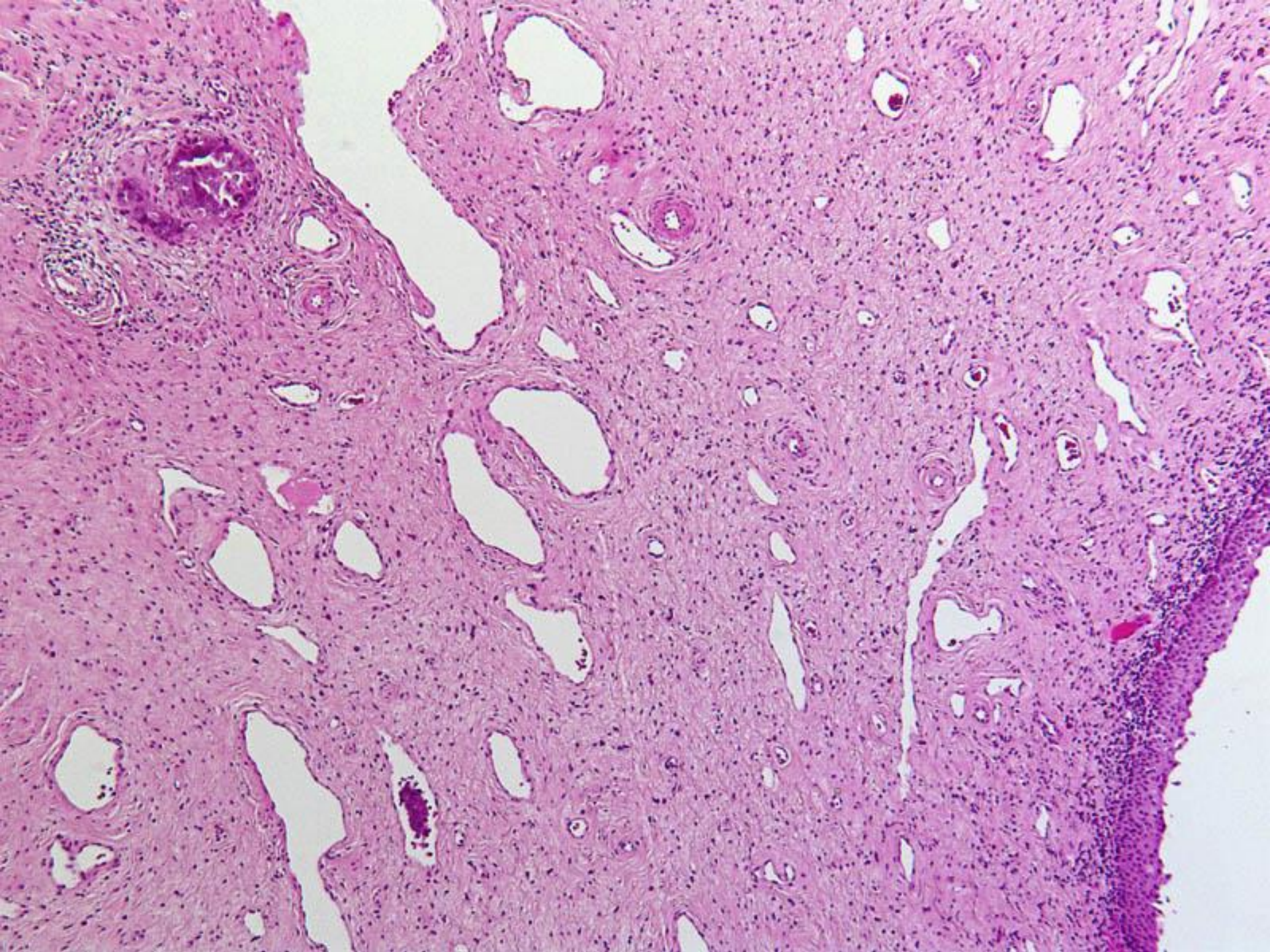
- Carcinosarcoma
- Leiomyosarcoma
- Adenosarcoma

Specific points about FIGO staging - uterus

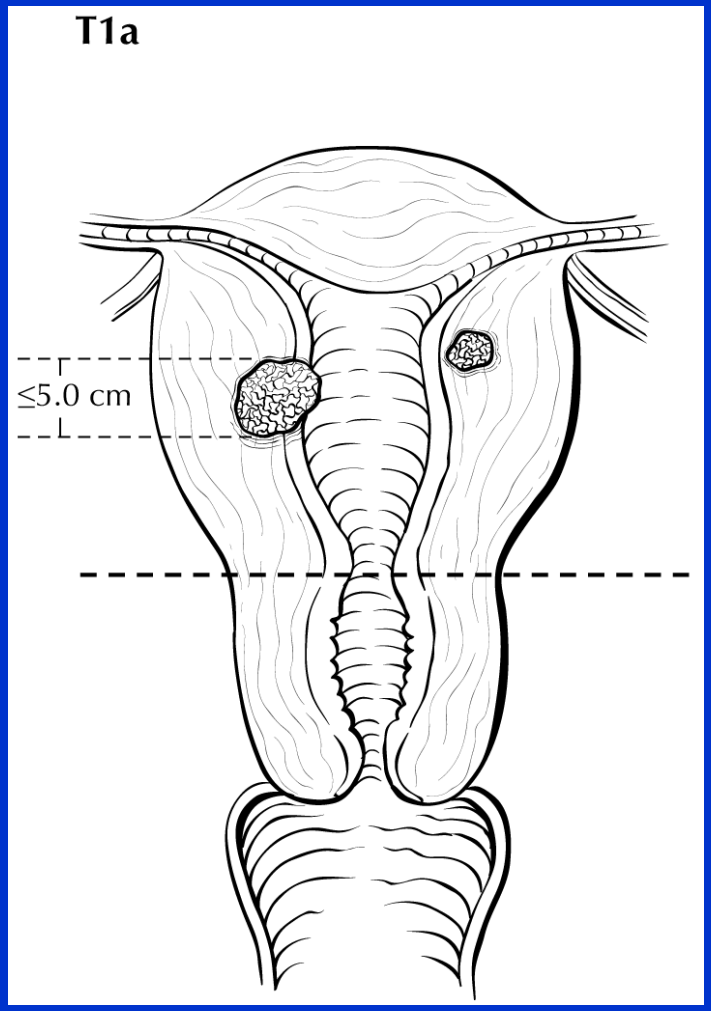
Carcinosarcoma (= metaplastic carcinoma)

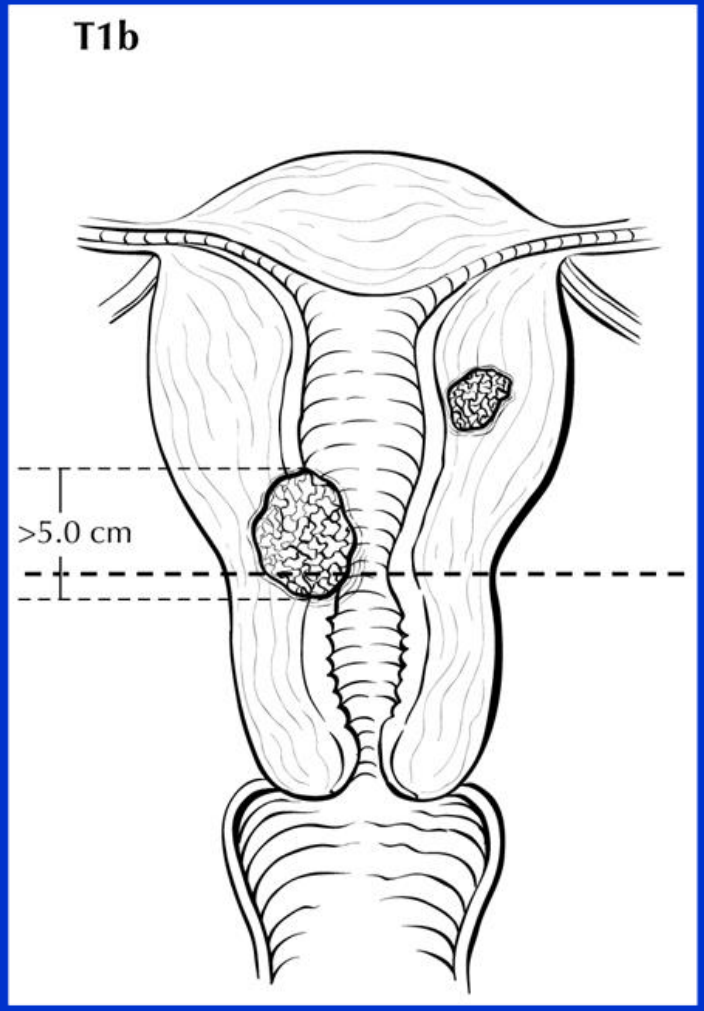
- Staged in the same way as endometrial carcinoma
- Lymphovascular invasion without tissue invasion does not count towards staging
- [Size is a predictor of poor prognosis/ ‘peritoneal failure’ for carcinomas]
- Cervical stromal involvement is FIGO stage II





Leiomyosarcoma





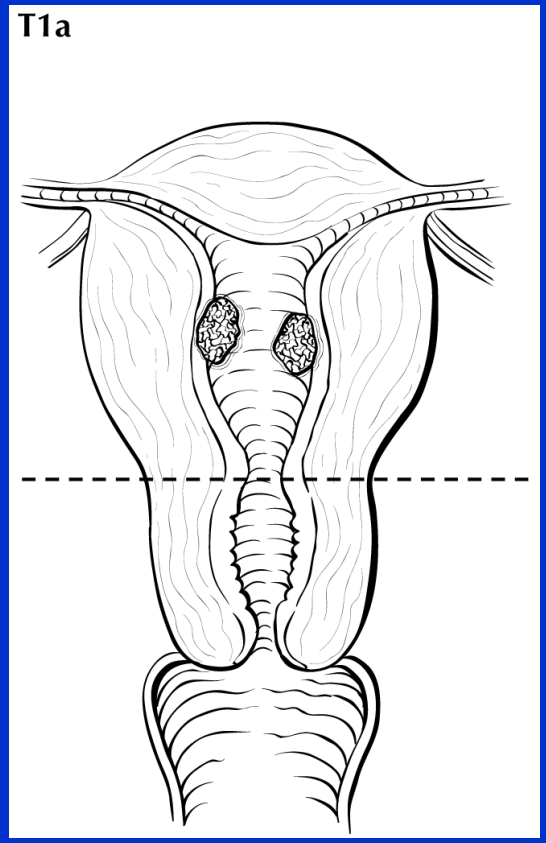
AJCC 2013

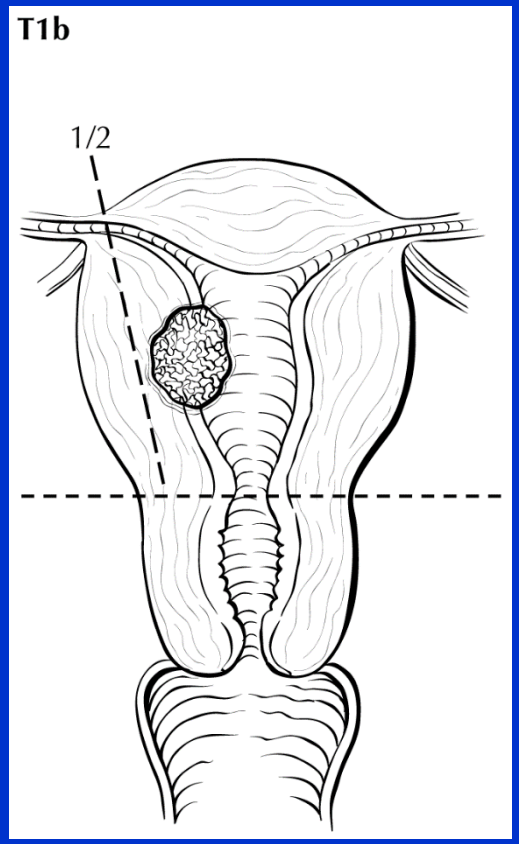
Specific points about FIGO staging - uterus

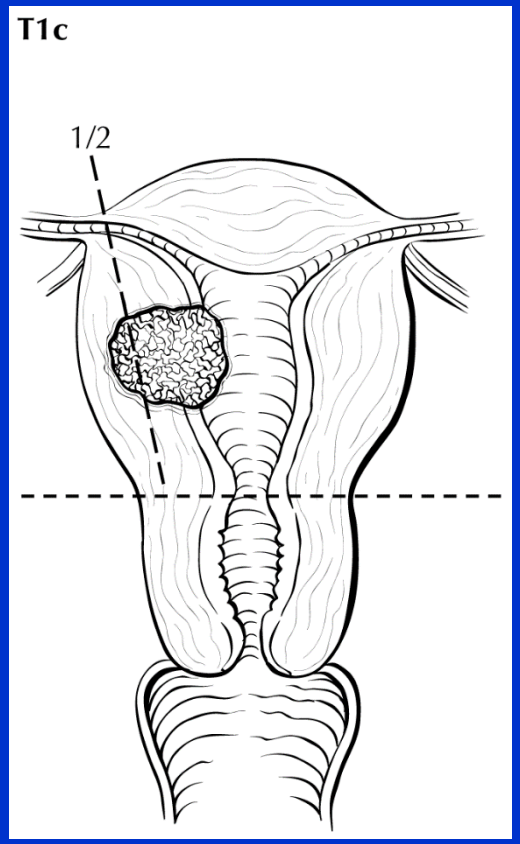
Leiomyosarcoma

- Staged in the same way as endometrial stromal sarcoma (usually myometrial based)
- Cervical involvement contributes to prognosis but not to stage
- Lymphovascular invasion without tissue invasion does not count towards staging
- Tumour size is important for staging
- FIGO stage = IB (>5 cm)

Adenosarcoma







AJCC 2013

Specific points about FIGO staging - uterus

Adenosarcoma

- Usually endometrial based.
- Stage I = same as 1988 system for endometrial carcinoma.
- Cervical involvement does not contribute to stage.
- Size is not important for staging.
- Lymphovascular invasion without tissue invasion does not count towards staging.
- FIGO stage = IC (outer ½ myoinvasion).

Specific points about FIGO staging – uterine sarcomas

- Corrigendum published in 2009
- Undifferentiated endometrial/uterine sarcoma
- Pure heterologous uterine sarcoma

Specific points about FIGO staging – ovary/FT/PPCa

- Subdivision of stage IC.
- No evidence to support upstaging because of adhesions.
- Stage IIIA – no evidence that size of nodal deposits (≤10 mm; >10 mm) is significant.
- Intraperitoneal node involvement = IIIC
- Cytological node involvement of unknown size = Stage IIIA1(i)

International Collaboration on Cancer Reporting

International Collaboration on Cancer Reporting
5 founding members

Incorporation September 2014

ICCR Board

- **Management issues**
- **Governance**
- **Finance**
- **Publicity**
- **Membership**
- **Strategic Alliances**

ICCR Steering Group

Dataset development
Dataset revision

International Collaboration on Cancer Reporting

Strategic Alliances:

UICC

FIGO

AJCC

EORTC

IARC

Alignment of ICCR dataset development with the IARC revision of the ‘Blue book’ series

Development of evidence-based ICCR cancer datasets

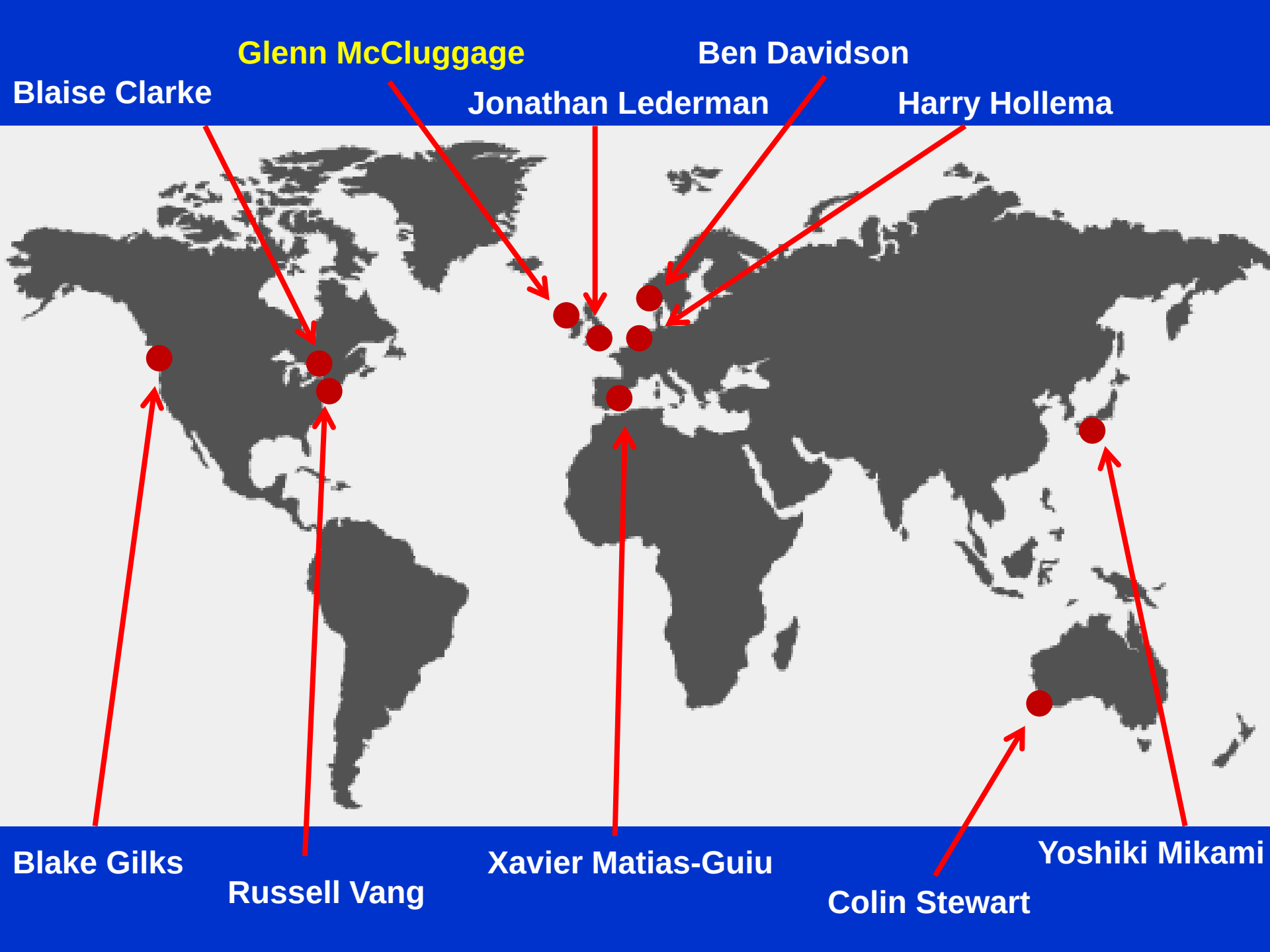
- Robust protocols for dataset development.
- Evidentiary support at NHMRC Level III-2 or above.
- Two key dataset components:

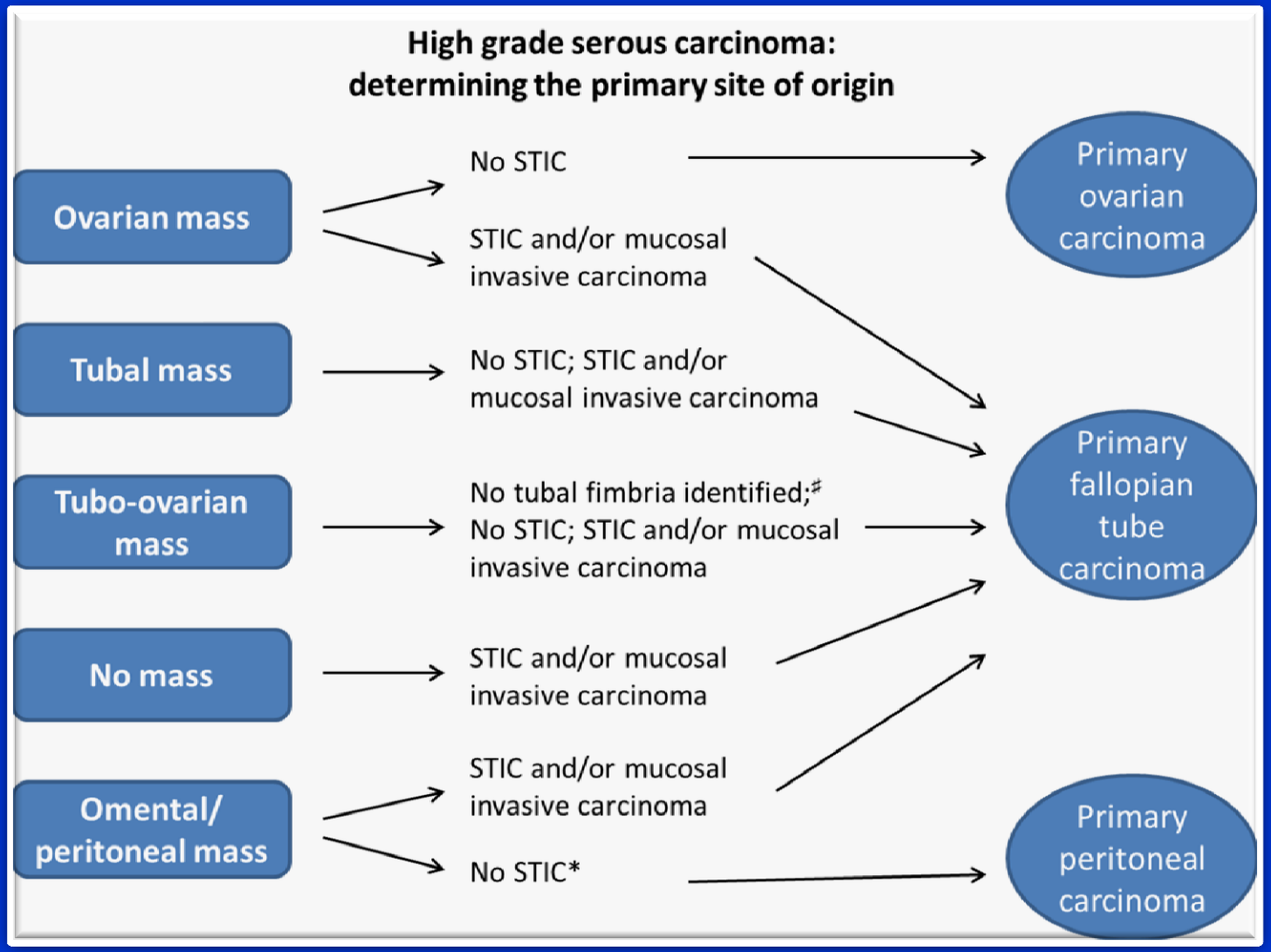
➢ REQUIRED elements, essential for histological diagnosis, clinical management, staging, prognosis.

➢ RECOMMENDED elements, non-mandatory, clinically important; recommended as good practice but not yet validated or regularly used in patient management.

4. Development of dataset for carcinoma of the ovary, fallopian tube and primary peritoneal site

- Single dataset for all 3 sites.
- Incorporates 2014 WHO classification of tumours of the female reproductive organs.
- Incorporates 2013 FIGO staging.
- Includes guidance about site assignment of primary tumours.
- Includes guidance about chemotherapy response score/CRS (tumour regression grading).


Glenn McCluggage
Ben Davidson
Blaise Clarke
Jonathan Lederman
Harry Hollema
Blake Gilks
Russell Vang
Xavier Matias-Guiu
Yoshiki Mikami
Colin Stewart



Failure to detect the tubal fimbria implies overgrowth by tumour
* Apply criteria as specified in the commentary

Primary peritoneal carcinoma

- Diagnosis only after complete examination of the fallopian tubes (including the non-fimbrial portions)
- Ovaries must be of normal size or enlarged by a benign process
- Involvement in extra-ovarian sites > involvement on the surface of either ovary
- Ovarian tumour involvement must be non-existent, confined to ovarian surface without stromal invasion or involve the cortical stroma with tumour size less than 5 x 5 mm.

Chemotherapy Response Score

- Applies to serous carcinomas only.
- Score on a single H&E-stained section.
- Use single block of involved omental tissue with *least* response to chemotherapy.
- Assess *viable* tumour. The presence of fibrosis may be helpful in marking the site of previous tumour infiltration.
- 3-tier system: as a guide, >95% of tumour should be viable for a score of 1, and <5% for a score of 3.

Chemotherapy Response Score (CRS)

Score	Criterion	Tumour Regression Grading
1	Mainly viable tumour with minimal regression-associated fibro-inflammatory changes* limited to a few foci.	No or minimal tumour response
2	Multifocal or diffuse regression-associated fibro-inflammatory changes, with viable tumour ranging from diffuse sheets, streaks or nodules, to extensive regression with multifocal but easily identifiable residual tumour.	Partial tumour response
3	Mainly regression, with few irregularly scattered individual tumour cells or cell groups (all measuring less than 2 mm), or no residual tumour identified.	Complete or near-complete response

*** Regression-associated fibro-inflammatory changes: fibrosis associated with macrophages, including foam cells, mixed inflammatory cells and psammoma bodies; to be distinguished from tumour-related inflammation or desmoplasia.**

Epidemiology and population health management

Monitoring of screening programmes

International comparison of patient outcomes

National comparison of patient outcomes

Robust data for translational and clinical research

Accurate registration of cancer specific data

Correct patient prognosis

Optimum patient management

Accurate diagnosis and tumour stage