WHO histological classification 2013
Tumours of the Ovary

Epithelial-stromal tumours

- Serous tumours
  - Benign
    - Serous cystadenoma
    - Serous surface papilloma
    - Serous adenofibroma
  - Borderline Tumours
  - Atypical proliferative serous tumor, Serous borderline tumor, usual type (Surface or Cystic)
  - Non-invasive micropapillary (low grade) serous carcinoma, Serous borderline tumor, micropapillary type
  - Malignant
    - Low grade serous adenocarcinoma
    - High grade serous adenocarcinoma
    - Transitional-like adenocarcinoma

WHO histological classification 2013
Tumours of the Ovary

Transitional cell tumours

- Benign Brenner tumour
- Atypical proliferative Brenner tumour, Borderline Brenner tumour
- Malignant Brenner tumour

Transitional Cell Carcinoma (TCC)

a) High-grade ovarian carcinomas with stromal invasion

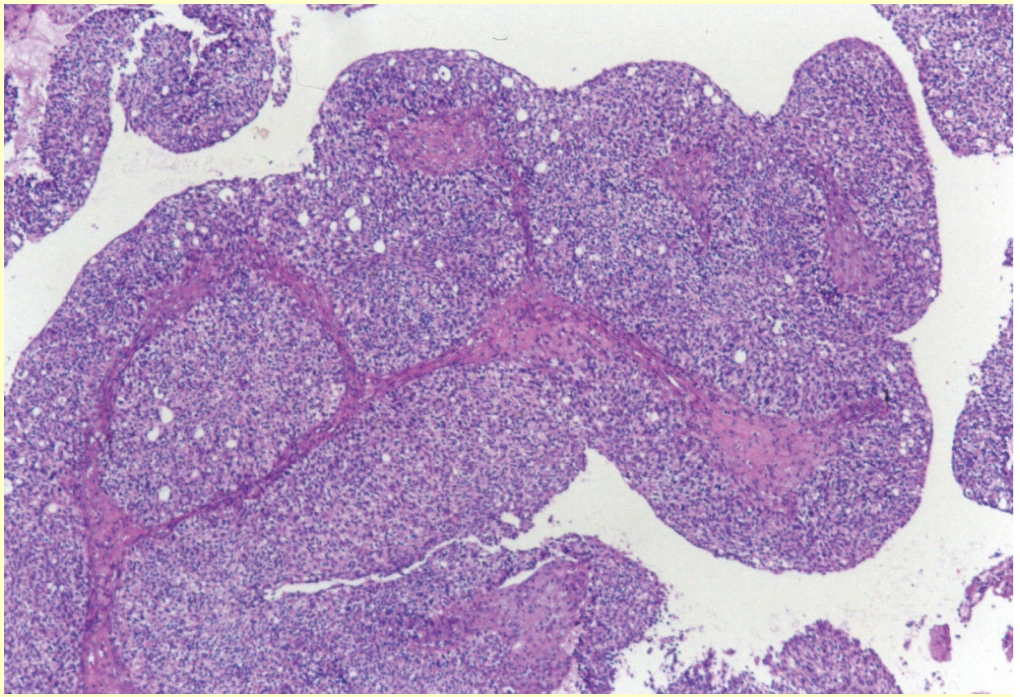
b) Urologic TCC component >10%

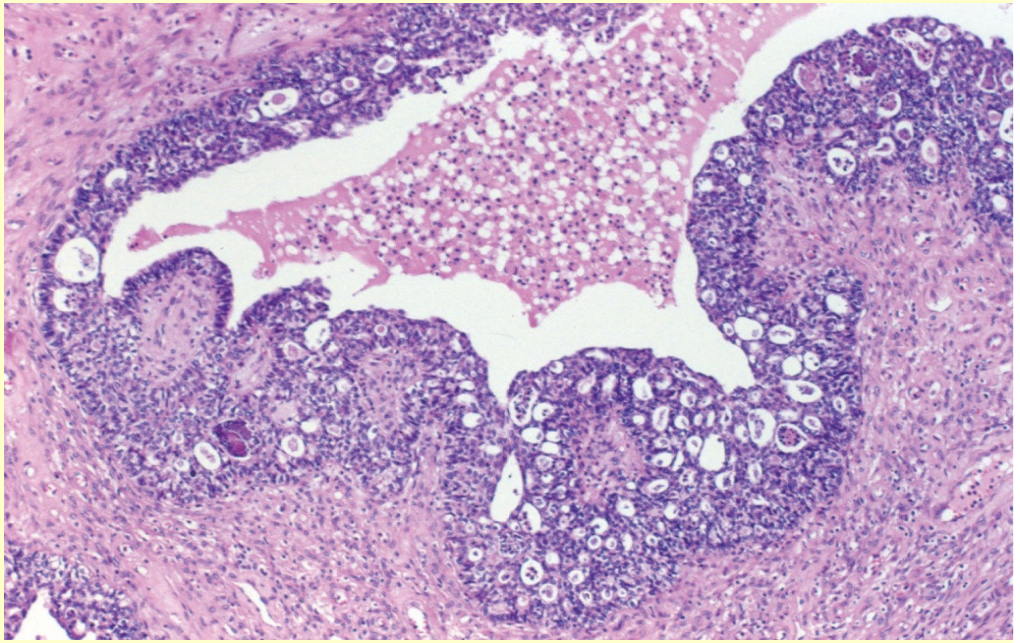
c) Large cystic spaces (70%), broad undulating papillae with smooth borders (60%), microspaces (90%)

d) Lack of benign or borderline Brenner component

e) Frequent high-grade serous carcinoma component

Eichhorn JH & Young RH Am J Surg Pathol 2004





Transitional Cell Tumors of the Ovary

A Comparative Clinicopathologic, Immunohistochemical, and Molecular Genetic Analysis of Brenner Tumors and Transitional Cell Carcinomas

Miriam Cuatrecasas, MD, Luis Catasus, PhD,* José Palacios, MD,† and Jaime Prat, MD, FRCPath**

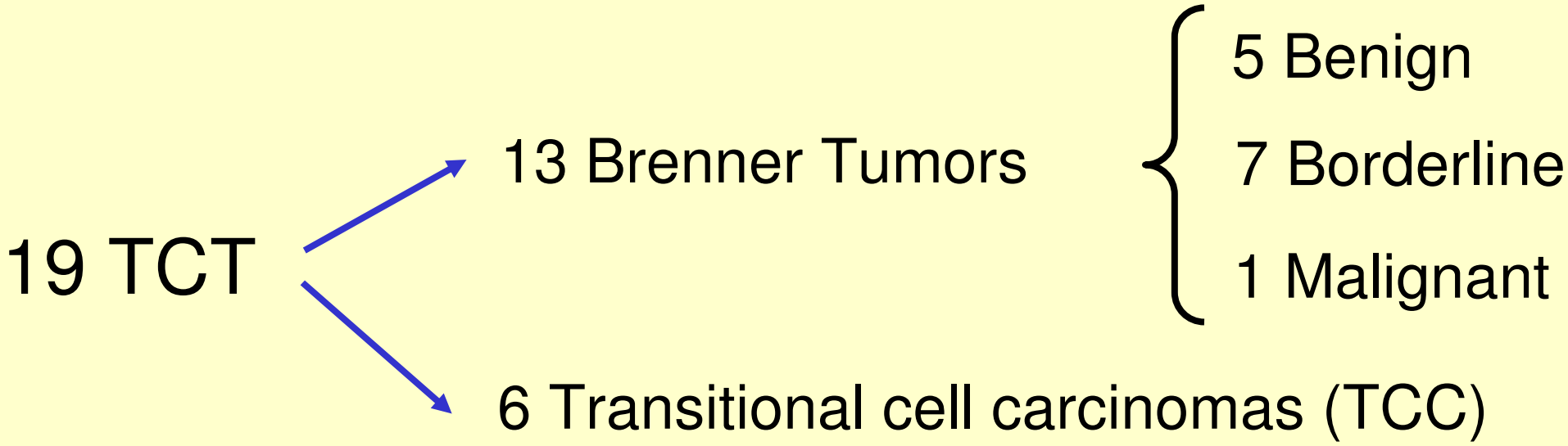
Abstract: Transitional cell tumors of the ovary include 2 distinct clinicopathologic categories: Brenner tumors and transitional cell carcinomas (TCCs). Their molecular genetic alterations have not been fully investigated. We have performed a clinicopathologic, immunohistochemical, and molecular genetic analysis of 19 transitional cell tumors including 13 Brenner tumors (5 benign, 7 borderline, and 1 malignant) and 6 TCCs. Immunoreactivity for epidermal growth factor receptor (EGFR), Ras, Cyclin D1, p16, Rb, and p53, as well as fluorescence in situ hybridization analysis for *EGFR* were assessed in all cases. Screening for mutations in *K-Ras*, *B-Raf*, *CTNNB1*, *PIK3CA*, and *p53* genes was also performed. The mean patient age was 58 years (range, 32 to 85 y). Abdominal p16, Rb, and p53, and strongly positive for Cyclin D1, Ras, and EGFR. In contrast, TCCs had *p53* mutations with p53 and p16 protein overexpression and showed a negative immunoreaction for EGFR, Cyclin D1, and Ras. Our results suggest that Brenner tumors and TCCs follow different tumorigenic pathways, whereas borderline and malignant Brenner tumors are low-grade neoplasms with activation of the PI3K/AKT pathway through EGFR, TCCs are high-grade tumors that have *p53* mutations and p16 and p53 protein overexpression.

Key Words: ovary, benign, borderline, and malignant Brenner tumors, transitional cell carcinoma, molecular genetics, mucinous signet-ring cells, p53, EGFR, PIK3CA

(*Am J Surg Pathol* 2009;33:556–567)

Transitional Cell Tumors (TCT)

(Material)



Cuatrecasas M et al. AJSP 2009

Transitional Cell Tumors (TCT)

(Methods)

Immunohistochemistry (TMA)

- EGFR
- RAS
- Cyclin D1
- p16
- Rb
- p53

FISH -- EGFR

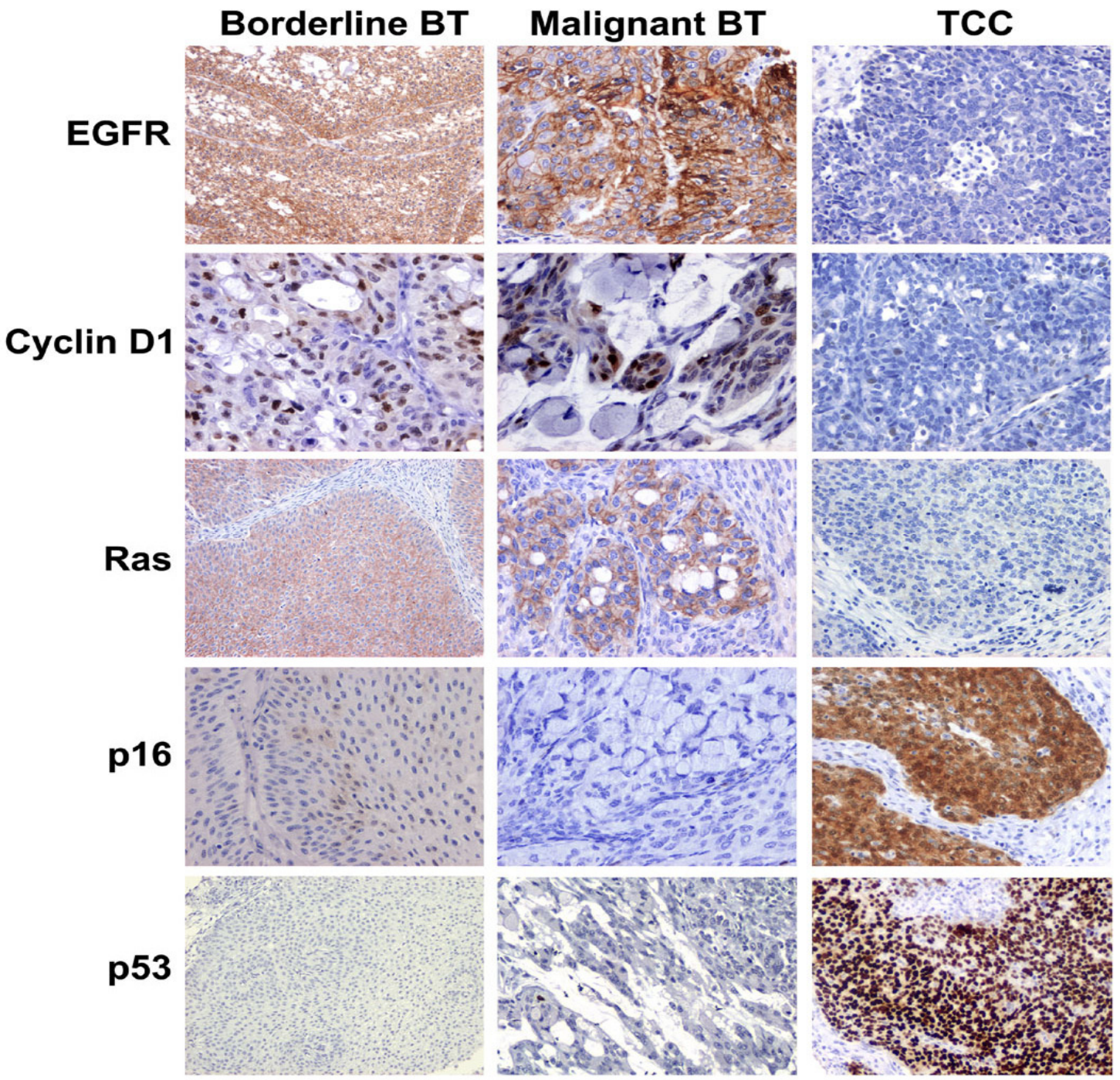
Mutational Analysis

- *K-RAS*
- *BRAF*
- *CTNNB1*
- *PIK3CA*
- *p53*

Hypermethylation

- *p16*
- *Rb*

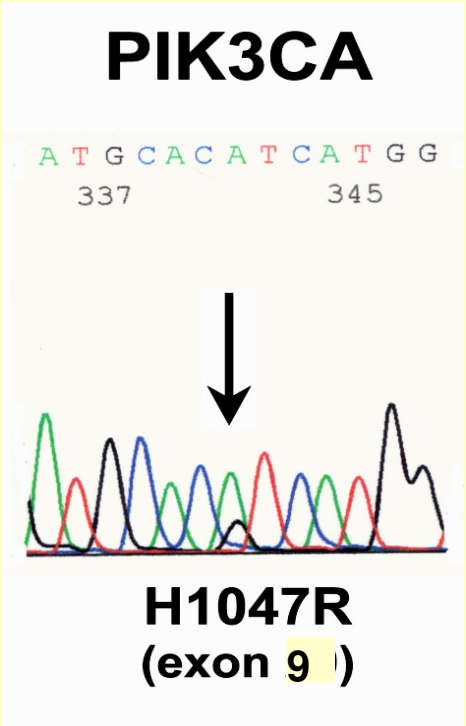
LOH -- *p16*



TCT

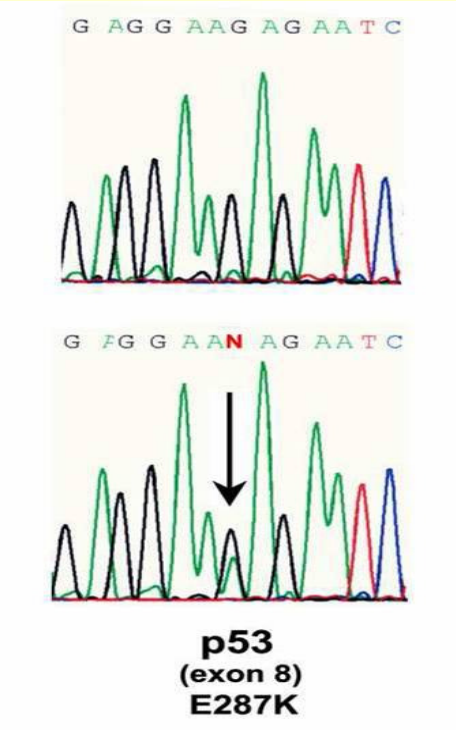
Transitional Cell Tumors of the Ovary
(Mutations)

Exon 9 *PIK3CA* mutations (2):
- Borderline Brenner (1)
- Malignant Brenner (1)



Malignant Brenner Tumor

p53 mutations (4/4)
Transitional cell carcinomas (4)



Transitional Cell Carcinoma

Cuatrecasas M et al. AJSP 2009

Molecular Genetics

	Malignant Brenner	TCC
EGFR-RAS-MAPK	+++	-
PIK3CA mutations	+	
p16 LOH	+	
P53 (chromosome instability)	-	+++

Cuatrecasas M. et al. AJSP 2009

International Journal of Gynecological Pathology
31:499–506, Lippincott Williams & Wilkins, Baltimore

Original Article

Transitional Cell Carcinoma of the Ovary is Related to High-grade Serous Carcinoma and is Distinct From Malignant Brenner Tumor

Rola H. Ali, M.D., Jeffrey D. Seidman, M.D., Margaret Luk, B.Sc., Steve Kalloger, M.Sc., and C. Blake Gilks, M.D., F.R.C.P.C.

	WT1	p53	ER	p16	Cyclin D1	PiK3ca
TCC	67%	86%	71%	29%		
Mg Brenner	-	-	-	-	+	+

	Malignant Brenner	TCC
Stage I	**80-90%**	30%
Stages II-IV	10-20%	**70-100%**
Stage I survival	90%	43%

FIGO Proposal for Staging Cancer of the Ovary, Fallopian Tube and Peritoneum

FIGO Gynecology Oncology Committee

Rome, October 2012

International Union Against Cancer (UICC)
TNM Annual Meeting, May 2013

Committee Members

- Lynette Denny (SA)
- Michael Quinn (Au)(GCIG)
- Sergio Pecorelli (It)
- Adriana Bermudez (Ar)
- Neville Hacker (Au)
- Jaime Prat (Sp)
- Elisabeth Avall-Lundqvist (Sw)
- Joanna Cain (USA)
- Shyam Shrivastava (In)
- Muhieddine Seoud (Lb)
- Franco Odicino (It)
- Keiichi Fujiwara (Jp)
- David Mutch (USA) (SGO)

Committee members
(Expanded)

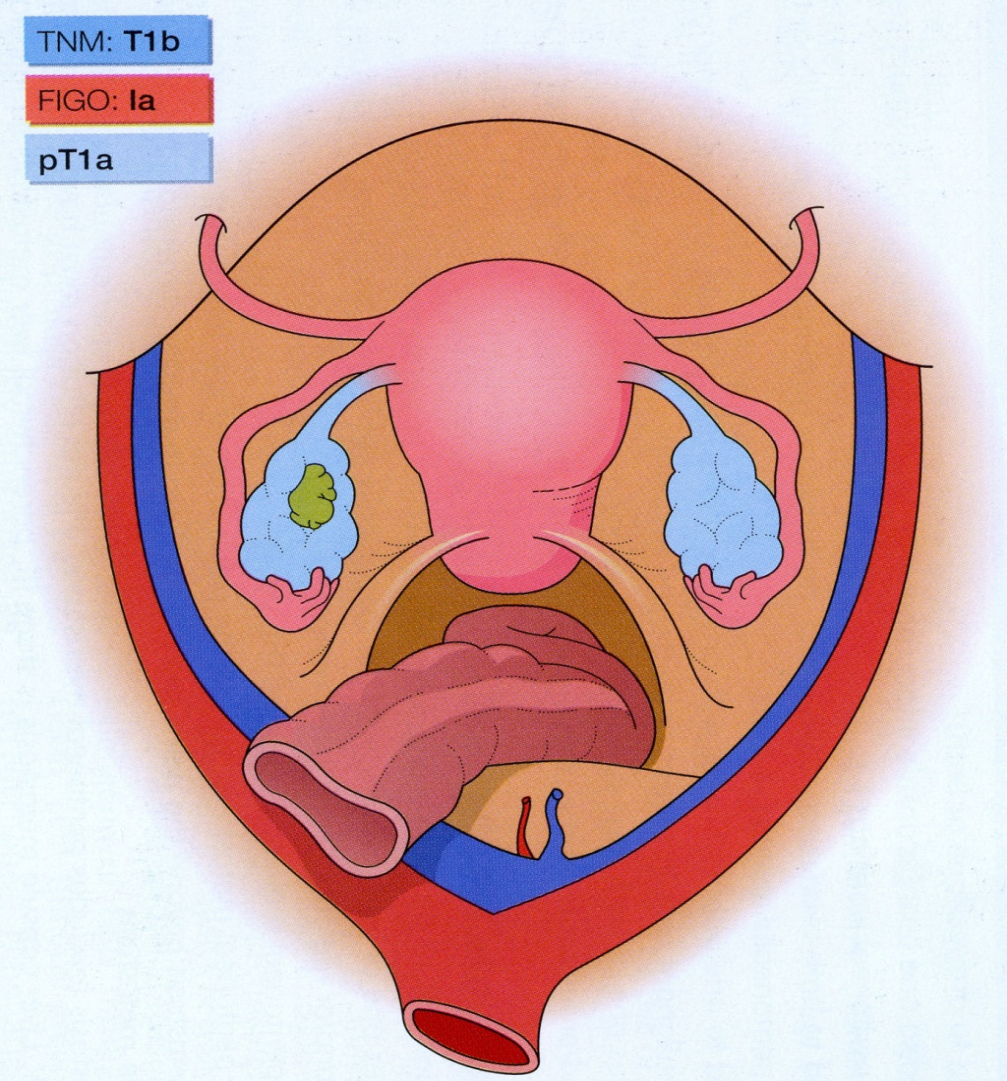
- Alexander Olawaiye (AJCC)
- Jim Brierly (UICC)
- Vesna Kesic (ESGO)
- Jonathan Lederman (NIH-UK)
- Antonio Gonzales (EORTC)
- Jonathan Berek (IGCS)
- Antonio Gonzales (EORTC)

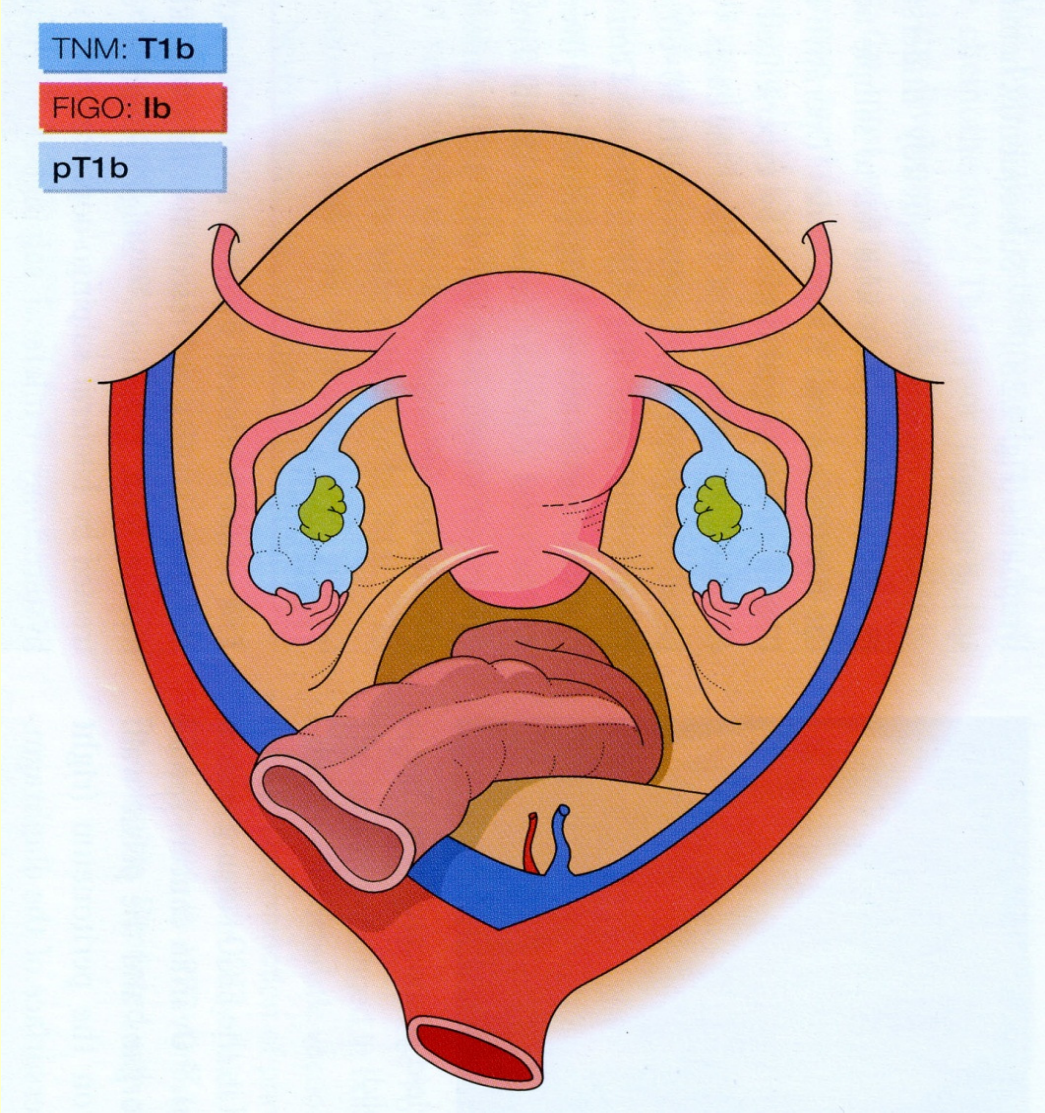
Organizations who gave input

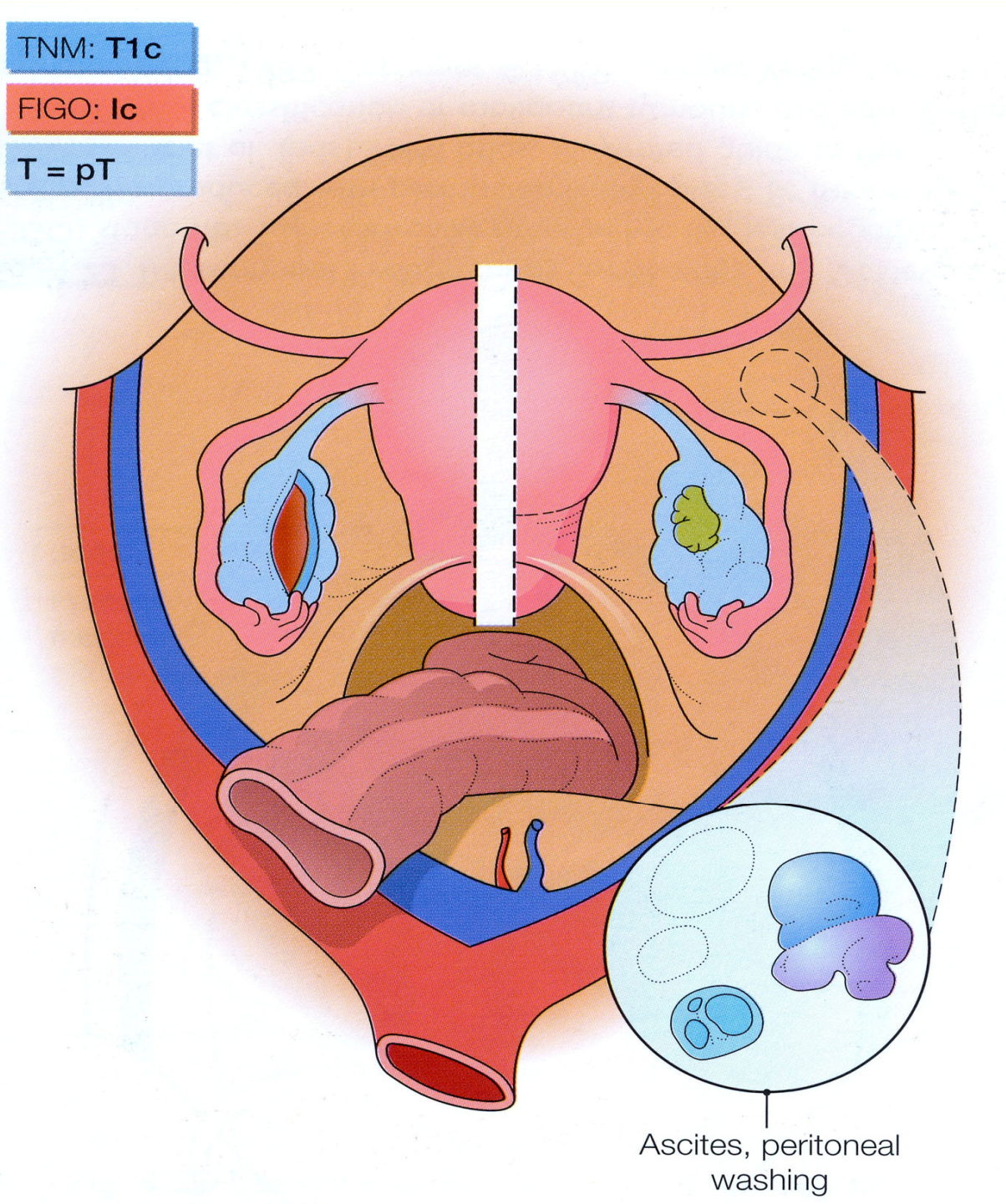
- AJCC
- SGO
- ESGO
- GCIG
- National cancer research group of National Institute for Health Research, UK
- EORTC
- UICC
- IGCS
- Korean Society of Gyn Oncology
- Japanese Society of Gyn Oncology

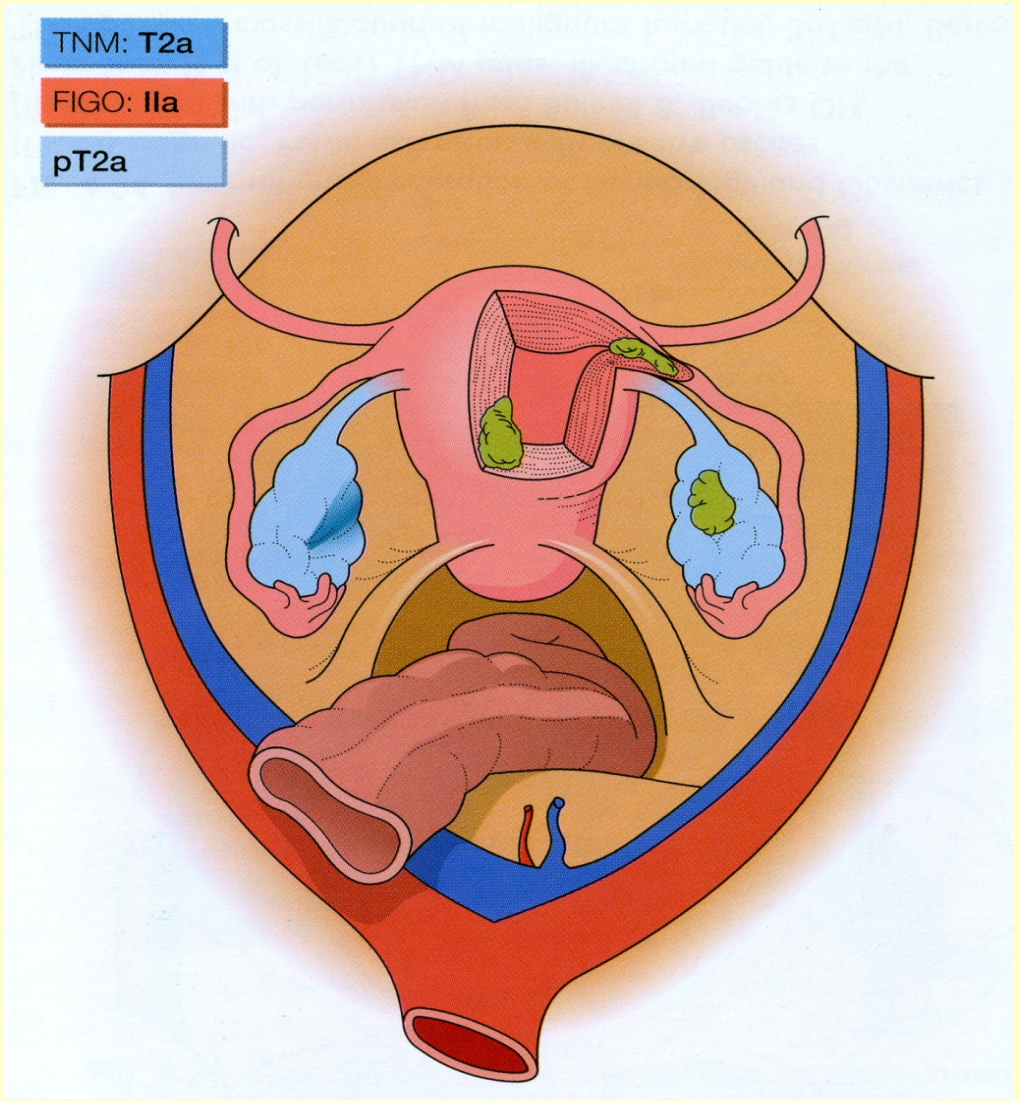
Clinical Staging of Ovarian Cancer (FIGO 1988)

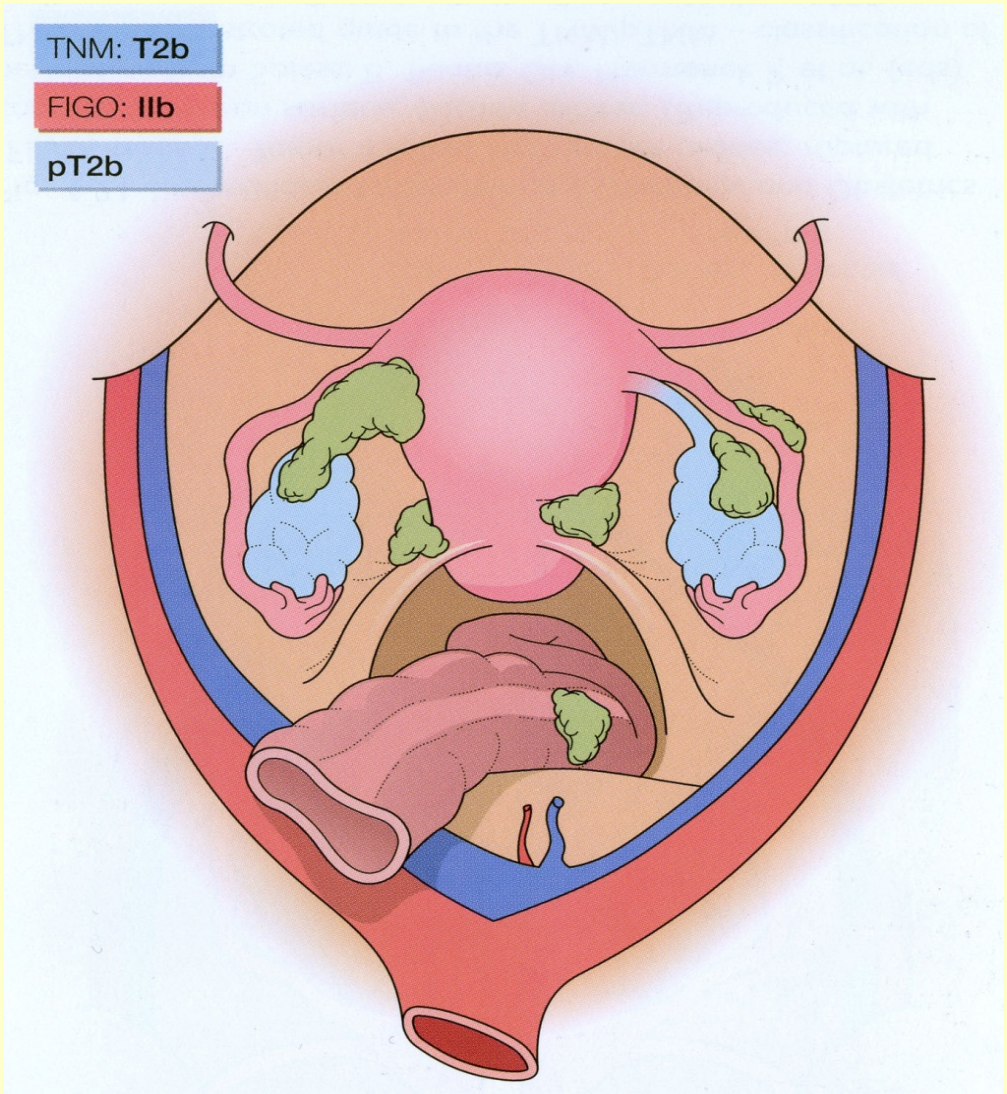
I	**Limited to ovaries**
Ia	One ovary; capsule intact; no tumor on surface; washings and ascites free of malignant cells
Ib	Both ovaries; capsule intact; no tumor on surface; washings and ascites free of malignant cells
Ic	Any of above, but with tumor on surface, or capsule ruptured (spontaneous or iatrogenic), or positive ascites or positive peritoneal washings
II	**One or both ovaries with pelvic extension**
IIa	Extension and/or metastases to uterus and/or tubes
IIb	Extension to other pelvic tissues
IIc	Any of above, but with tumor on surface, or capsule ruptured, or ascites or positive peritoneal washings
III	**One or both ovaries with microscopically confirmed peritoneal metastases outside the pelvis and/or positive regional lymph nodes.**
IIIa	Microscopic peritoneal metastases beyond pelvis
IIIb	Macroscopic peritoneal metastases beyond pelvis ≤ 2 cm
IIIc	Peritoneal metastases beyond pelvis >2 cm or positive regional lymph nodes
IV	**Distant metastases beyond peritoneal cavity. Liver metastases must be parenchymal (liver capsule metastases is stage III). If pleural effusion present, positive cytology required.**

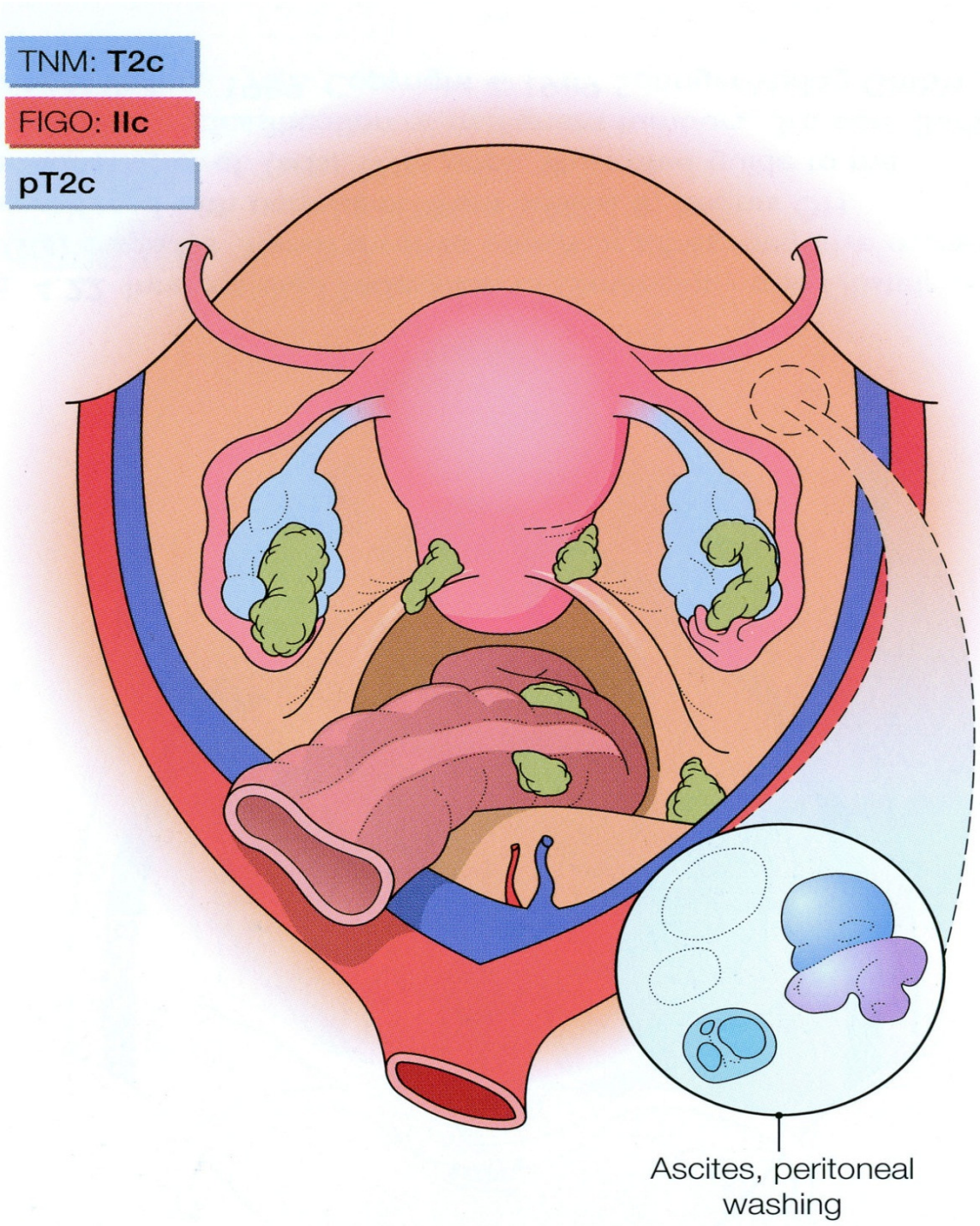

TNM: T1b
FIGO: Ia
pT1a


TNM: T1b
FIGO: Ib
pT1b


TNM: T1c
FIGO: Ic
T = pT
Ascites, peritoneal washing


TNM: T2a
FIGO: IIa
pT2a

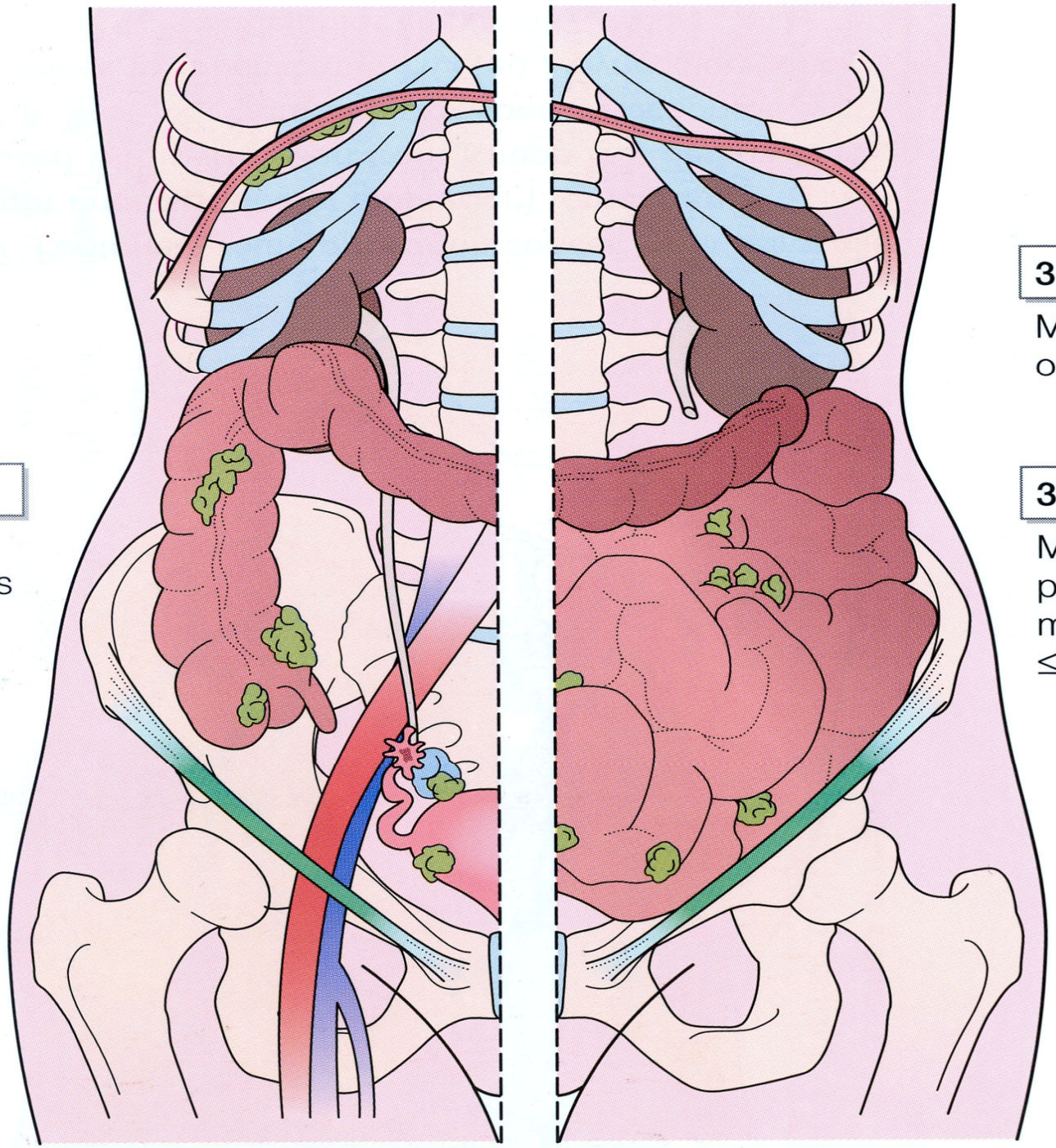

TNM: T2b
FIGO: IIb
pT2b


TNM: **T2c**
FIGO: **IIc**
pT2c
Ascites, peritoneal washing

TNM: **T3**

FIGO: **III**

T=pT



3a/IIIa

Microscopic only

3b/IIIb

Macroscopic peritoneal metastases ≤2cm

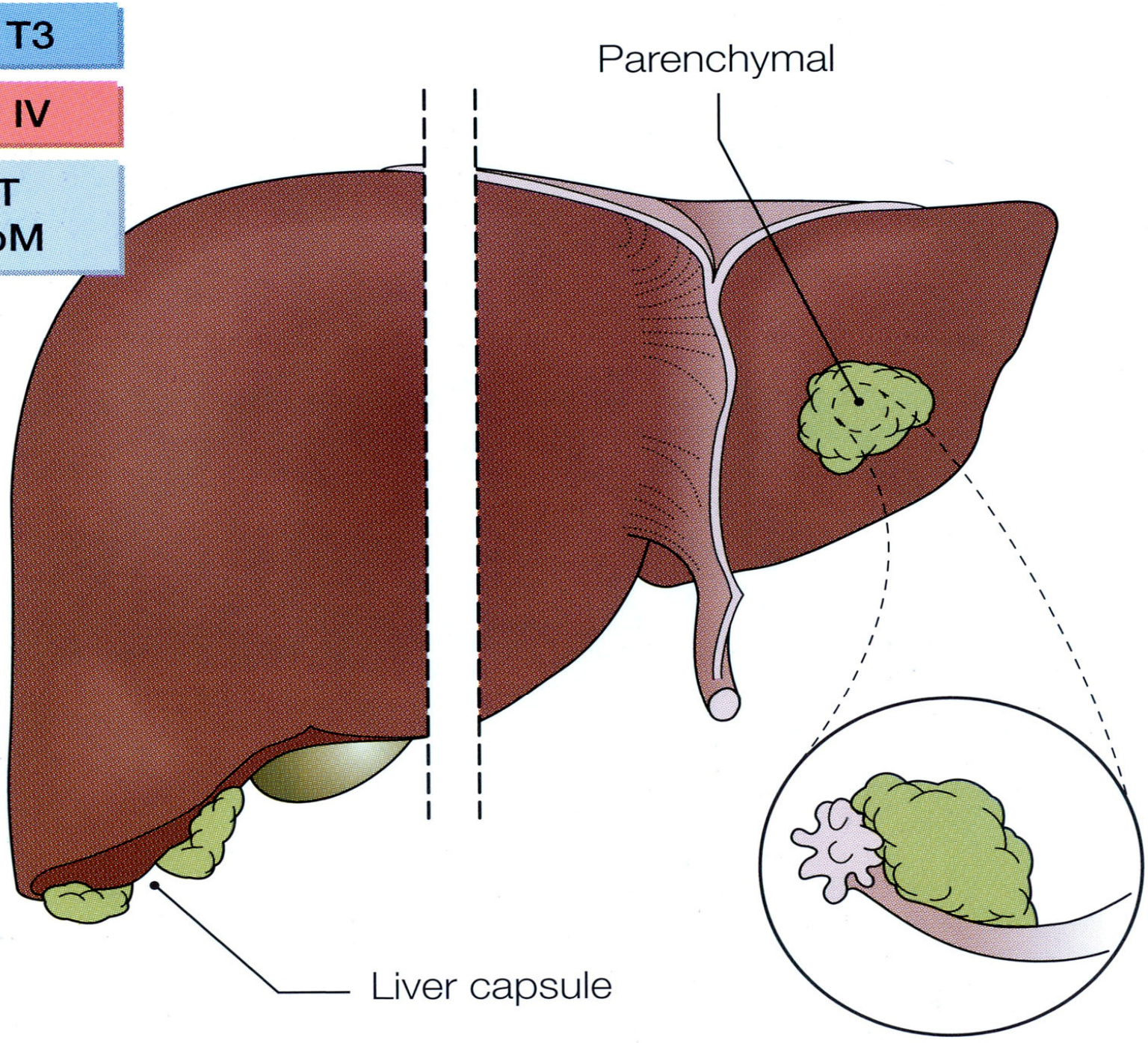
3c/IIIc

Peritoneal metastases >2cm

TNM: **T3**

FIGO: **IV**

T = pT
M = pM



FIGO ROME 2012

XX FIGO WORLD CONGRESS OF GYNECOLOGY AND OBSTETRICS

Organised by

FIGO
INTERNATIONAL FEDERATION OF GYNECOLOGY & OBSTETRICS

7TH - 12TH OCTOBER 2012
NUOVA FIERA DI ROMA
ROME, ITALY

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Clinical Staging of Cancer of the Ovary, Fallopian Tube and Peritoneum (FIGO 2012)

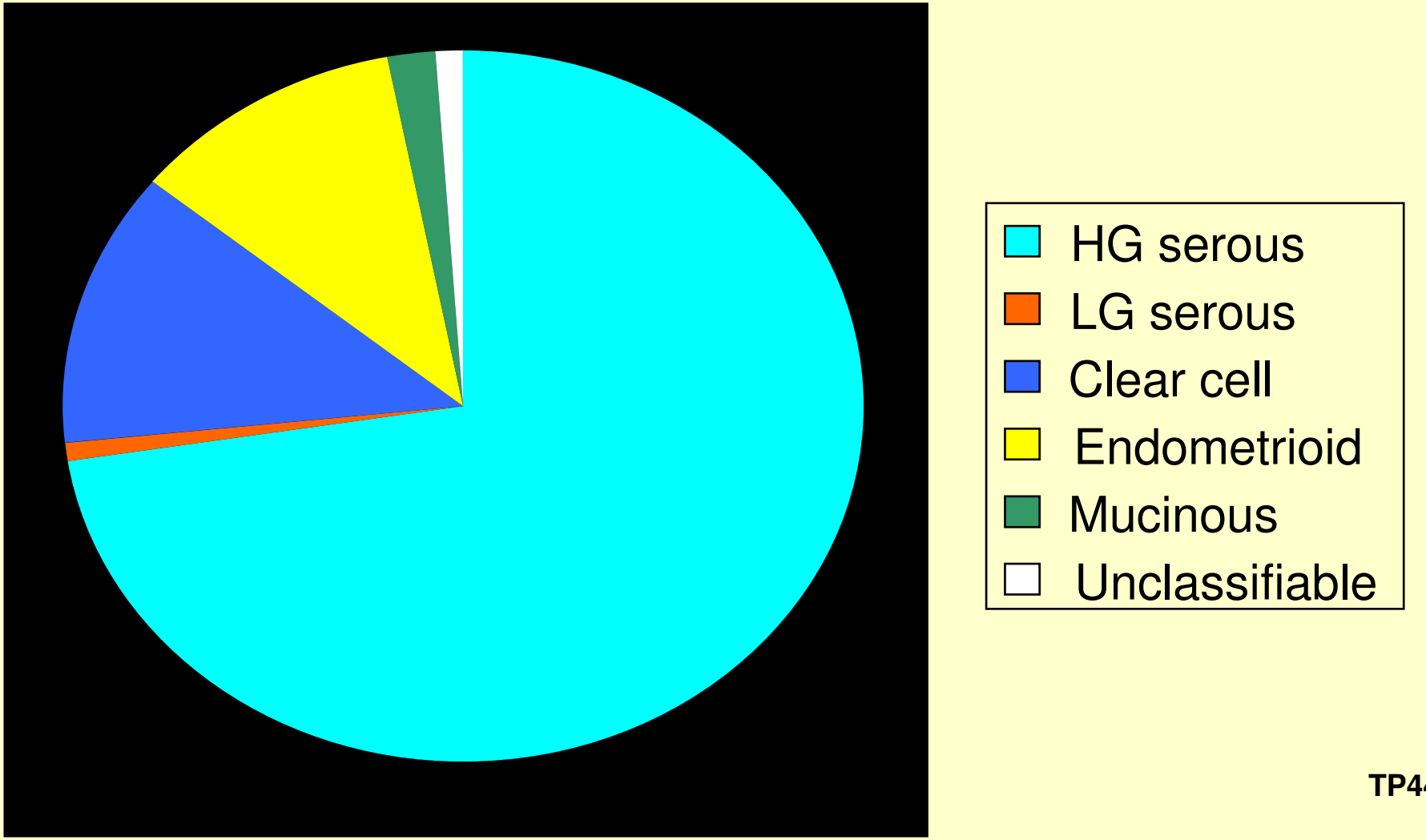
Clinical Staging of Cancer of the Ovary Fallopian Tube and Peritoneum (FIGO 2012)

OV	Primary tumor, ovary	Tov
FT	Primary tumor, fallopian tube	Tft
P	Primary tumor, peritoneum	Tp
U	Primary tumor cannot be assessed	Tu

Histologic Subtypes of Ovarian Carcinomas

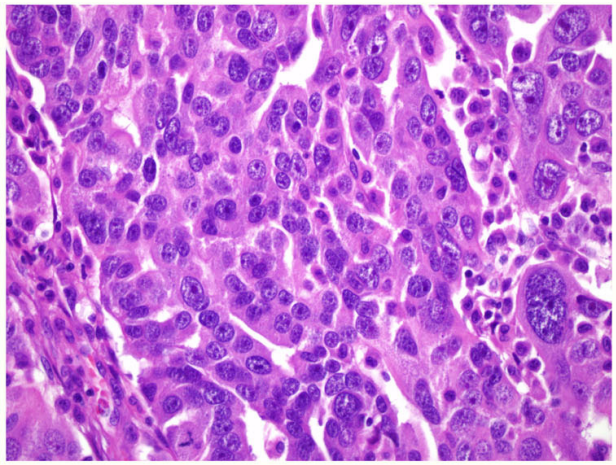
- Serous – high grade
- Serous – low grade
- Clear cell
- Endometrioid
- Mucinous

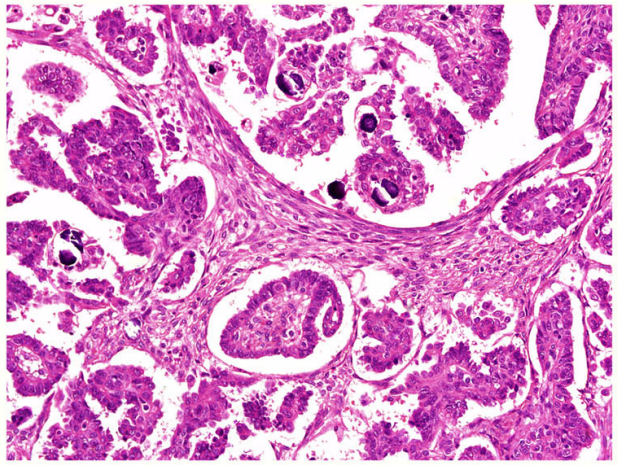
New classification: Frequency



TP44

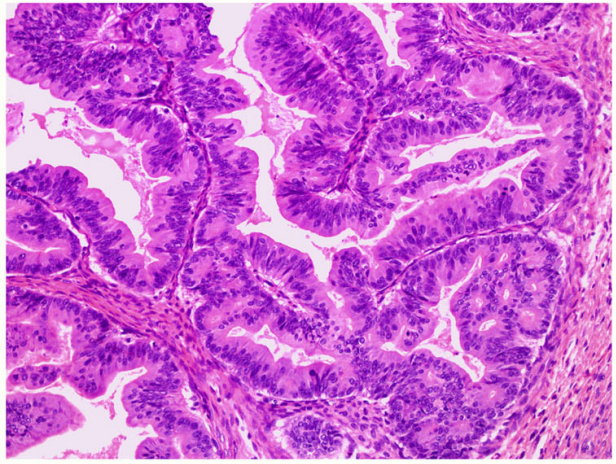
HGC

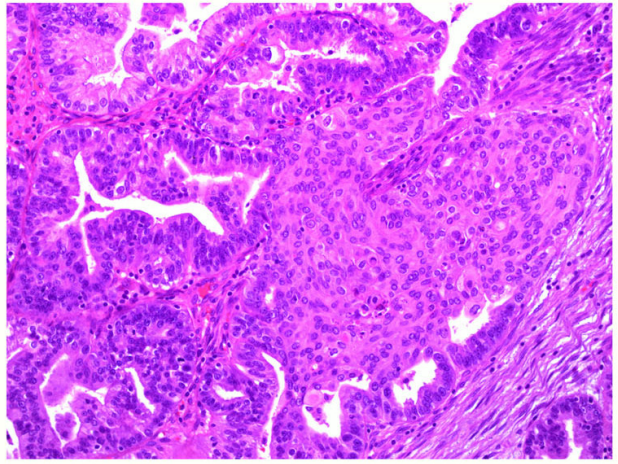




LGSC

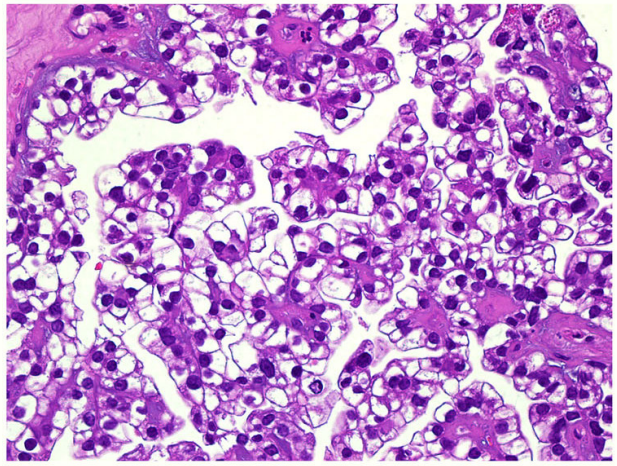
MC





EC

CCC



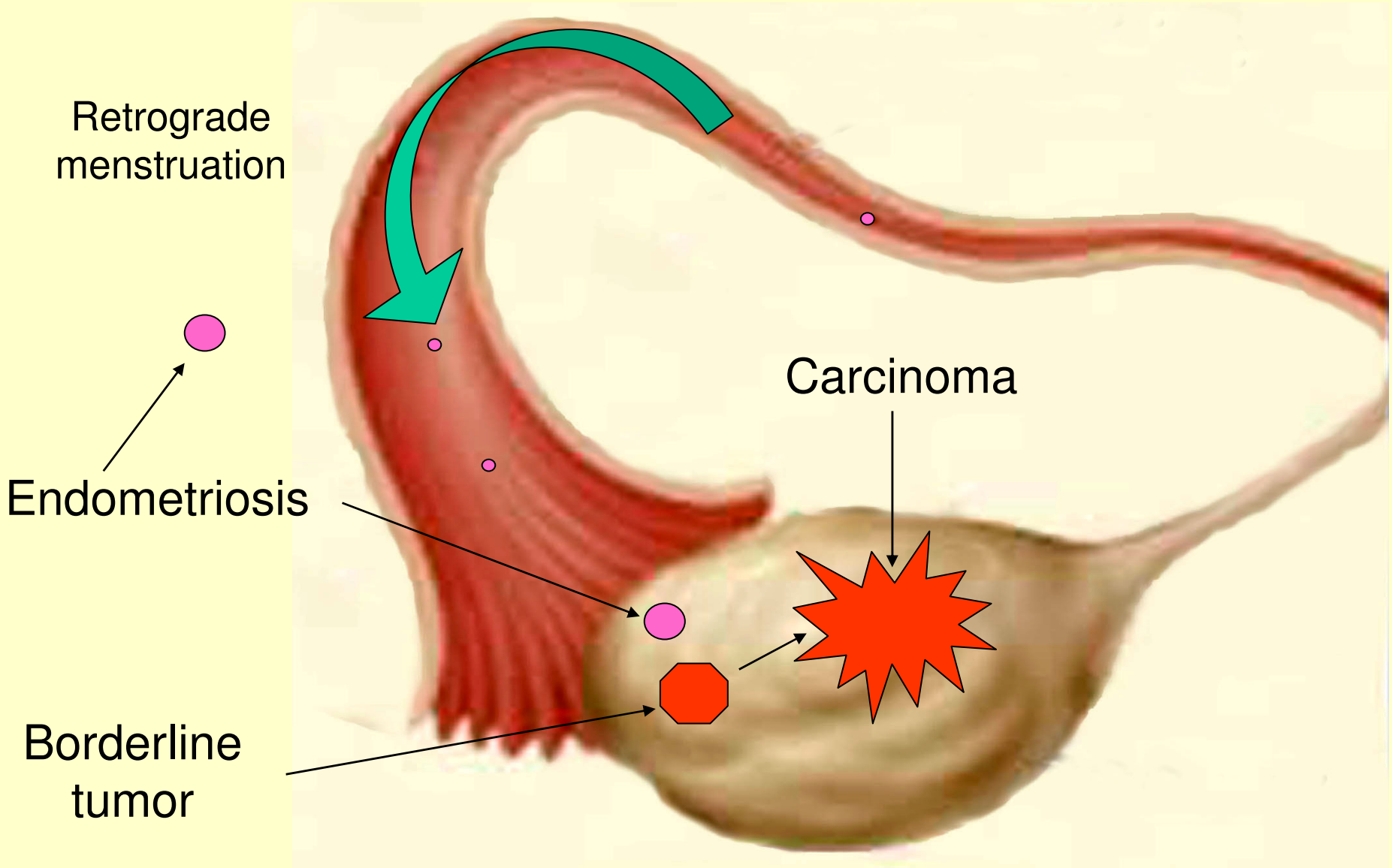
Ovarian Carcinomas:

Stage at presentation (early vs advanced) according to Histologic Subtype

Stage	Clear Cell	Endometrioid	Mucinous	Low-Grade Serous	High-Grade Serous	Carcinoma NOS
I-II	26.2%	29.4%	8.5%	1.9%	30%	4.0%
III-IV	4.9%	3.5%	1.1%	4.9%	84.2%	1.4%
All	10.4%	10.3%	3.6%	3.5%	70%	2.1%

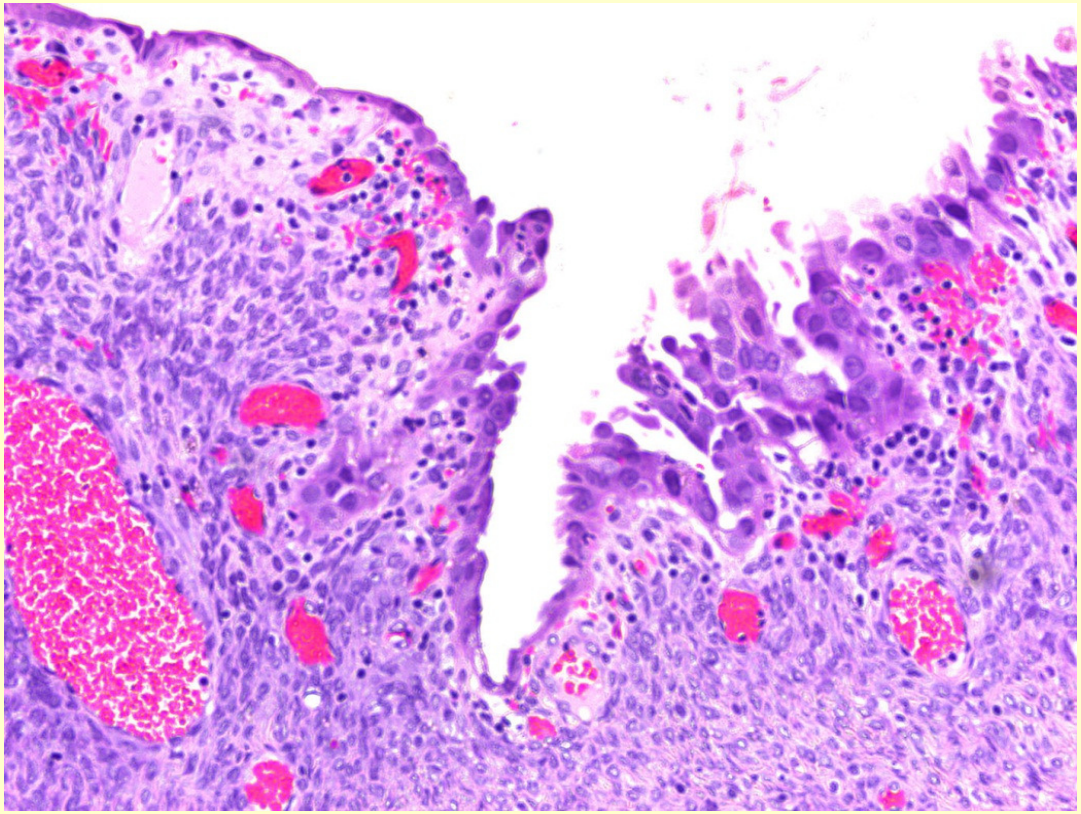
Gilks CB et al.
Mod Pathol 2009; 22:215A

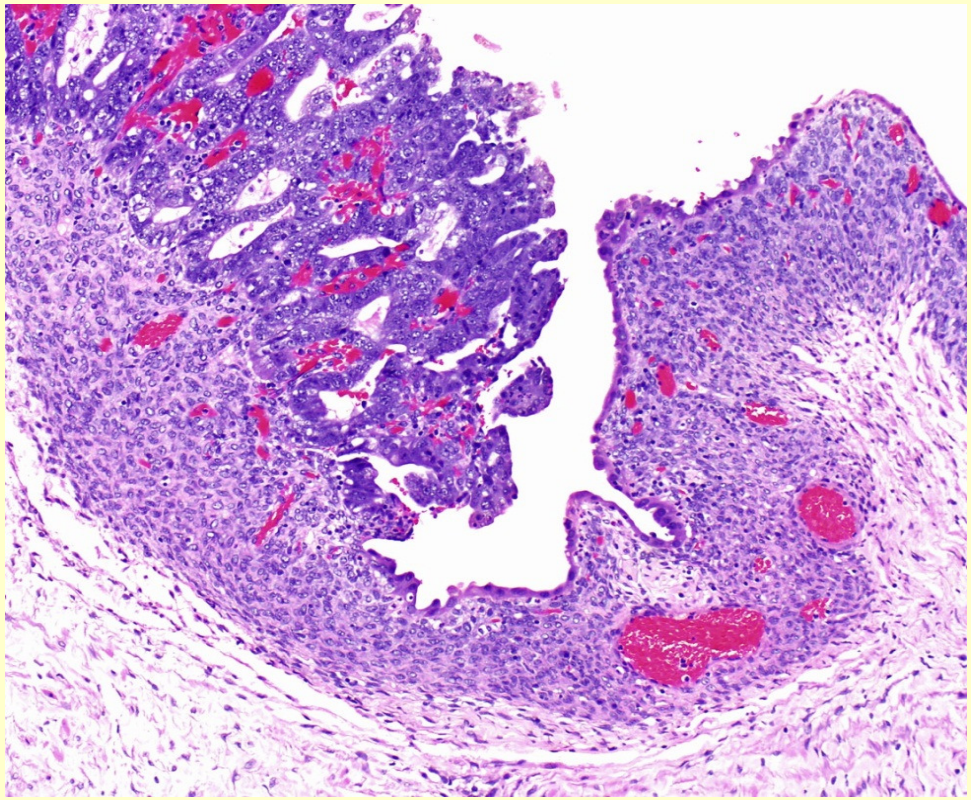
Endometrioid and Clear Cell Tumors develop from Ovarian Endometriosis

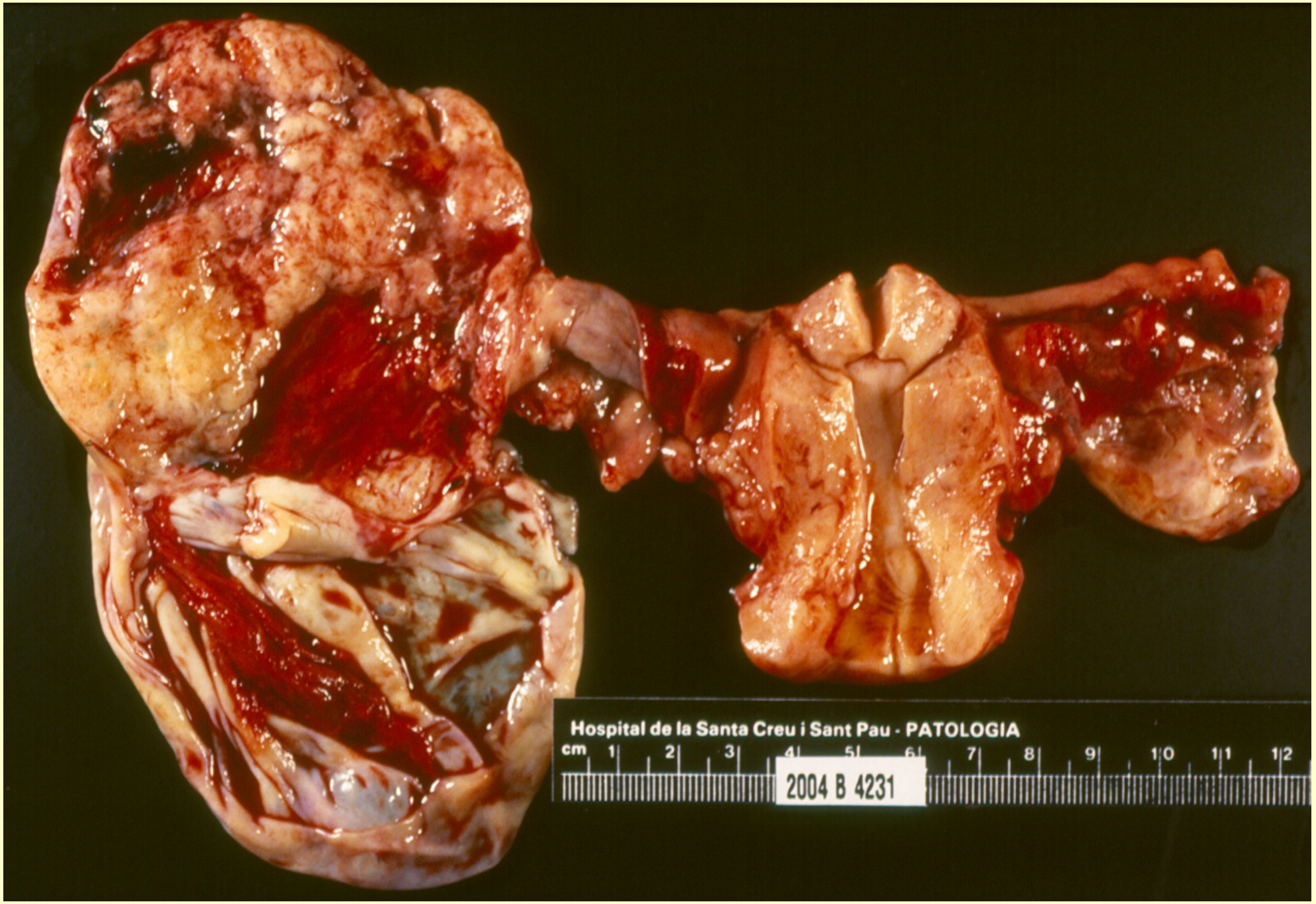


Ovarian Atypical Endometriosis → Endometrioid or Clear Cell Carcinomas

15-32% of cases







Clear cell carcinoma

Designate Histological type

- High-grade serous (HGSC)
- Endometrioid (EC)
- Clear cell (CCC)
- Mucinous (MC)
- Low grade serous (LGSC)
- Other
- Cannot be classified
- Germ cell (GCT)
- Sex cord stromal tumour (SCST)

I	**Tumor confined to ovaries or fallopian tube(s)**	**T1**
IA	Tumor limited to one ovary (capsule intact) or fallopian tube, No tumor on ovarian or fallopian tube surface No malignant cells in the ascites or peritoneal washings	T1a
IB	Tumor limited to both ovaries (capsules intact) or fallopian tubes No tumor on ovarian or fallopian tube surface No malignant cells in the ascites or peritoneal washings	T1b
IC	Tumor limited to one or both ovaries or fallopian tubes,	T1c

with any of the following:

IC1 Surgical spill

IC2 Capsule ruptured before surgery or tumor on ovarian or fallopian tube surface

IC3 Malignant cells in the ascites or peritoneal washings

Stage 1 Peritoneal Cancer

- FIGO staging system is used with the understanding that *it is not possible to have a stage I peritoneal cancer*

II **Tumor involves one or both ovaries or fallopian tubes with pelvic extension** (below pelvic brim) or primary peritoneal cancer **T2**

IIA Extension and/or implants on the uterus and/or fallopian tubes/and/or ovaries T2a

IIB Extension to other pelvic intraperitoneal tissues T2b

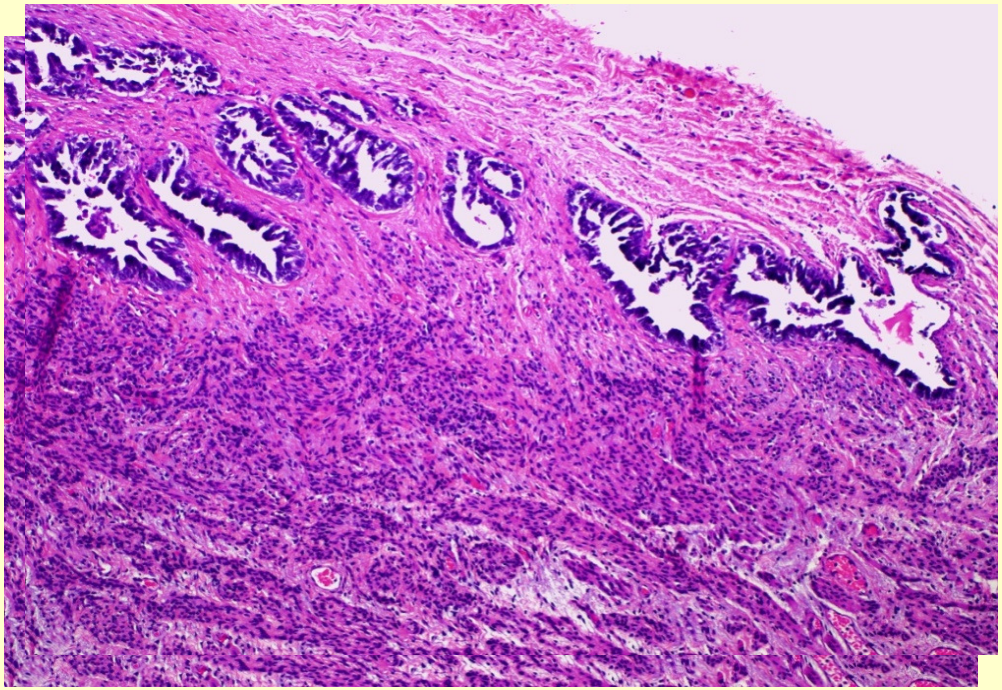
IIC Any of above, but with ascites or positive peritoneal washings

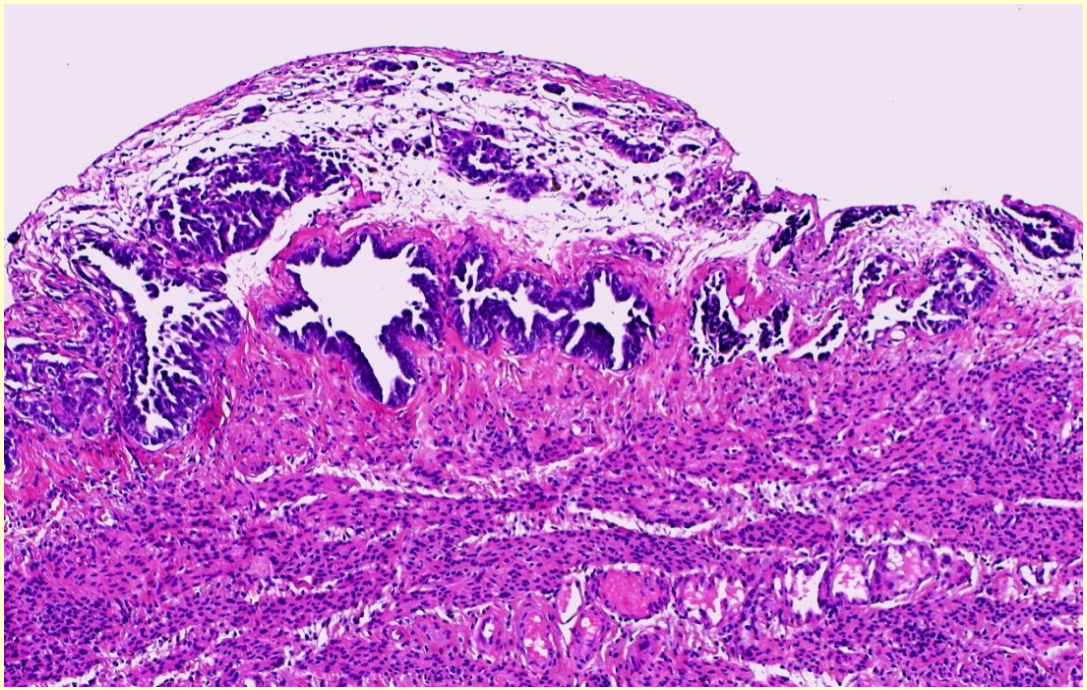
II Tumor involves one or both ovaries or fallopian tubes ~~with~~ ~~pelvic extension~~ (~~below pelvic brim~~) ~~or primary peritoneal cancer~~ (EPL)

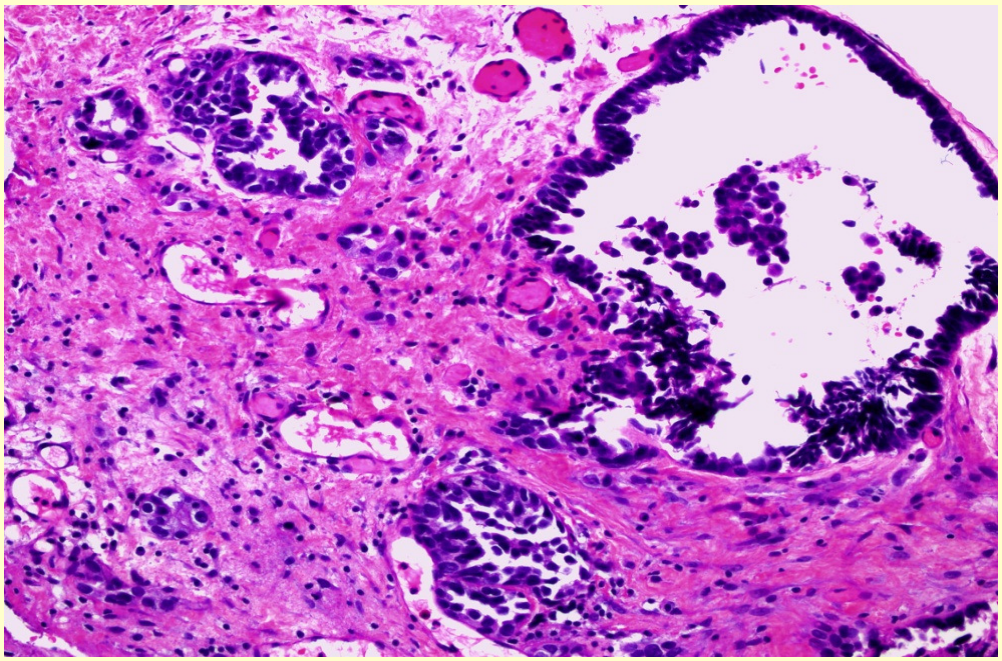
IIA Extension ~~and/or implants on~~ in (EPL) the uterus and/or fallopian tubes/and/or ovaries

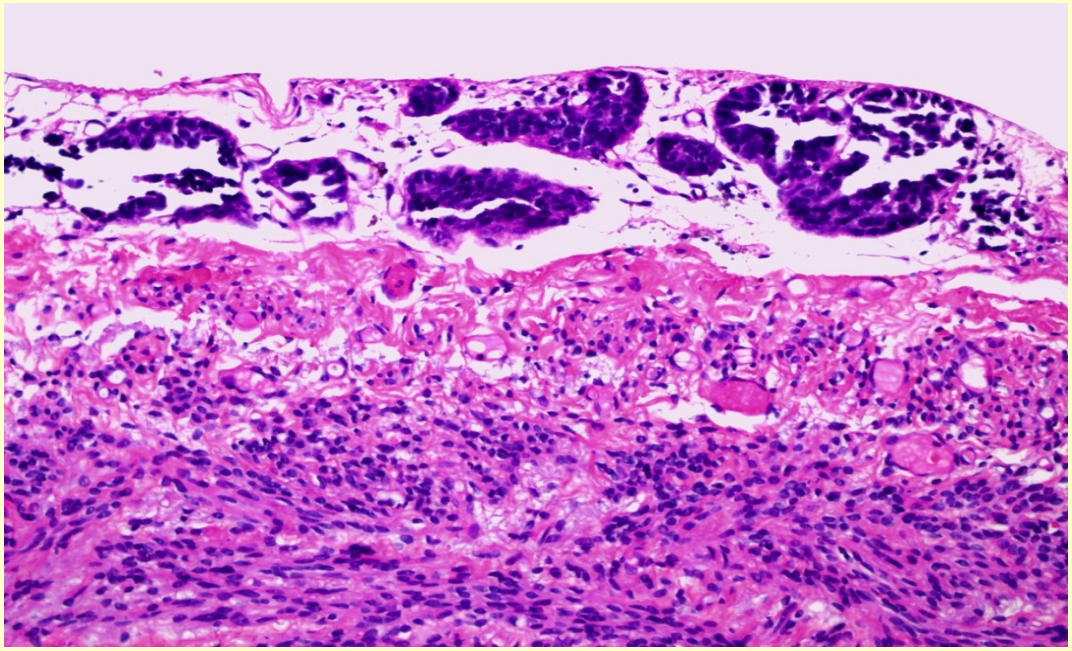
~~IIB Extension to other pelvic intraperitoneal tissues~~ (EPL)

~~IIC Any of above, but with ascites or positive peritoneal washings~~









Uterine serosa

Ovarian Carcinomas involving Retroperitoneal LNs

- Less than 10% of ovarian carcinomas have extended beyond the pelvis with **exclusively** Retroperitoneal **Lymph Node** involvement

- Literature evidence indicates that these cases have **better prognosis** than tumors with abdominal peritoneal involvement

- **No** pathological distinction between high-grade serous and low-grade serous carcinomas

New Stage III - FIGO 2012

III One or both ovaries, fallopian tubes, or primary peritoneal cancer with pathologically proved spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes

IIIA **Metastasis to the retroperitoneal lymph nodes** with or without microscopic peritoneal involvement beyond the pelvis

IIIA1 Positive retroperitoneal lymph nodes only

IIIA1(i) Metastasis (≤ 1 cm in size)
IIIA1(ii) Metastasis (> 1 cm in size)

IIIA2 Microscopic extrapelvic peritoneal involvement with or without positive retroperitoneal lymph nodes

IIIB Macroscopic peritoneal metastasis beyond the pelvis 2 cm or less with or without metastasis to the retroperitoneal lymph nodes

IIIC Macroscopic peritoneal metastasis beyond the pelvis more than 2 cm with or without metastasis to the retroperitoneal lymph nodes

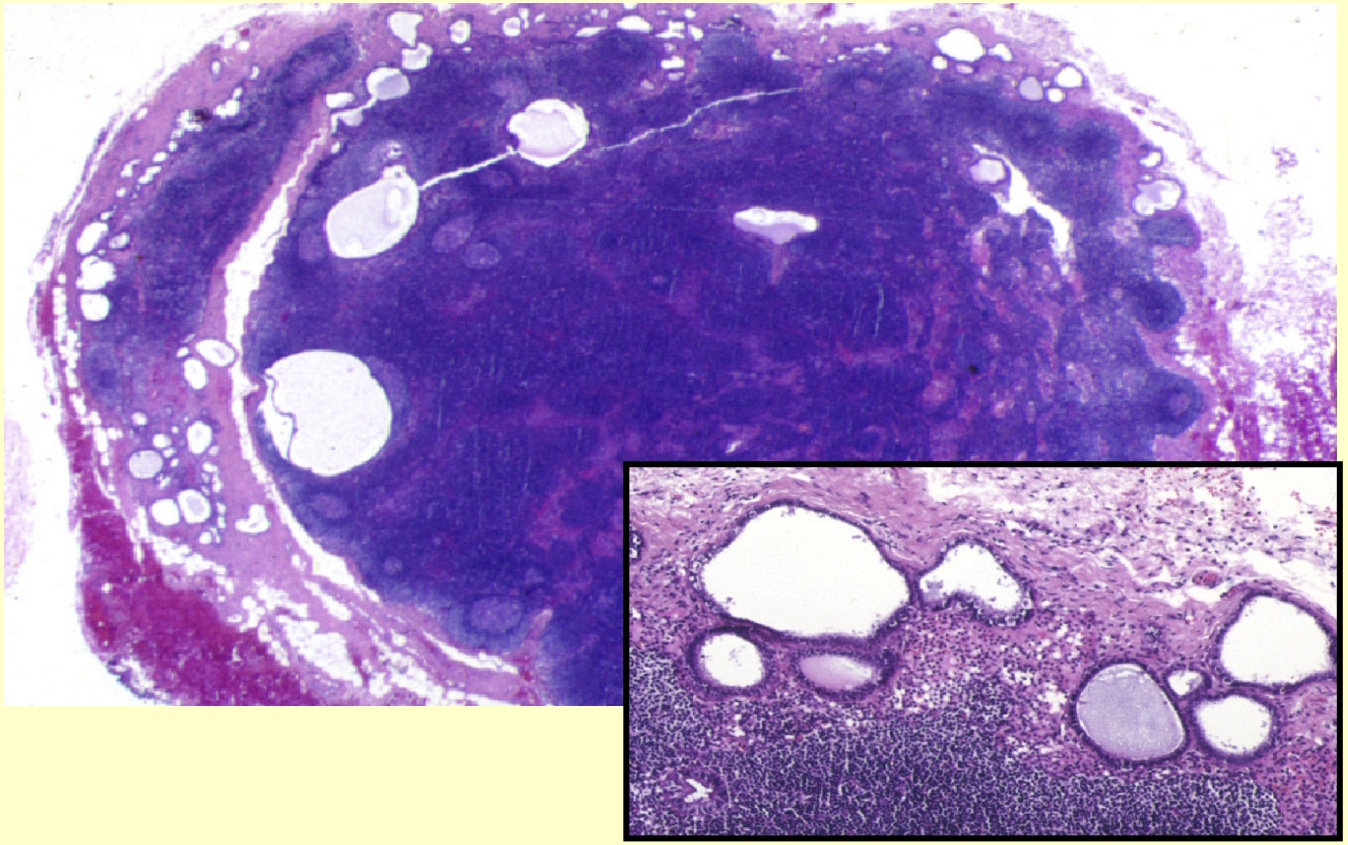
(Note 1: includes extension of tumor to capsule of liver and spleen without parenchymal involvement of either organ)

Ovarian Carcinomas

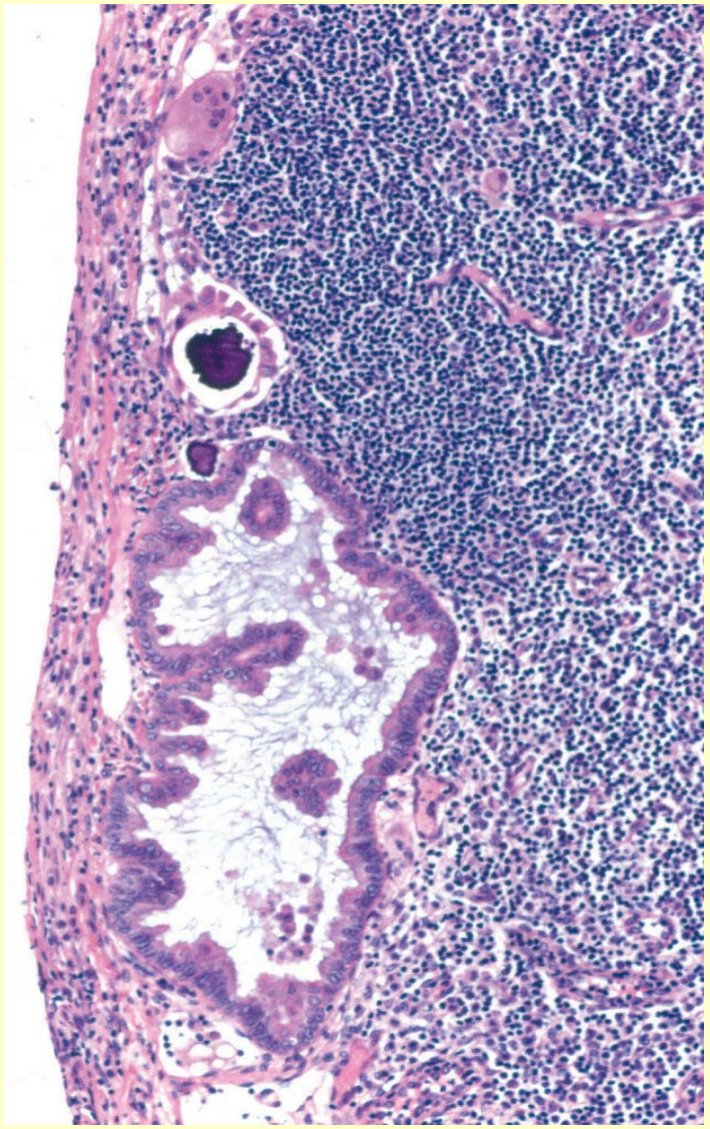
Low-grade serous carcinomas may arise in lymph nodes from endosalpingiosis

Djordjevic B, Malpica A.
Am J Surg Pathol 2010, 2012

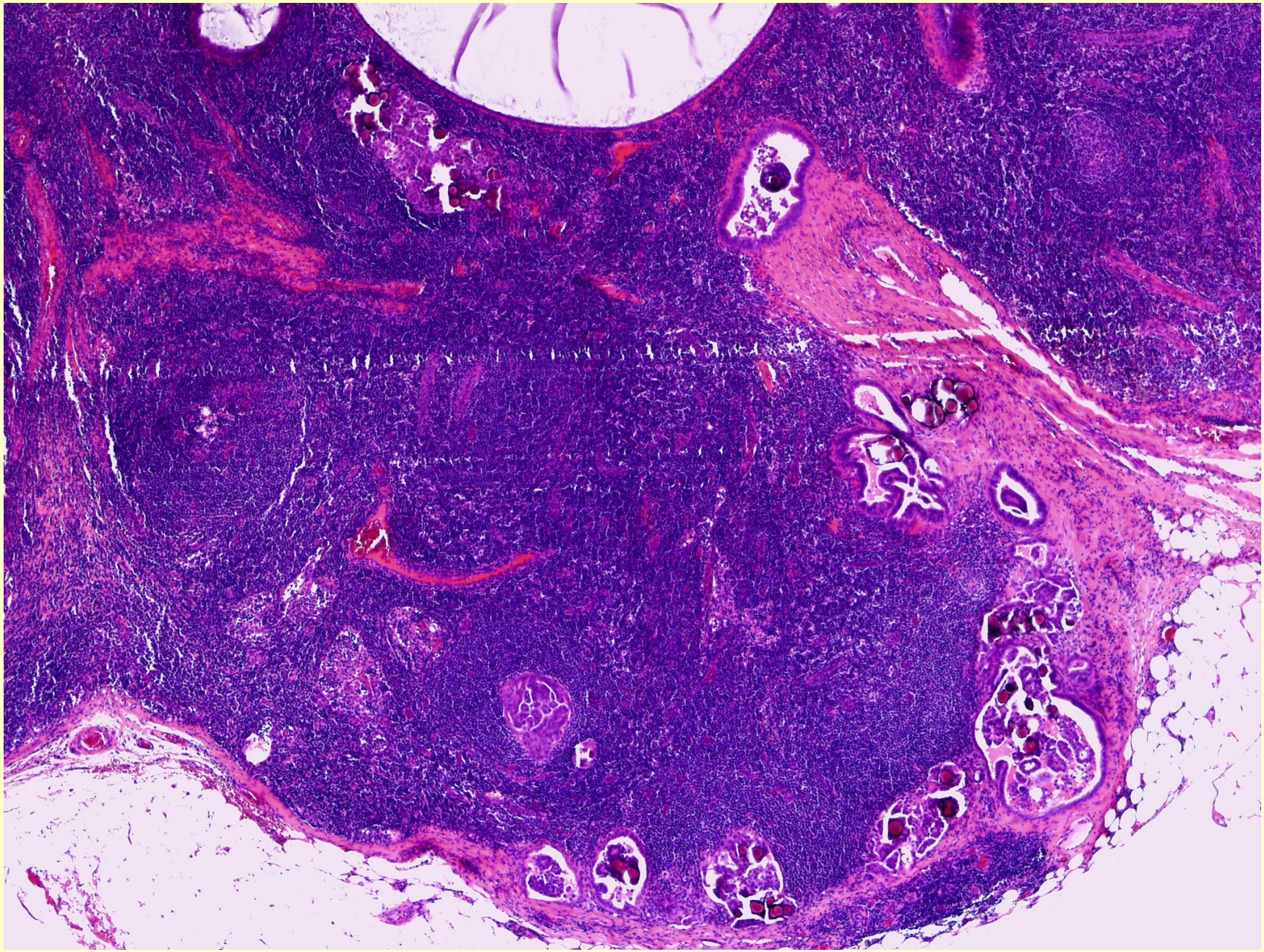
SBT in Lymph Nodes (30%)



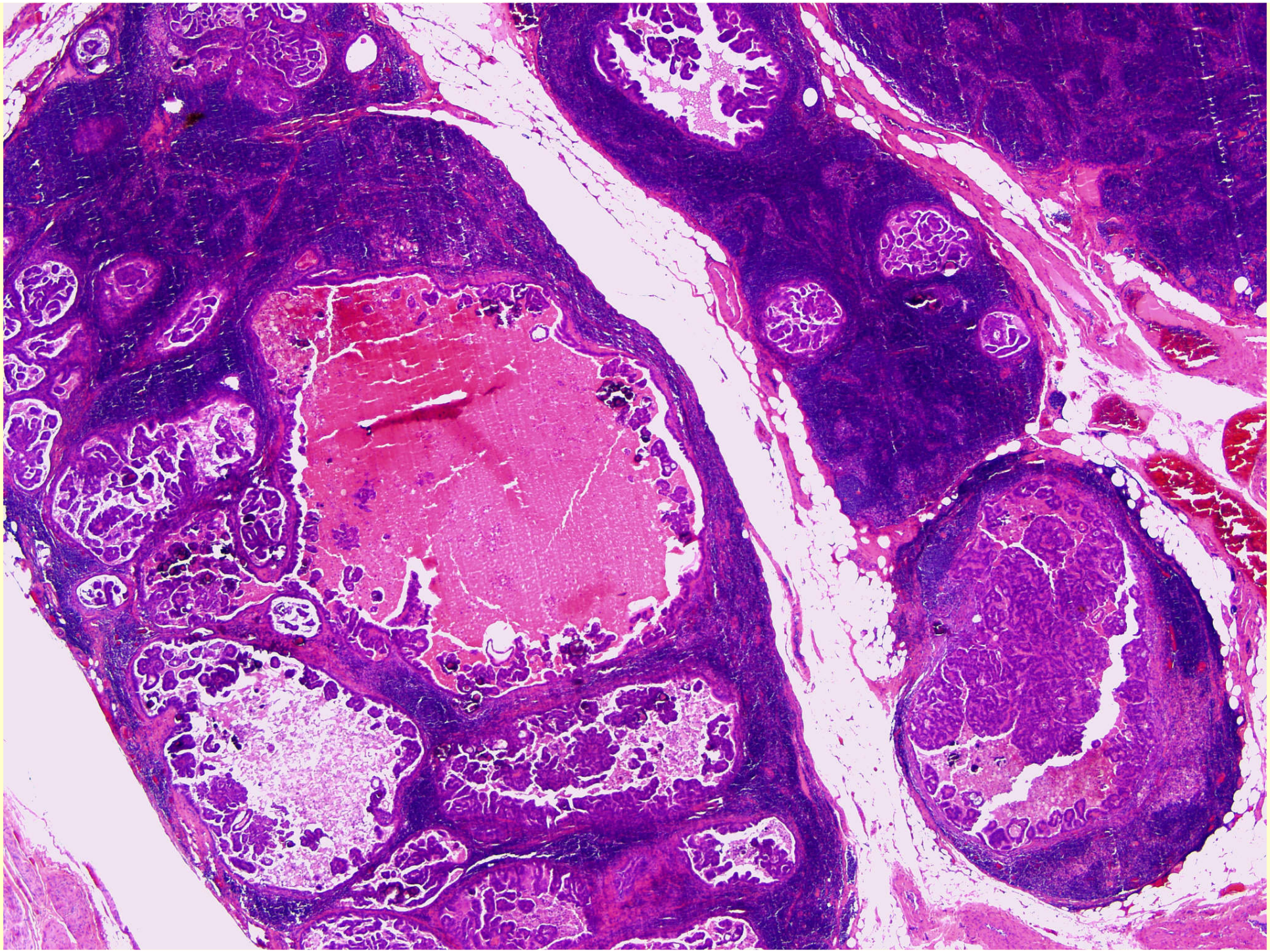
LN: Mullerian cysts (endosalpingiosis)

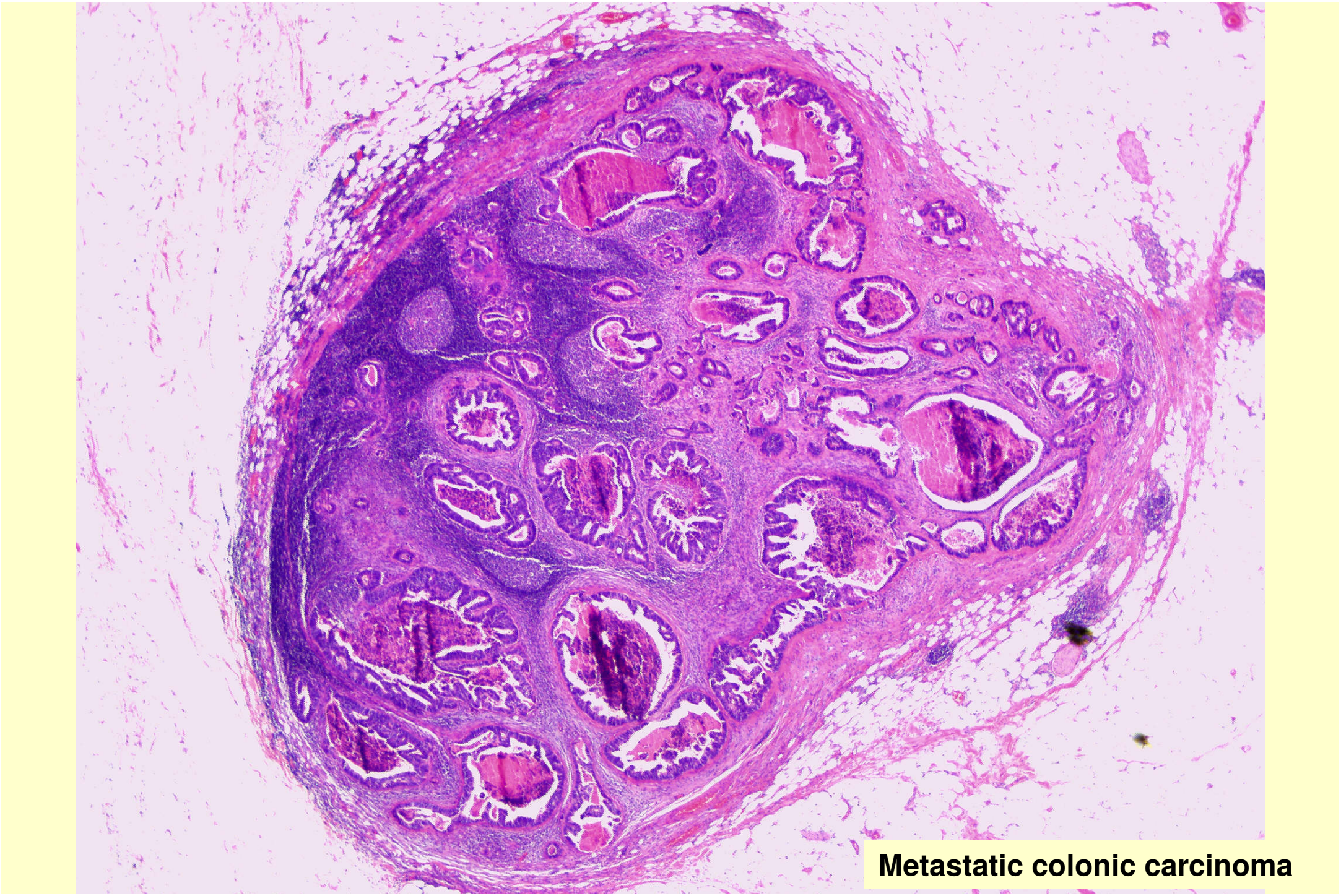


SBT in lymph node

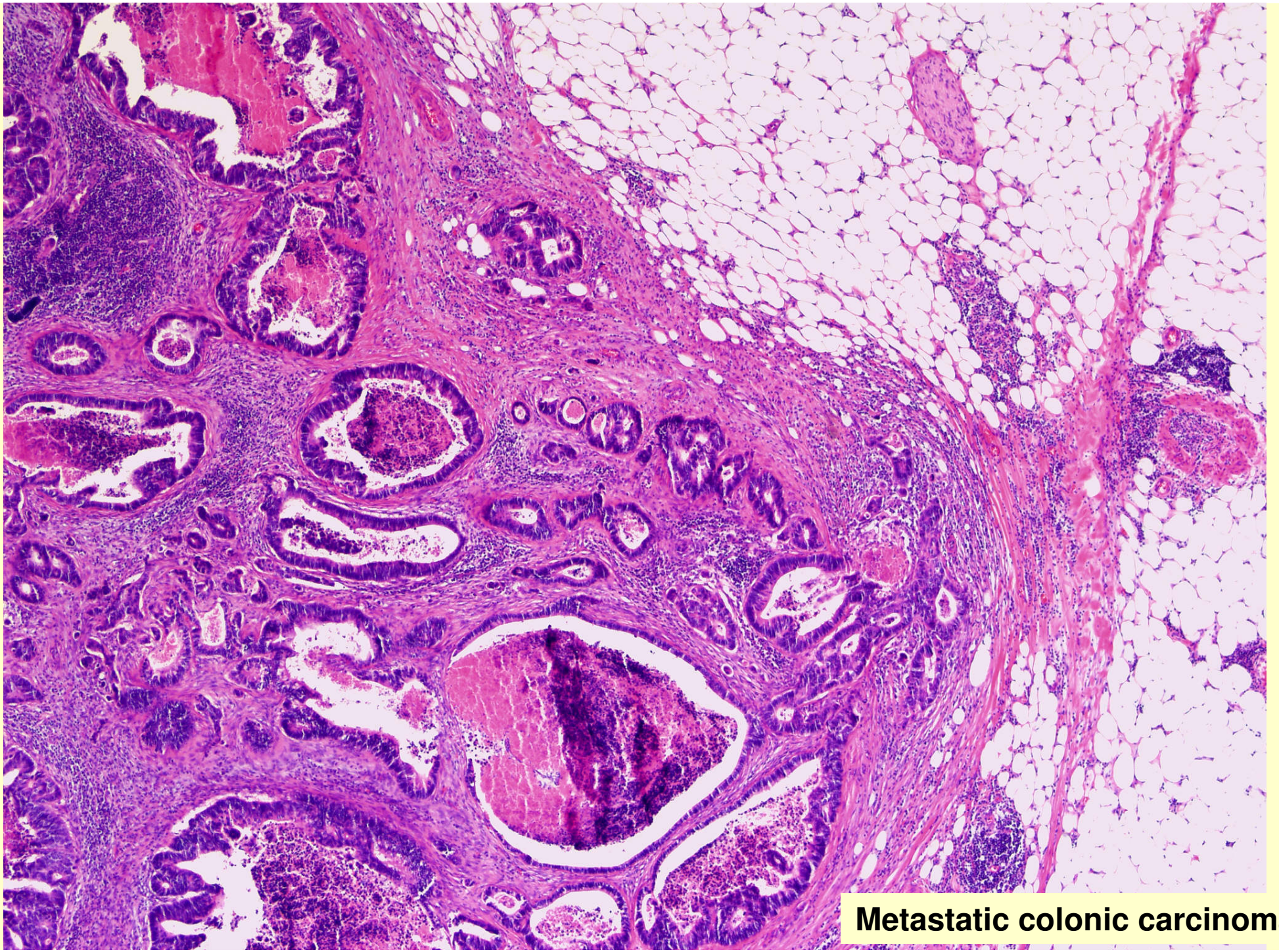


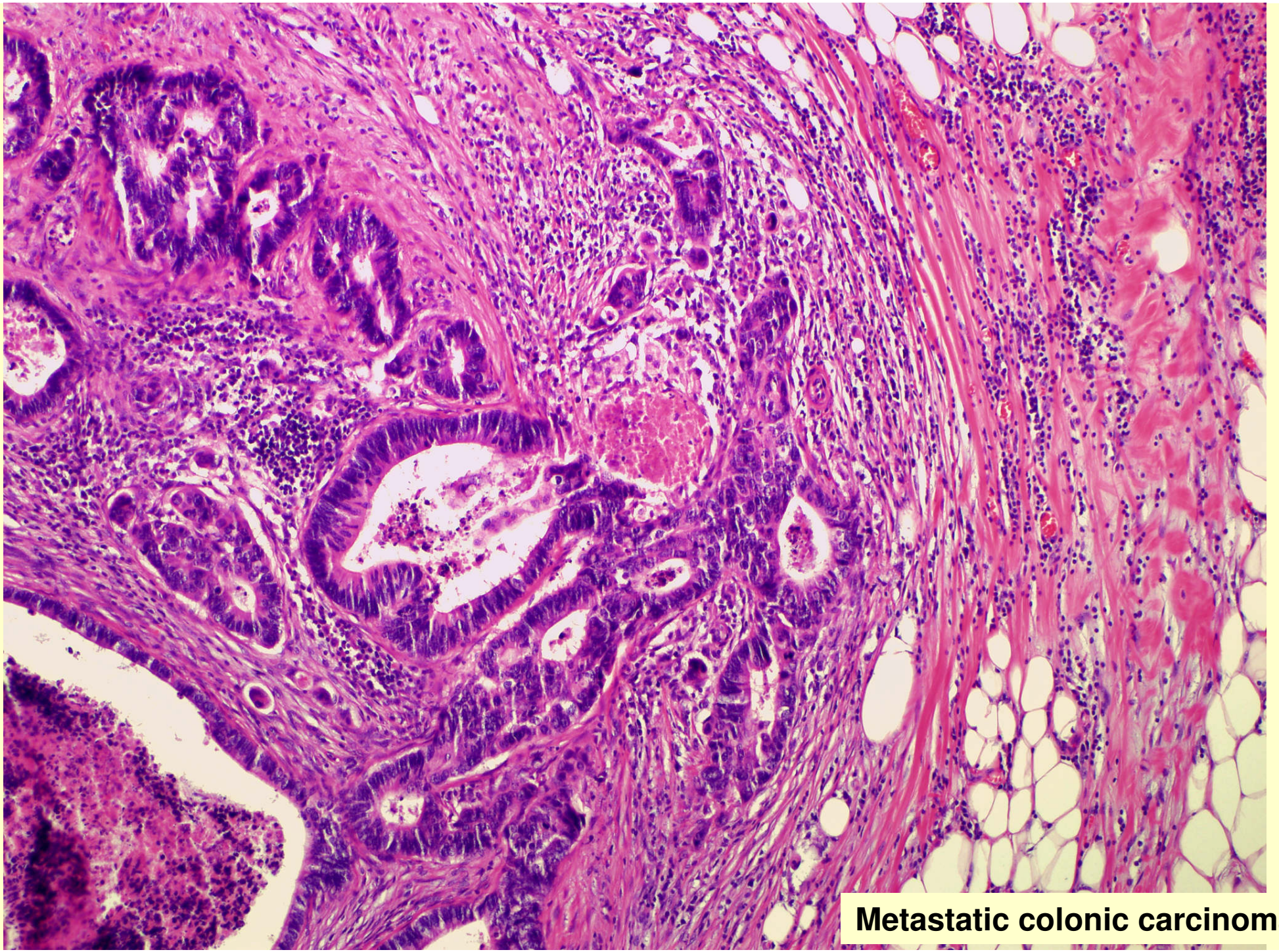
SBT in lymph node



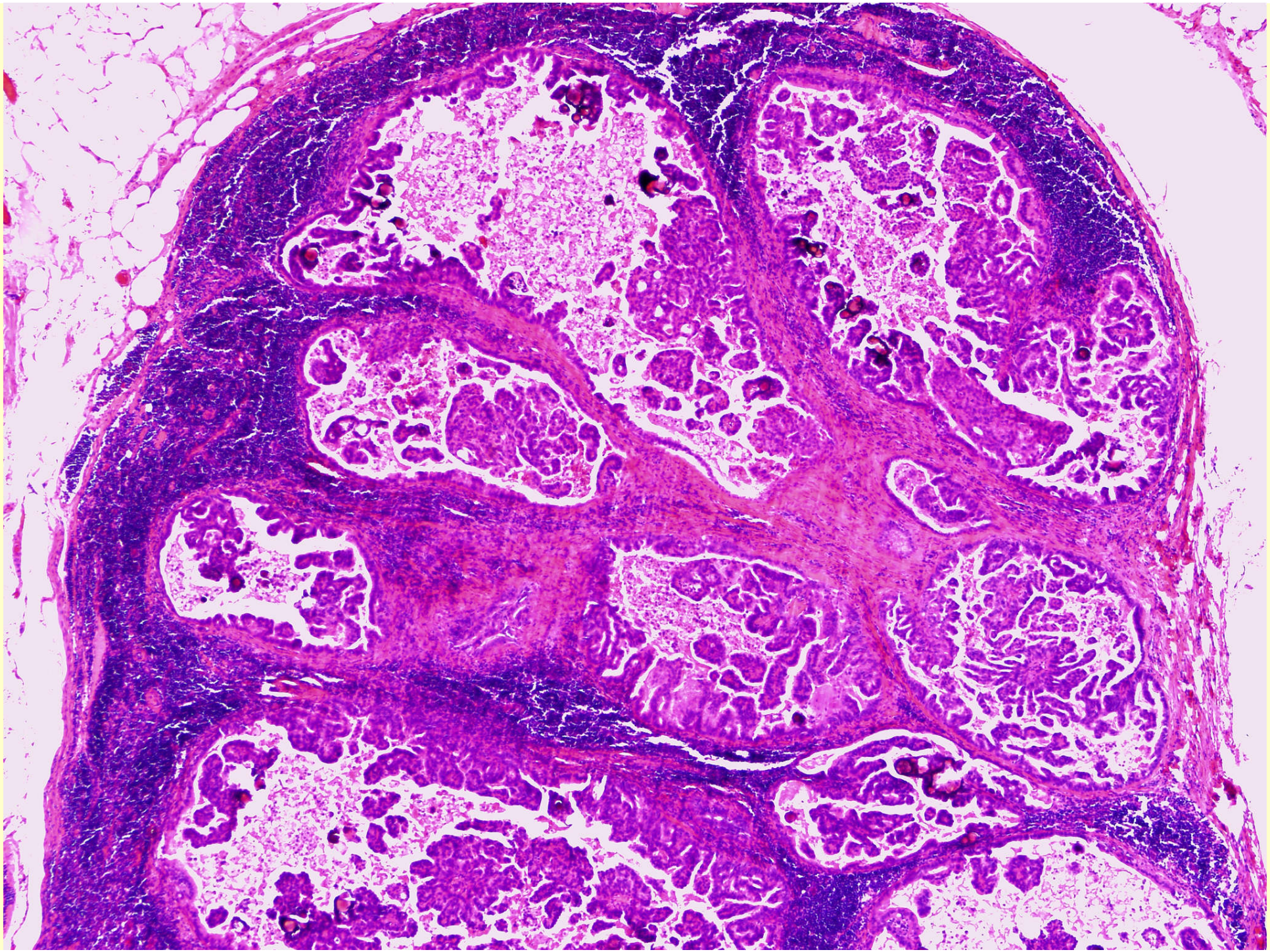


Metastatic colonic carcinoma


Metastatic colonic carcinoma



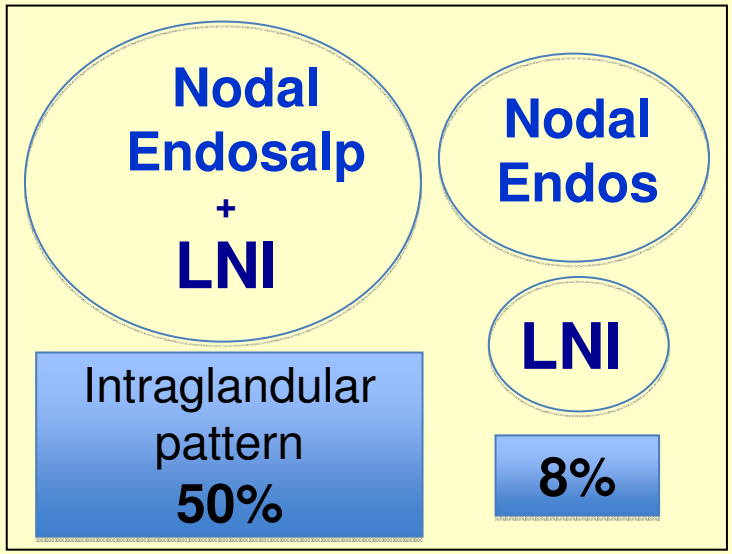
Metastatic colonic carcinoma



Nodal Endosalpingiosis in Ovarian Serous Borderline Tumors with Lymph Node Involvement

	Ovarian SBT	Cervical ADCa	Endometrial Endometrioid ADCa	SBT with LNInv	SBT without LNInv
N. Cases	30	30	30	36	36
Nodal Endosalp	**33 %**	0%	3%	**66%**	14%

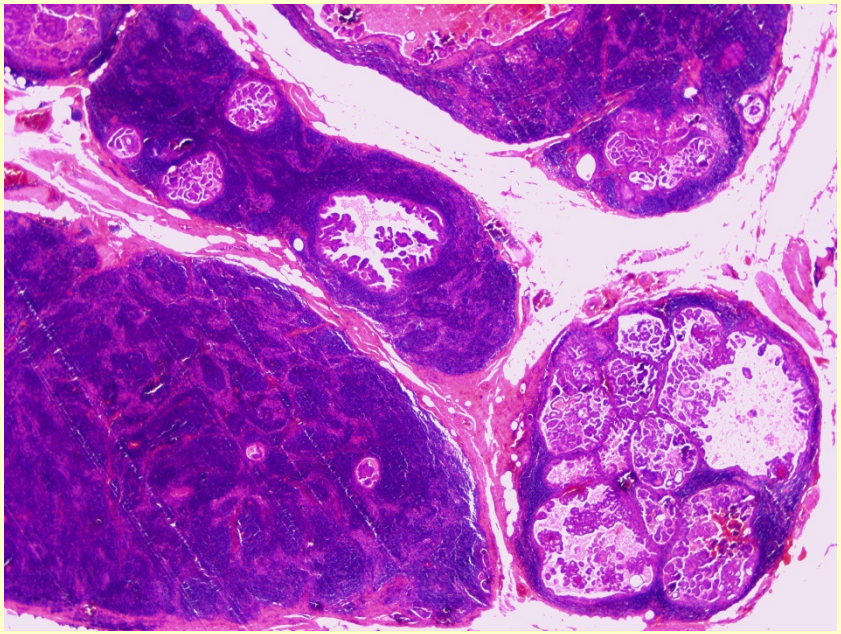
Djordjevic et al
Am J Surg Pathol 2010



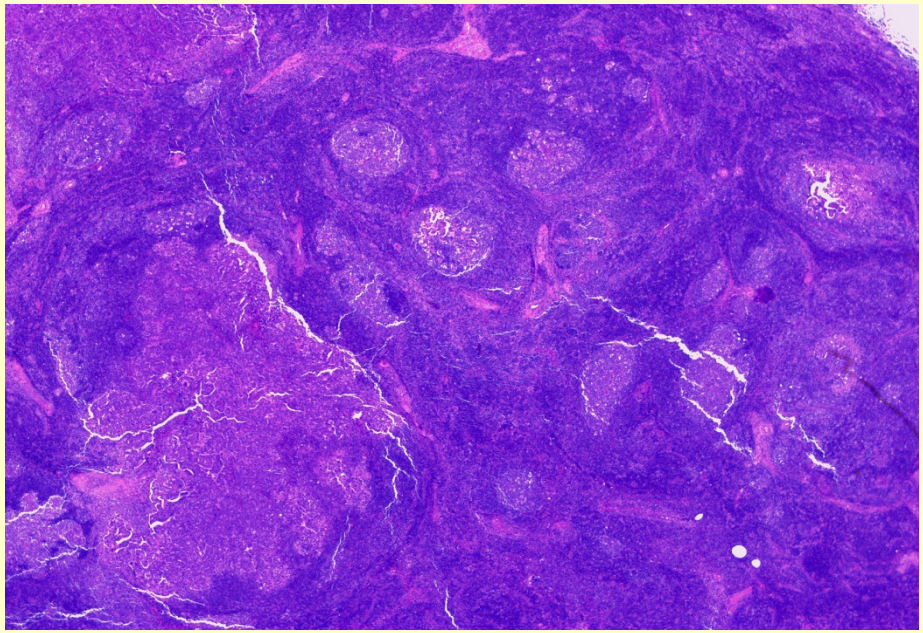
Diagnosis

(PCS-5514)

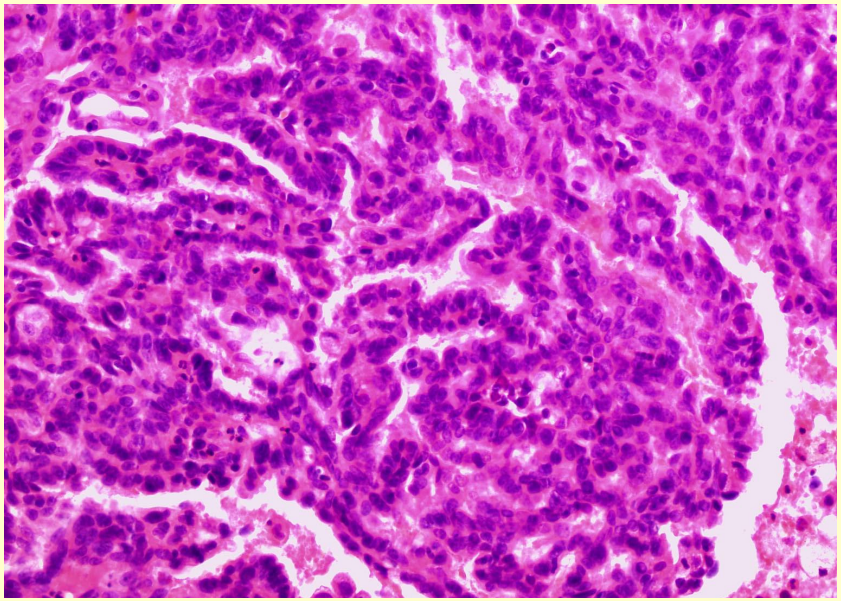
Serous borderline tumor and low-grade serous carcinoma (in situ and microinvasive) arising from extensive nodal endosalpingiosis

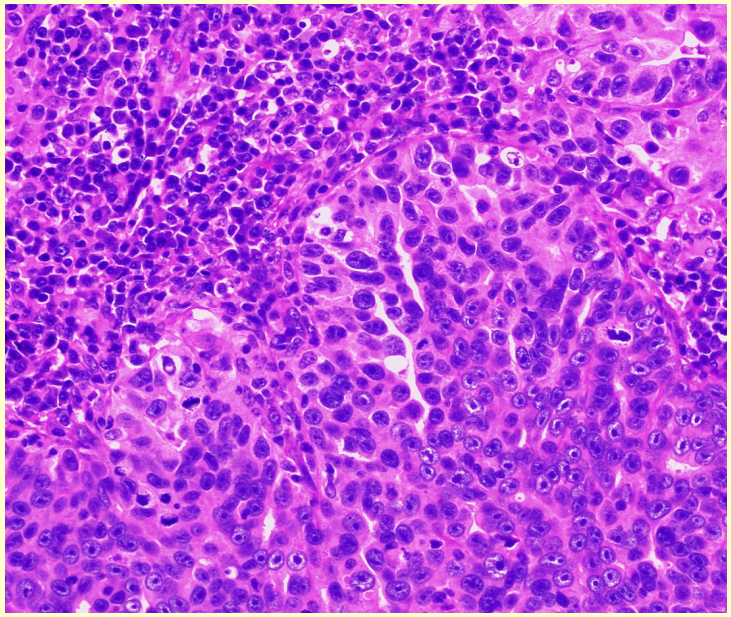


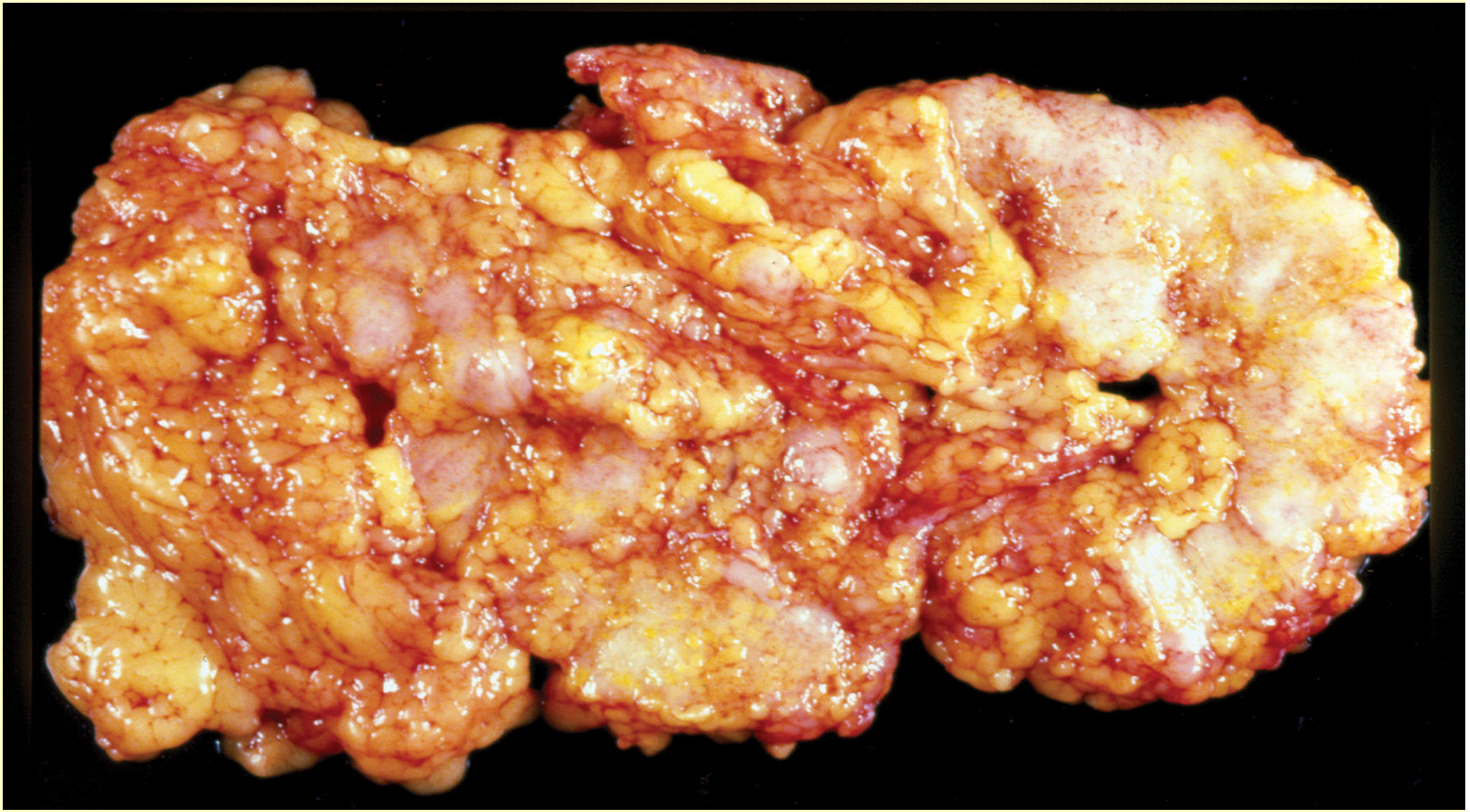
LN – Endosalpingiosis → SBT → LGSC

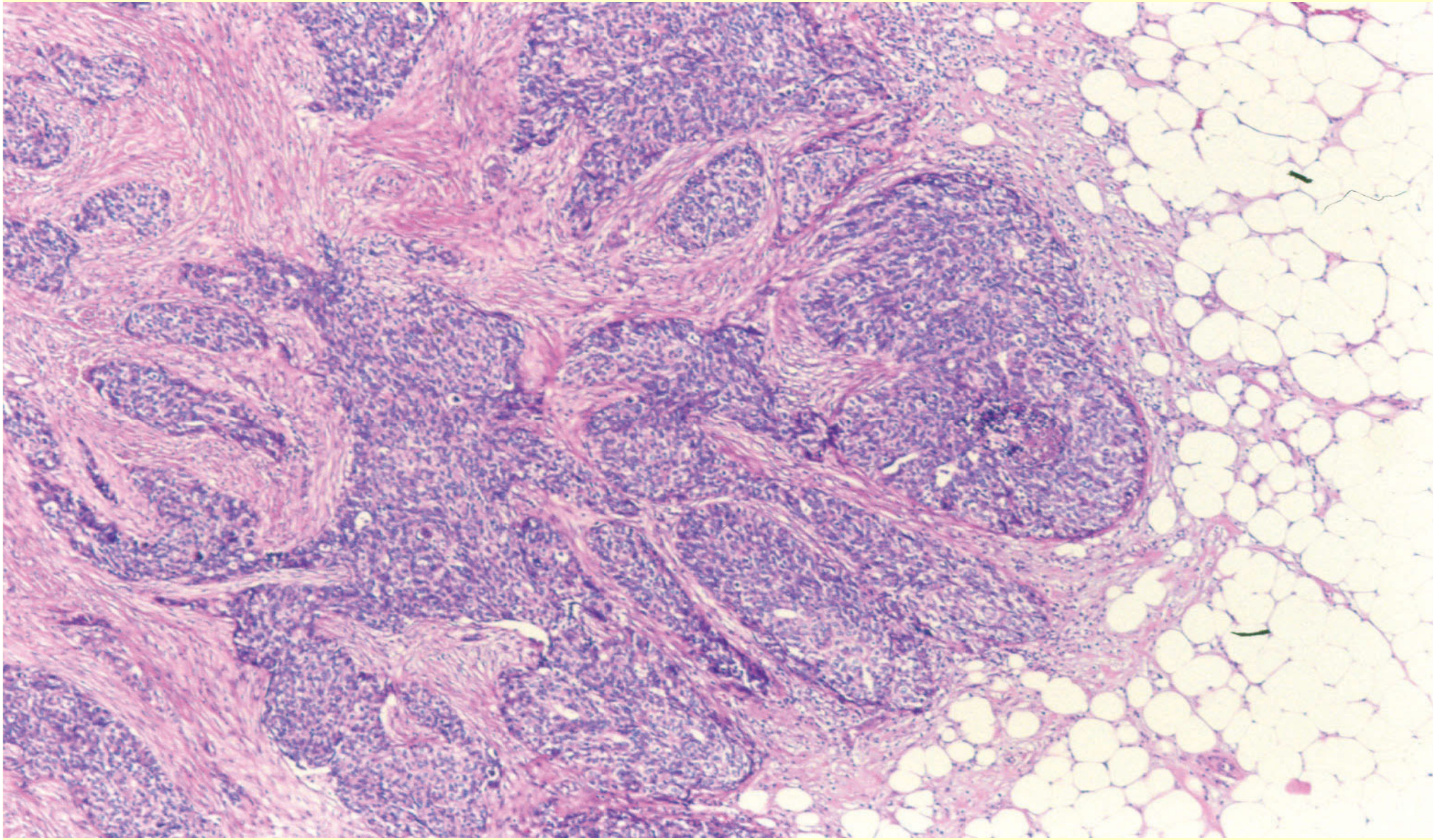


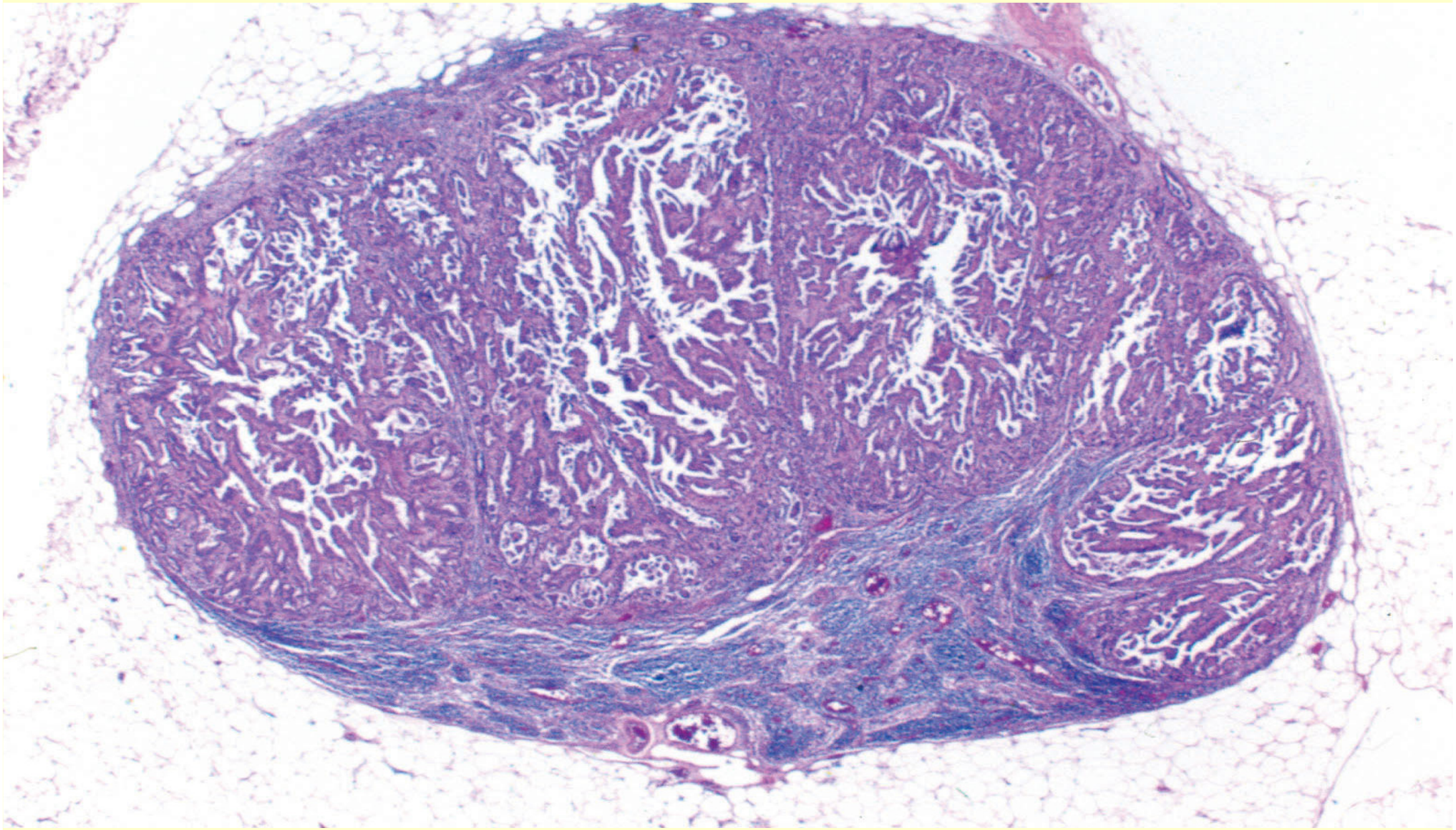
Metastatic HGSC in LN











Ovarian Carcinomas involving Lymph Nodes

- Less than 10% of ovarian carcinomas have extended beyond the pelvis with **exclusively** Retroperitoneal **Lymph Node** involvement
- Literature evidence indicates that these cases have **better prognosis** than tumors with abdominal peritoneal involvement
- **Low-grade serous carcinomas** may arise in lymph nodes from **endosalpingiosis**
- **Most of these cases probably represent separate primary low-grade serous carcinomas arising in lymph nodes from endosalpingiosis which explains their favorable prognosis**

New Stage III - FIGO 2012

III One or both ovaries, fallopian tubes, or primary peritoneal cancer with pathologically proved spread to the peritoneum ~~outside the pelvis~~ (EPL) and/or metastasis to the retroperitoneal lymph nodes

III A **Metastasis to the retroperitoneal lymph nodes** with or without microscopic peritoneal involvement ~~beyond the pelvis~~ (EPL)

IIIA1 Positive retroperitoneal lymph nodes only

IIIA1(i) Metastasis (≤ 1 cm in size)
IIIA1(ii) Metastasis (> 1 cm in size)

IIIA2 Microscopic ~~extrapelvic~~ (EPL) peritoneal involvement with or without positive retroperitoneal lymph nodes

IIIB Macroscopic peritoneal metastasis ~~beyond the pelvis 2 cm or less~~ (EPL) with or without metastasis to the retroperitoneal lymph nodes

~~IIIC Macroscopic peritoneal metastasis beyond the pelvis more than 2 cm with or without metastasis to the retroperitoneal lymph nodes (EPL)~~

(Note 1: includes extension of tumor to capsule of liver and spleen without parenchymal involvement of either organ
Note 2: maximum size of peritoneal metastasis needs to be reported) (EPL)

Stage III

III Tumor involves one or both ovaries, fallopian tubes, or primary peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes

T1/T2/T3aN1

IIIA1 Positive retroperitoneal lymph nodes only (cytologically or histologically proven)

IIIA1 (i) Metastasis ≤ 10 mm in greatest dimension

IIIA1 (ii) Metastasis > 10 mm in greatest dimension

IIIA 2 Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes

T3a/T3aN1

Stage III

IIIB Macroscopic peritoneal metastasis beyond the pelvis 2 cm or less in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes

T3b/T3bN1

IIIC Macroscopic peritoneal metastasis beyond the pelvis more than 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes (Note 1)

T3c/T3cN1

[Note 1: includes extension of tumour to capsule of liver and spleen without parenchymal involvement of either organ] **T3c/T3cN1**

Stage IV

- Stage IVA: Pleural effusion with positive cytology
- Stage IVB: Parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of abdominal cavity)

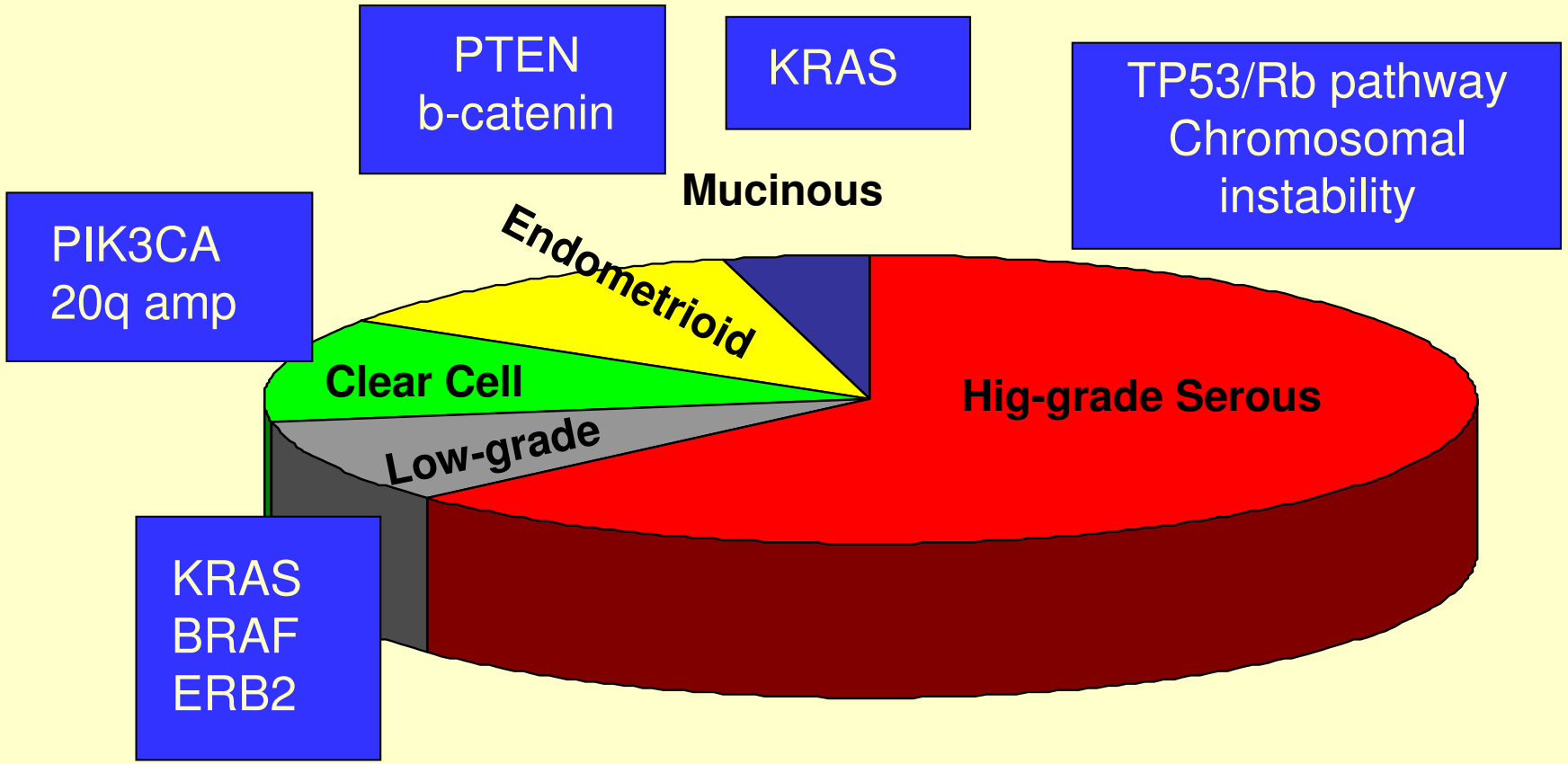
Any T, Any N, M1

Notes

- The primary site i.e: ovary, fallopian tube or peritoneum, should be designated where possible.
- In some cases, it may not be possible to clearly delineate the primary site and these should be listed as ***'undesignated'***
- The histological type should be recorded
- The staging includes a revision of the stage III patients and allotment to stage IIIA1 is based on spread to the ***retroperitoneal lymph nodes without intraperitoneal dissemination***, because an analysis of these patients indicates that their survival is significantly better than those who have intraperitoneal dissemination

Notes

- Involvement of retroperitoneal lymph nodes must be proven cytologically or histologically
- Extension of tumor from omentum to spleen or liver (Stage IIIC) should be differentiated from isolated parenchymal metastases (Stage IVB)


PTEN
b-catenin
KRAS
TP53/Rb pathway
Chromosomal
instability
PIK3CA
20q amp
Mucinous
Endometrioid
Clear Cell
Low-grade
Hig-grade Serous
KRAS
BRAF
ERB2