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Actualización en cáncer de endometrio

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Clínica Alemana-UDD

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Objetivos

Conocer los principales cambios en cáncer de endometrio relacionados con:

- Tipos histológicos y clasificación tumoral
- Sistema de graduación
- Permeaciones tumorales linfáticas
- Linfonodo centinela

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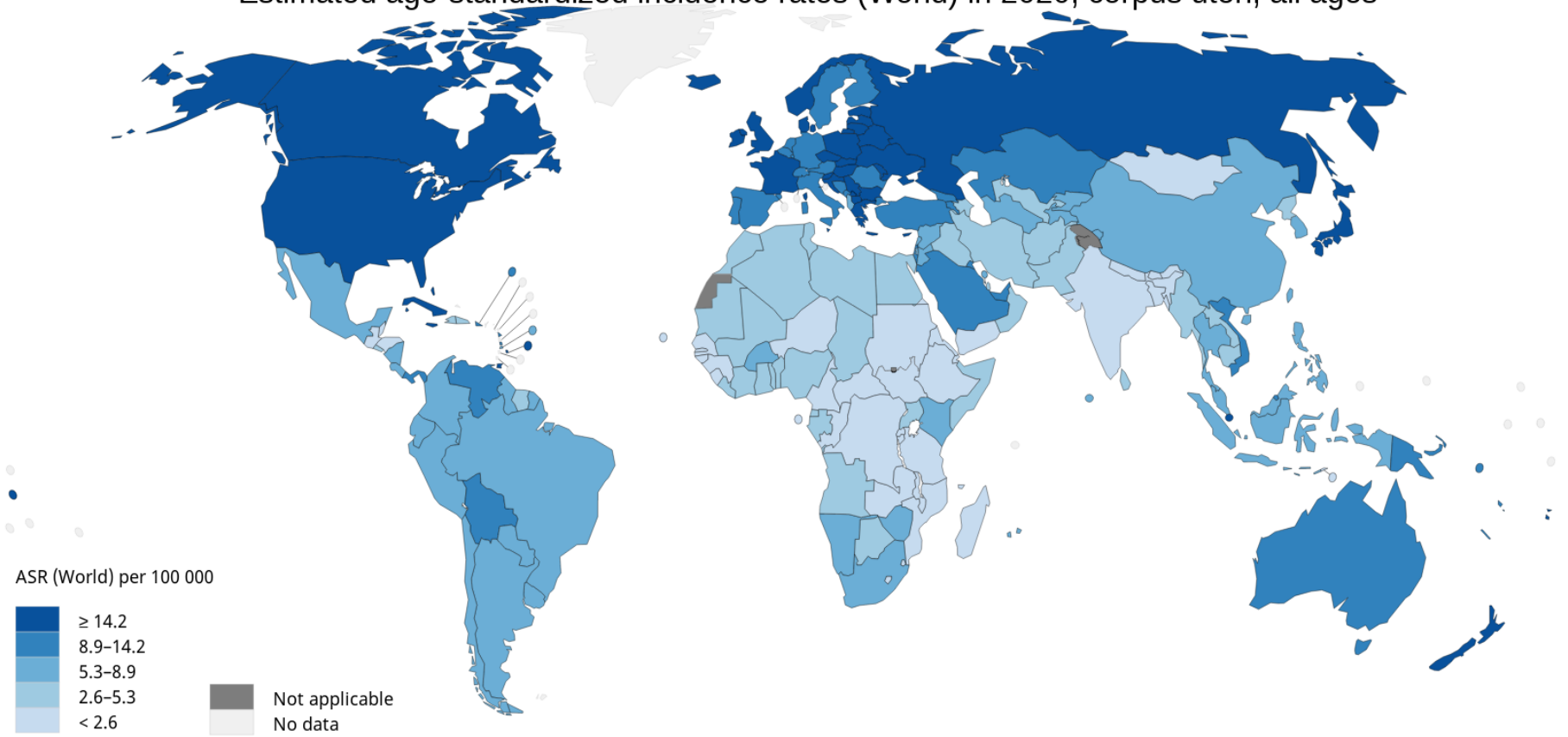
Estimated age-standardized incidence rates (World) in 2020, corpus uteri, all ages



Data source: GLOBOCAN 2020
Graph production: IARC (http://gco.iarc.fr/today)
World Health Organization

World Health Organization

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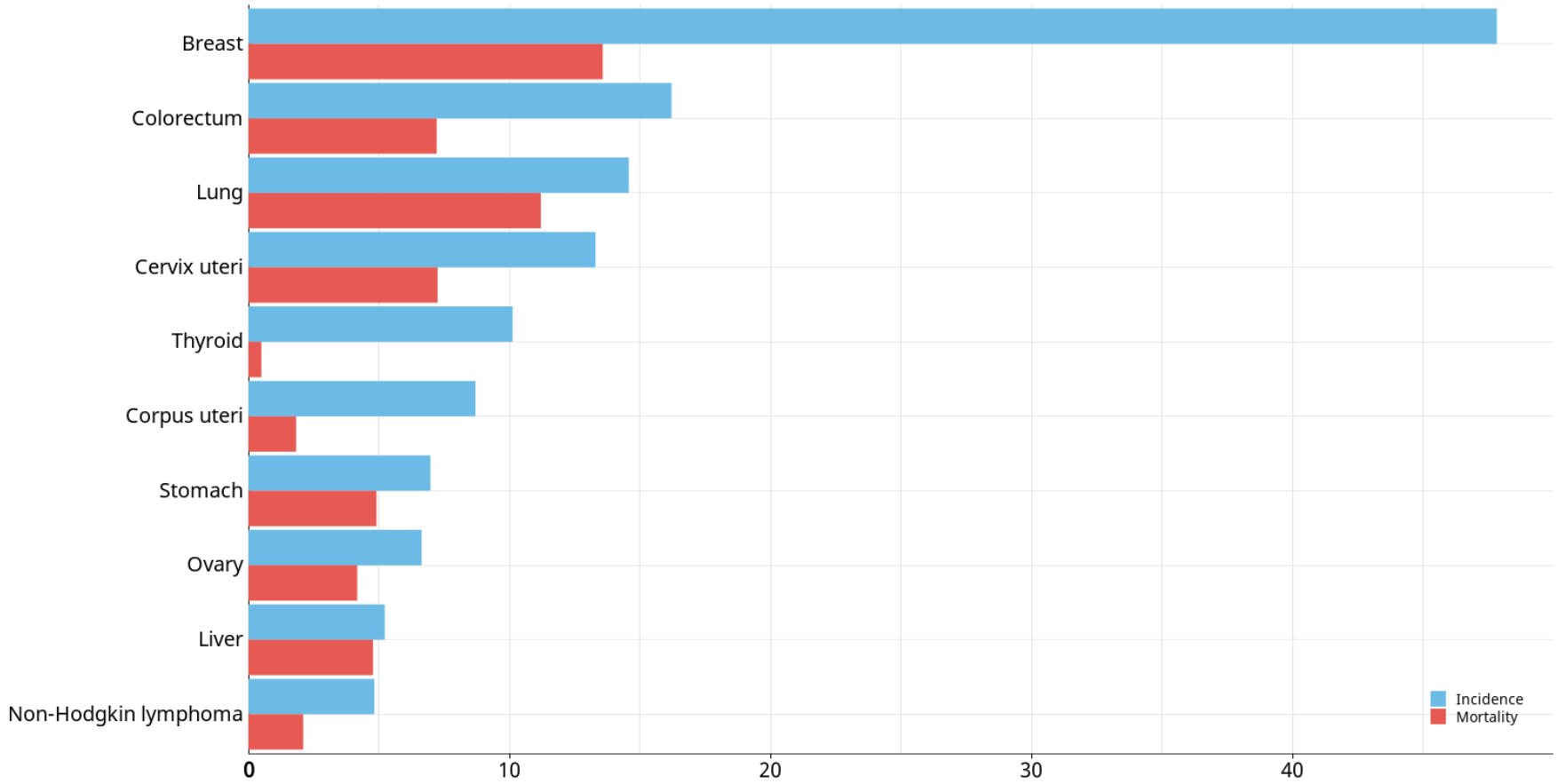
Estimated age-standardized incidence and mortality rates (World) in 2020, worldwide, females, all ages



Data source: Globocan 2020
Graph production: Global Cancer Observatory (http://gco.iarc.fr)

International Agency for Research on Cancer
World Health Organization

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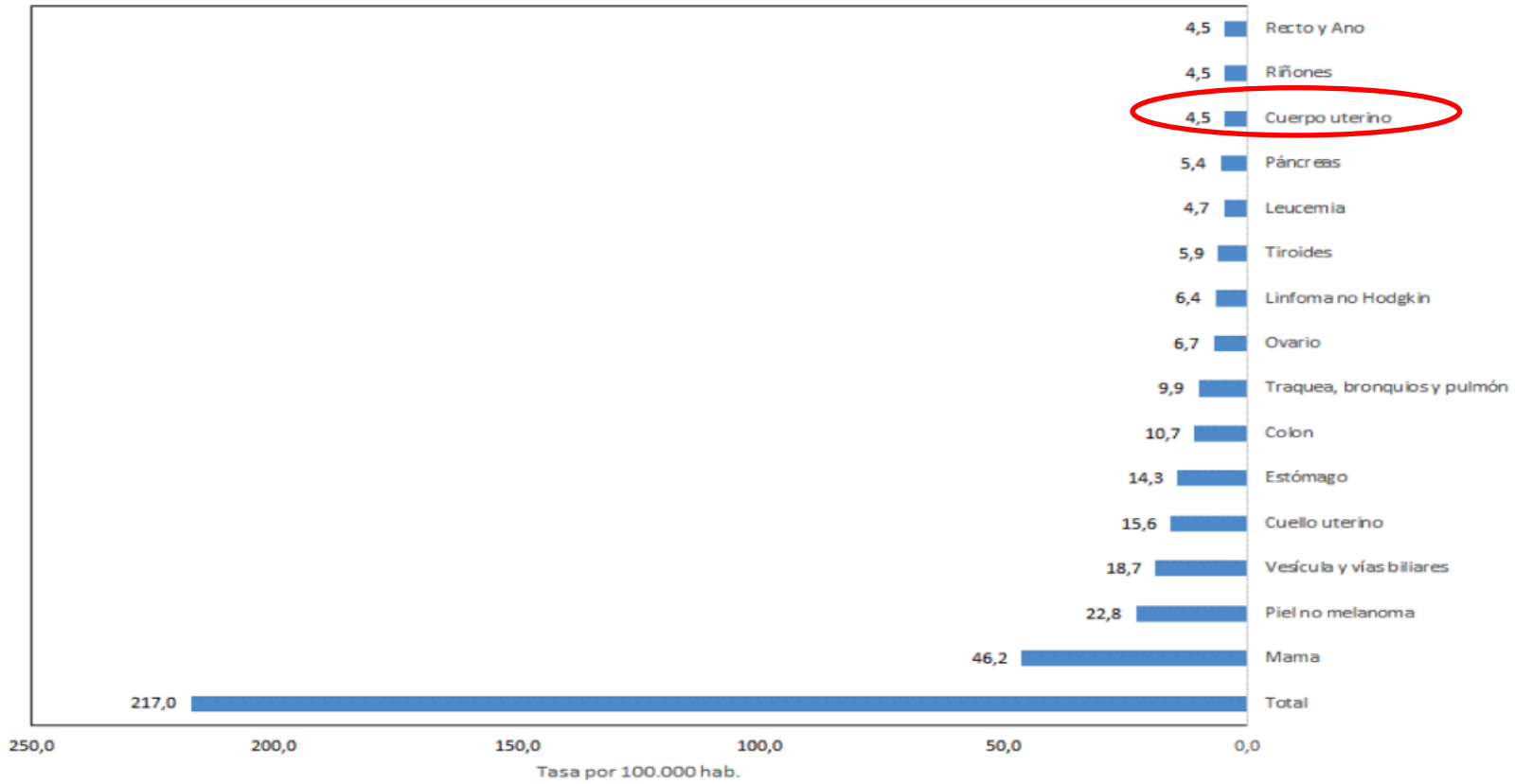
FIGURA 11. ESTIMACIONES DE INCIDENCIA DE CÁNCER EN MUJERES. CHILE 2003–2007. (TASA BRUTA DE INCIDENCIA POR 100.000 HAB.).



Fuente: Puesta al día de la Situación Epidemiológica del cáncer en Chile, Departamento de Epidemiología, MINSAL,http://epi.minsal.cl/wp-content/uploads/2018/10/PUESTA_AL_DIA_DE_SITUACION_EPIPEMIOLOGIA_DEL_CANCER_EN_CHILE_2018_DEPT_EPIDEMIOLOGIA_junio_2018.pdf.

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Cáncer de endometrio:

- 2ª neoplasia maligna ginecológica
- 80-90% de las neoplasias malignas del útero
- 90% en > 50 años (63 años promedio)
- 2-5% en < 40 años
- 95%: esporádicos
- 5%: predisposición hereditaria (S. de Lynch)

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GYNECOLOGIC ONCOLOGY **15,** 10–17 (1983)

Two Pathogenetic Types of Endometrial Carcinoma

JAN V. BOKHMAN, M.D.

Department of Gynecology, N. N. Petrov Research Institute of Oncology, USSR Ministry of Health, Leningrad, USSR

Received May 6, 1981

TABLE 2

INFLUENCE OF PATHOGENETIC TYPE OF THE DISEASE ON TUMOR PECULIARITIES

Tumor peculiarity	Pathogenetic type	
	I	II
Duration of symptoms	Usually long duration	Usually short duration
Degree of tumor differentiation	Highly or moderately differentiated (more frequent G_1 or G_2)	Poorly differentiated (more frequent G_3)
Depth of invasion in the myometrium	Frequent prevalence of superficial invasion	Frequent prevalence of deep invasion
Potentiality for lymphogenic metastatic spread	Not high	High
Sensitivity to progestogens	High	Not high
Primary multiple tumors	Ovaries, breast, colon	Not characteristic
Prognosis	Favorable	Doubtful

Clinicopathologic types of endometrial carcinoma

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	Type I	Type II
Age	Pre- and perimenopausal	Postmenopausal
Unopposed estrogen	Present	Absent
Hyperplasia precursor	Present	Absent
Grade	Low	High
Myometrial invasion	Minimal	Deep
Histologic types	Endometrioid carcinoma and variants, mucinous carcinoma	Serous, clear cell, squamous cell, and undifferentiated carcinoma
Behavior	Stable	Progressive
Molecular abnormalities	Microsatellite instability (hMLH1) PTEN, ARID1A, PIK3CA and KRAS mutations beta-catenin nuclear accumulation	p53 alterations, and loss of heterozygosity (LOH) at different loci

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Cáncer de endometrio:

- Grupo heterogéneo de tumores con características clínico-patológicas que definen grupos de riesgo con diferentes pronósticos y tratamientos

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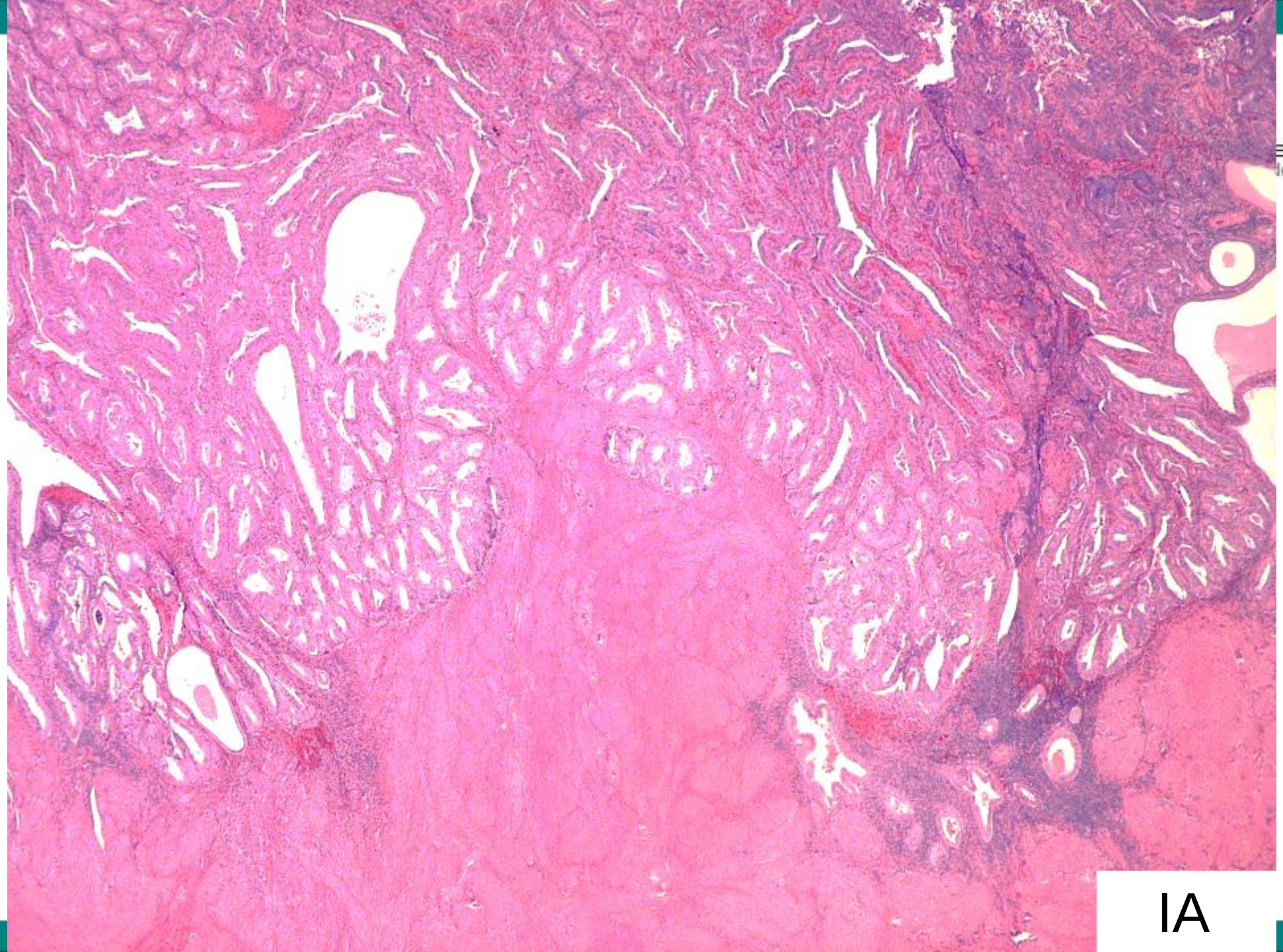
Estratificación de riesgo

- Estadío
- Tipo histológico
- Grado histológico
- Invasión linfovascular



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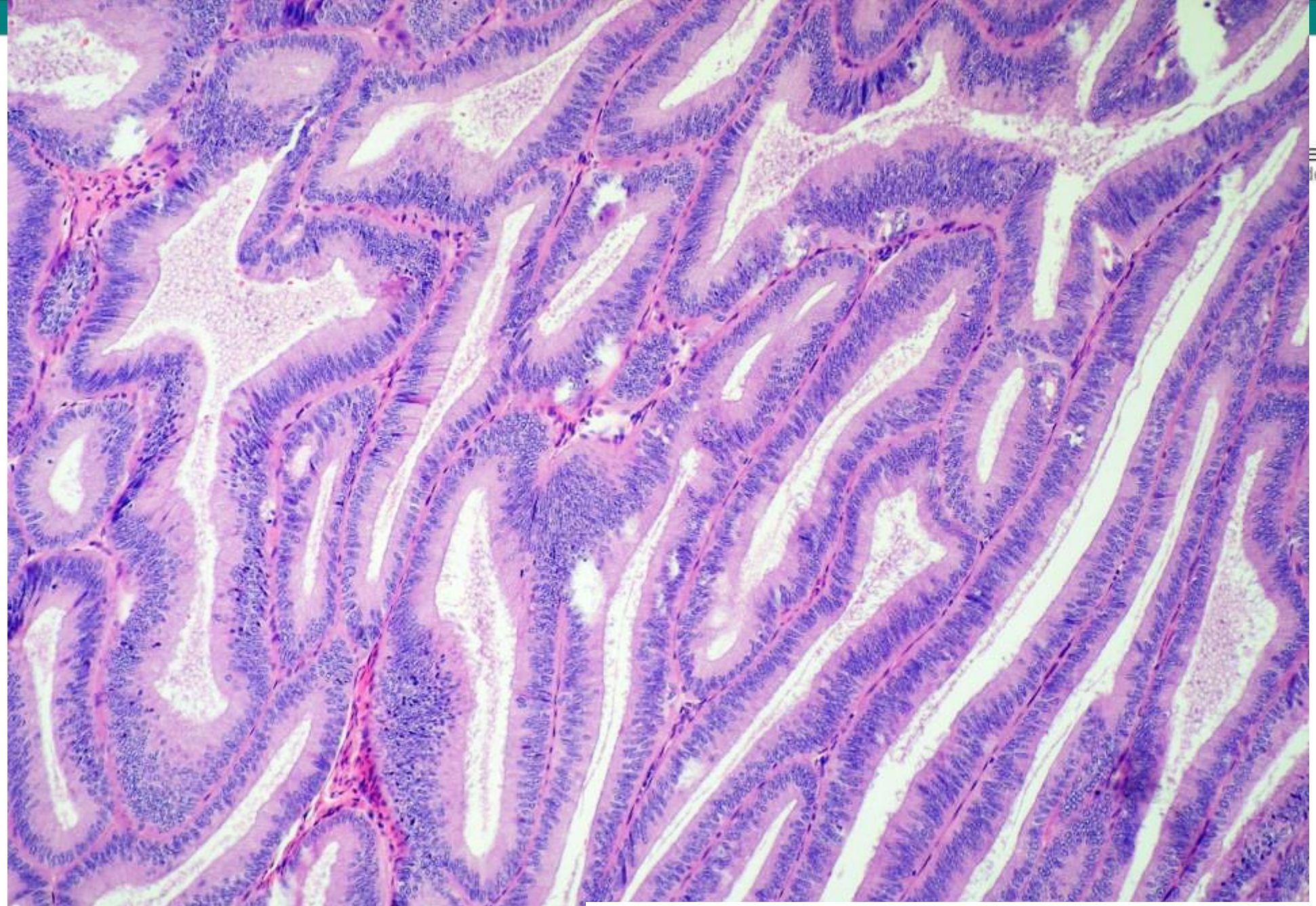
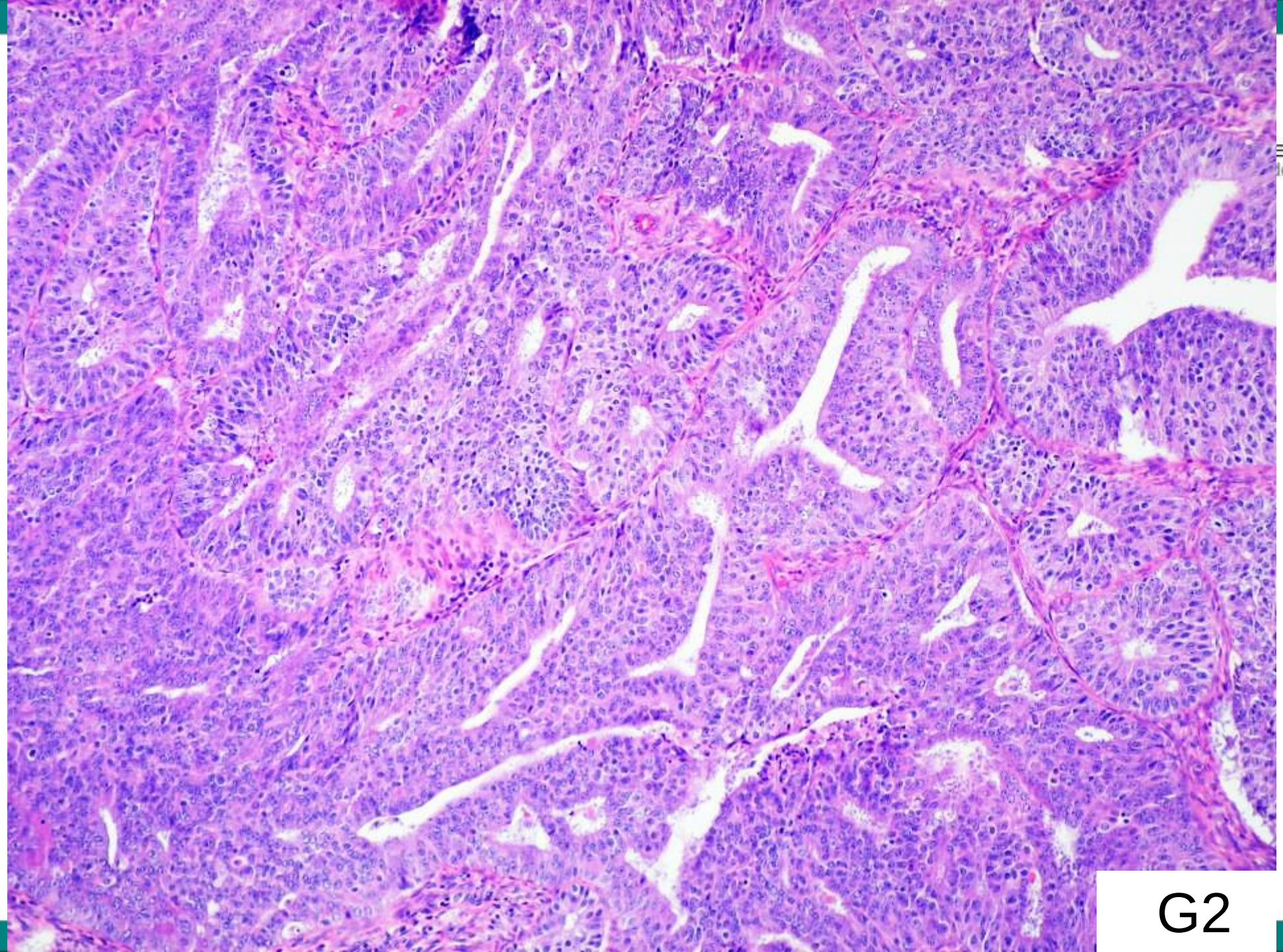
IA



Carcinoma endometrioide G1



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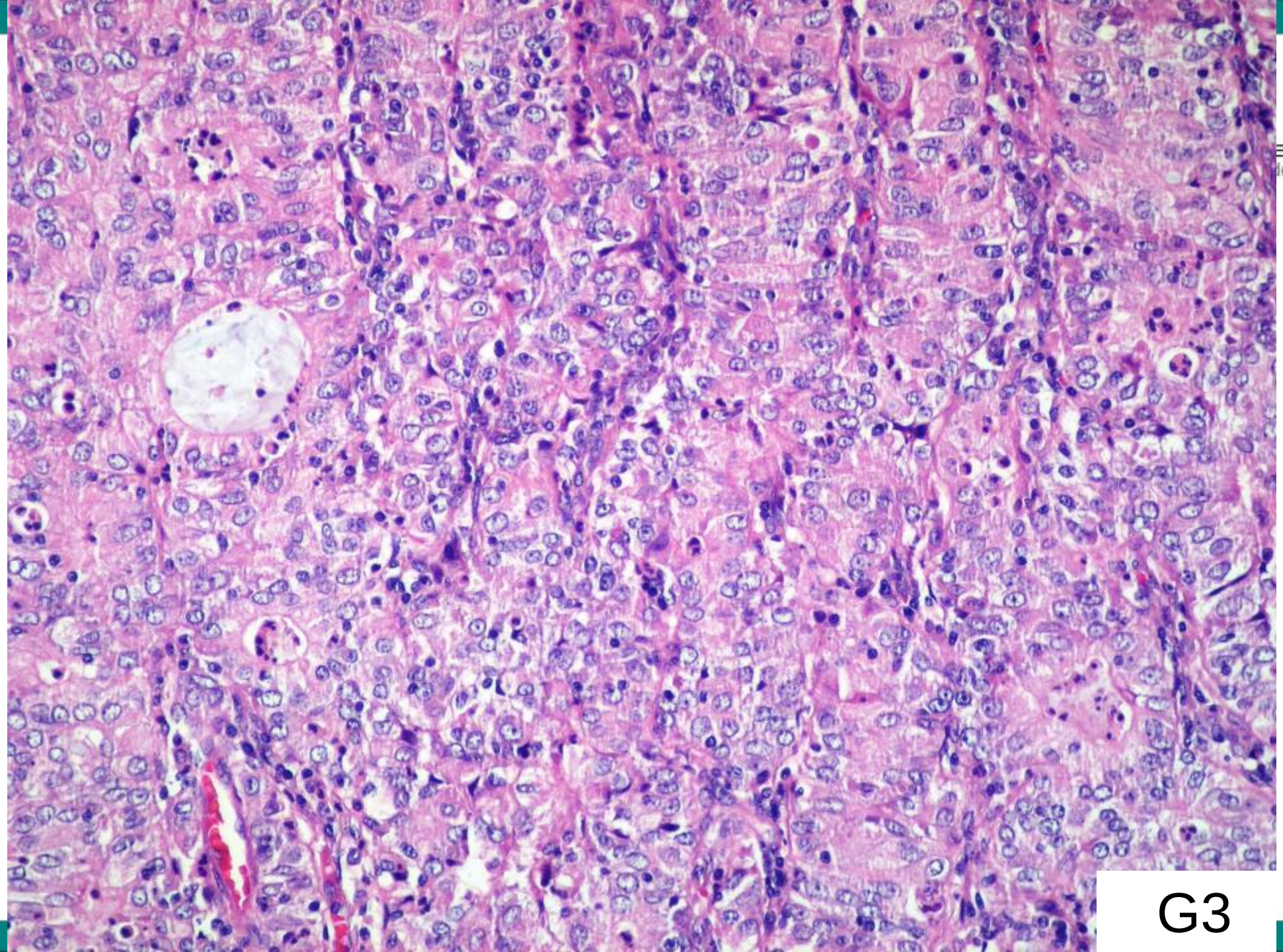
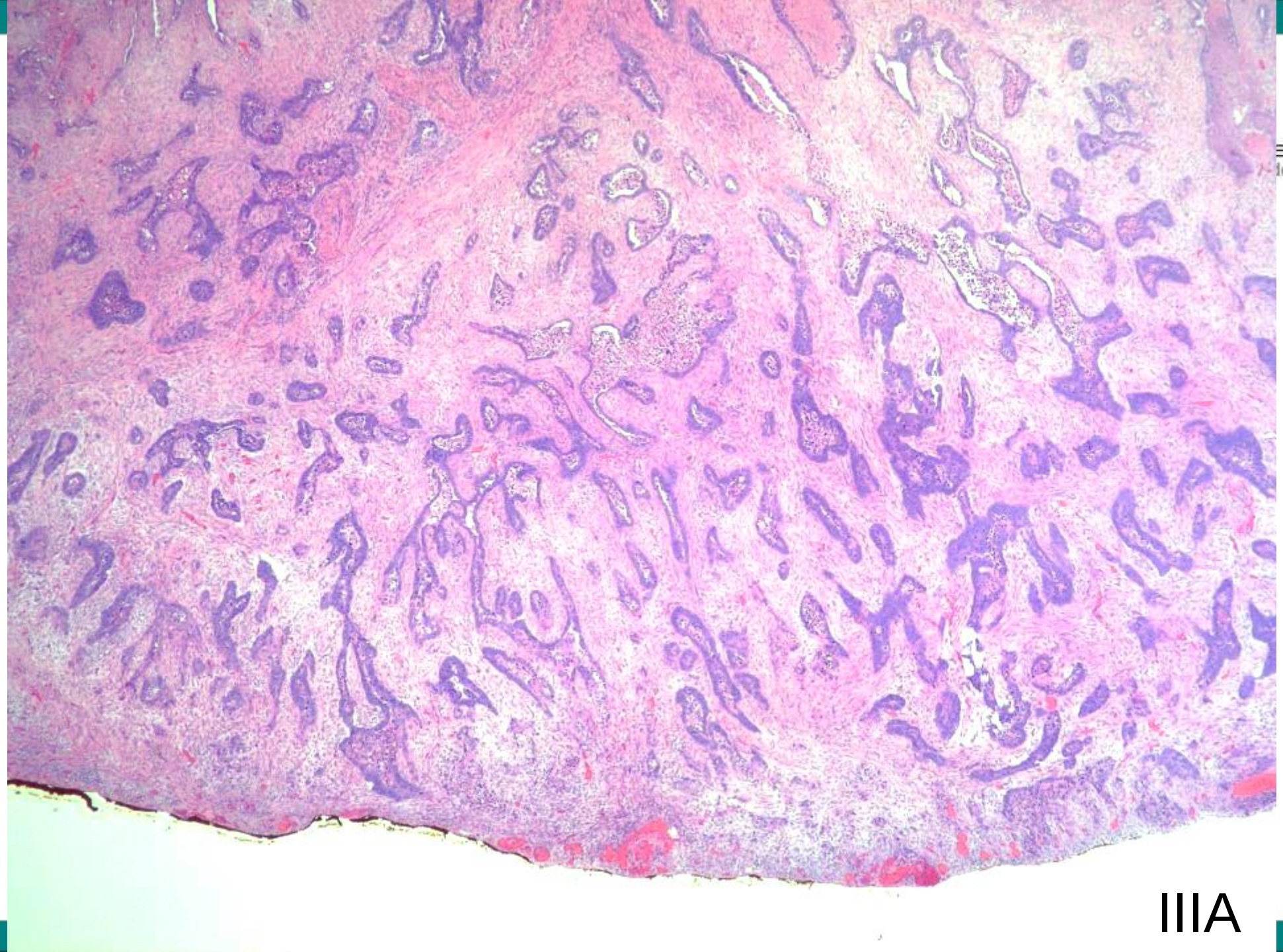
G2



G3



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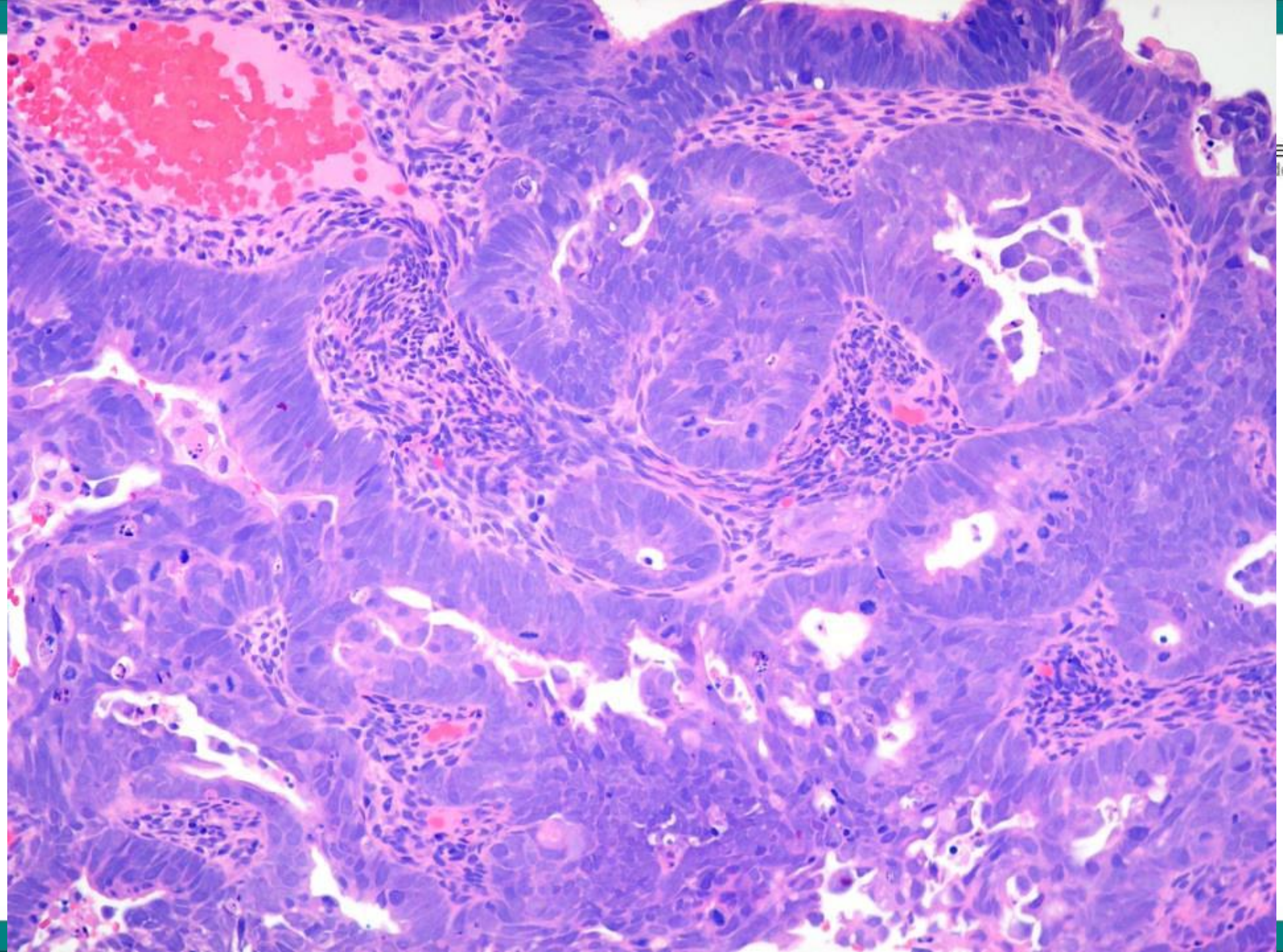
IIIA



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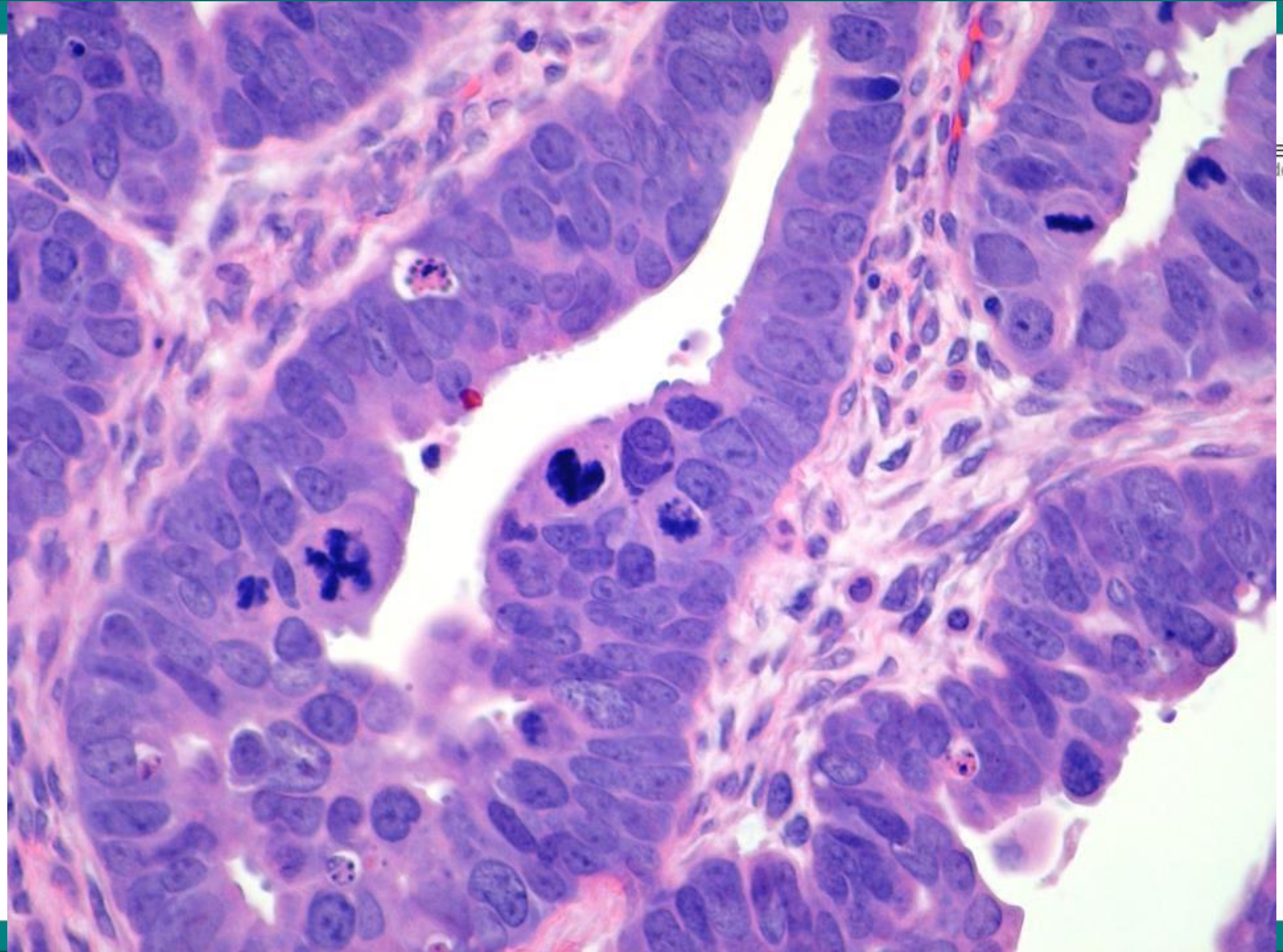

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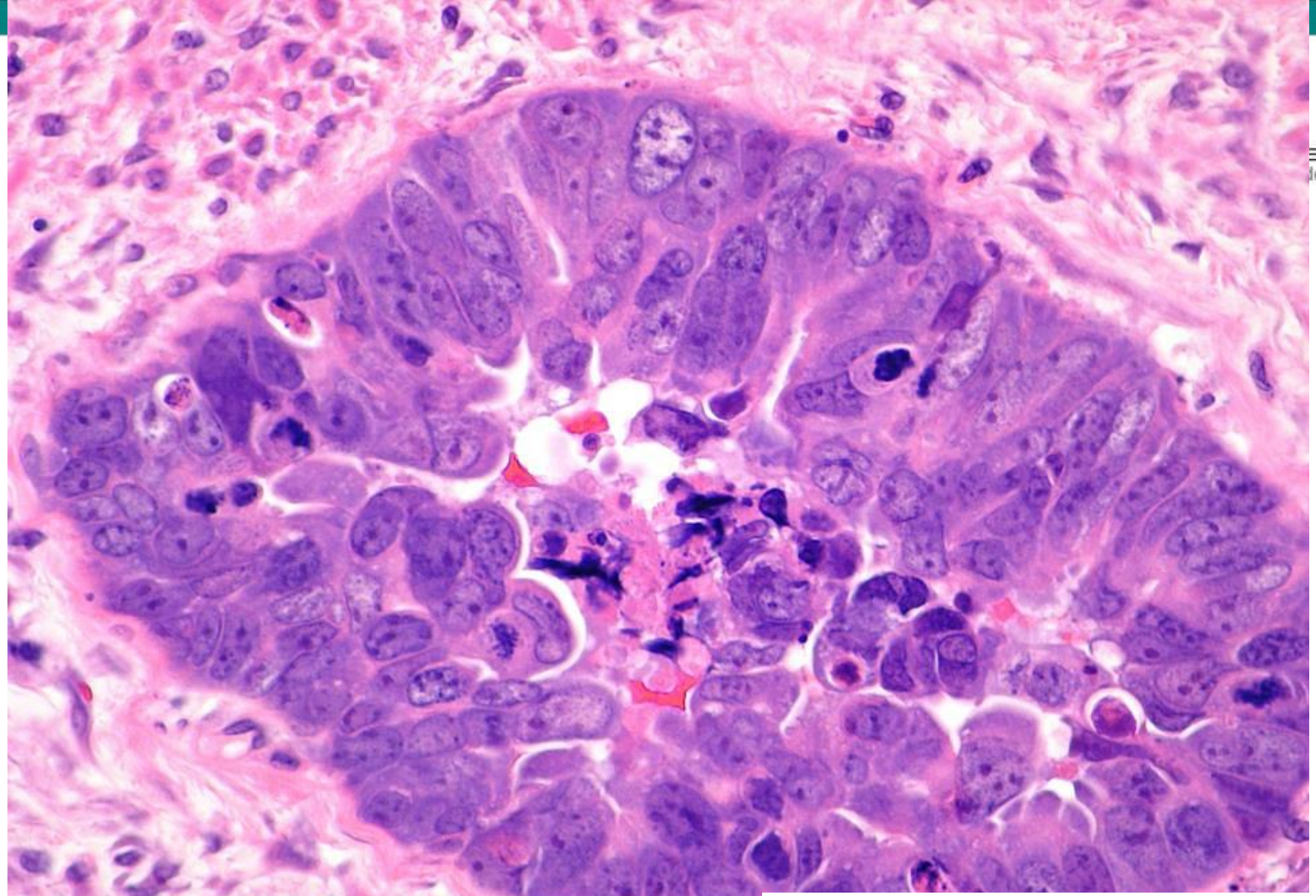
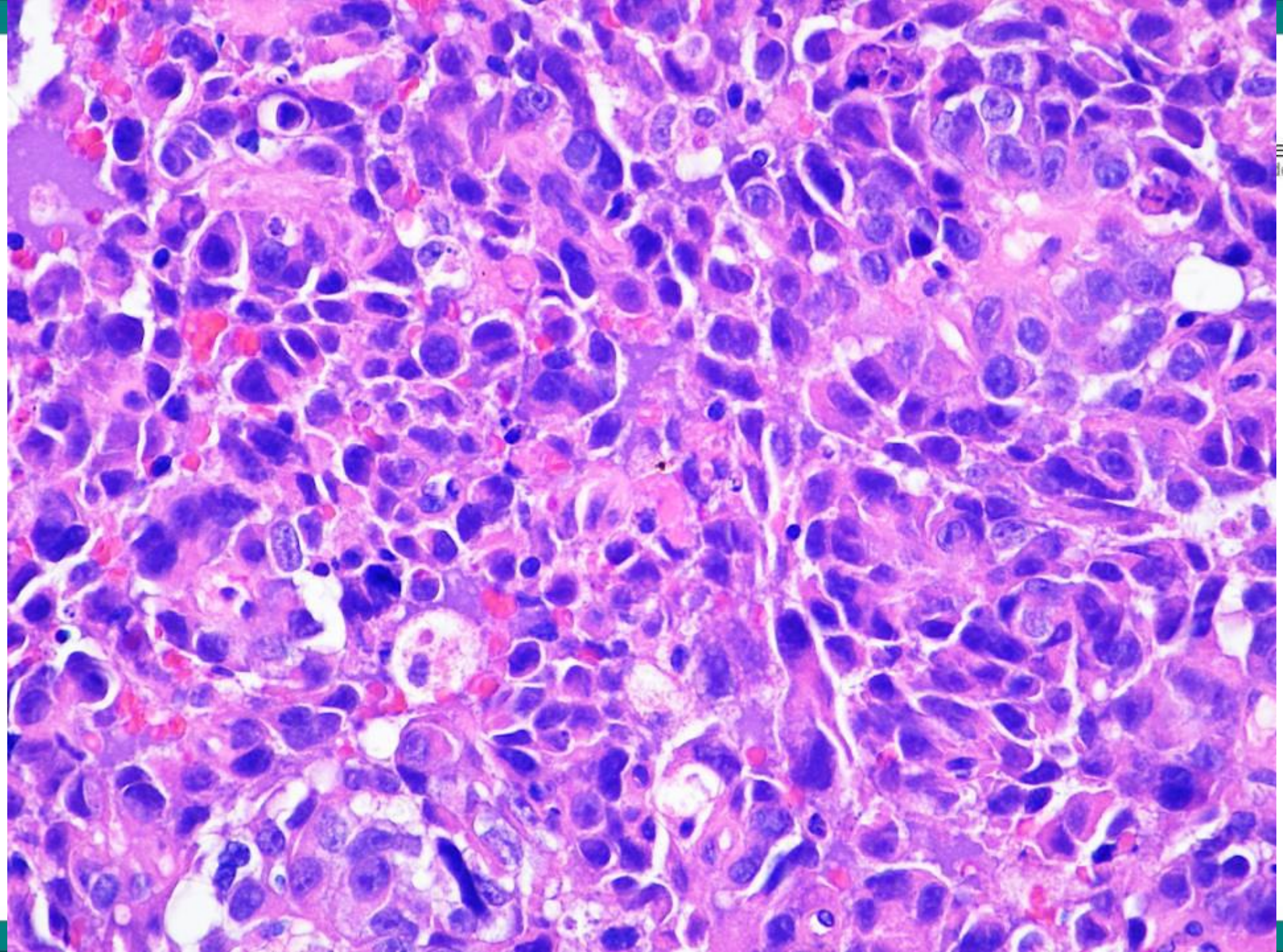


Carcinoma seroso



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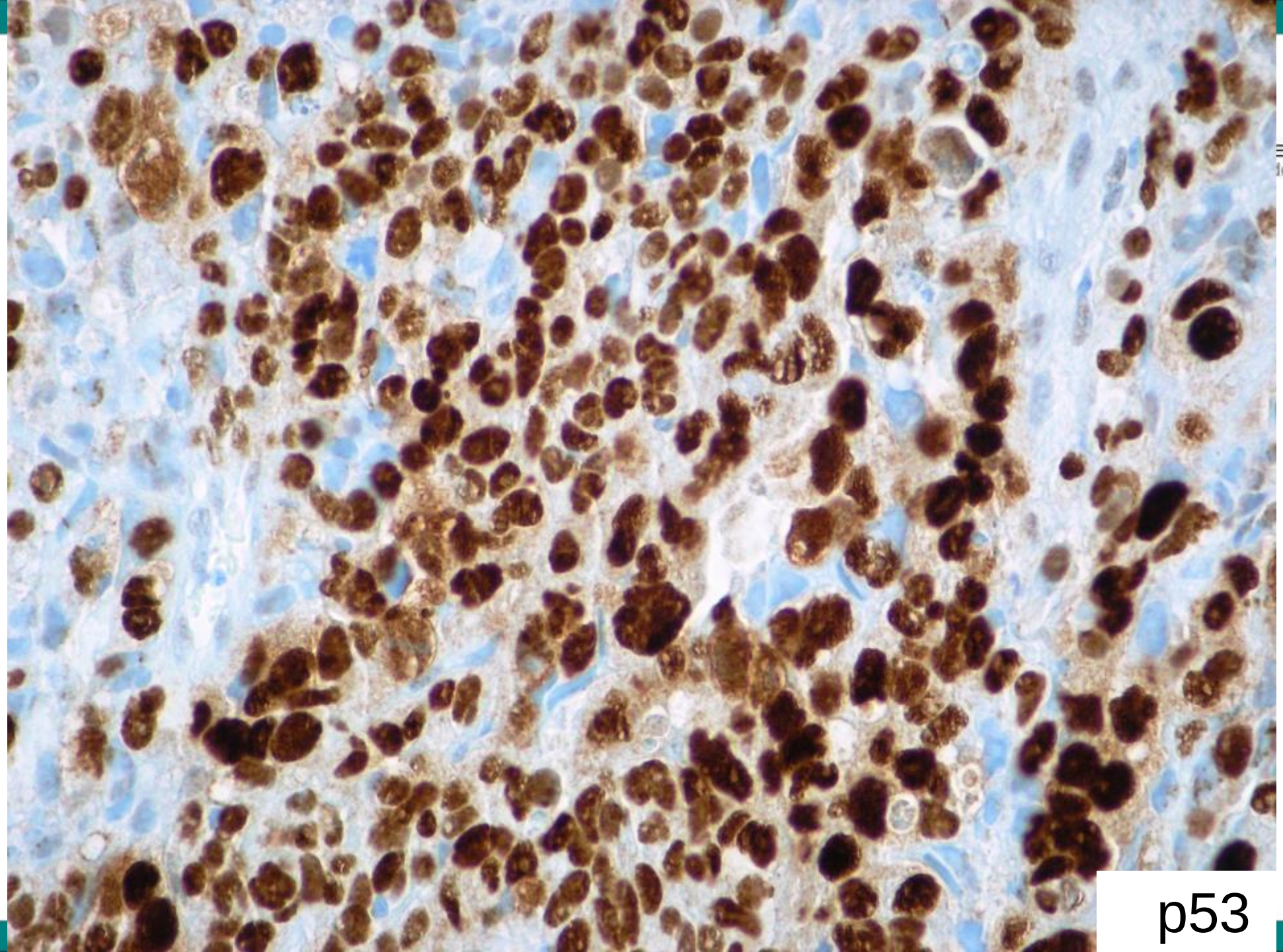
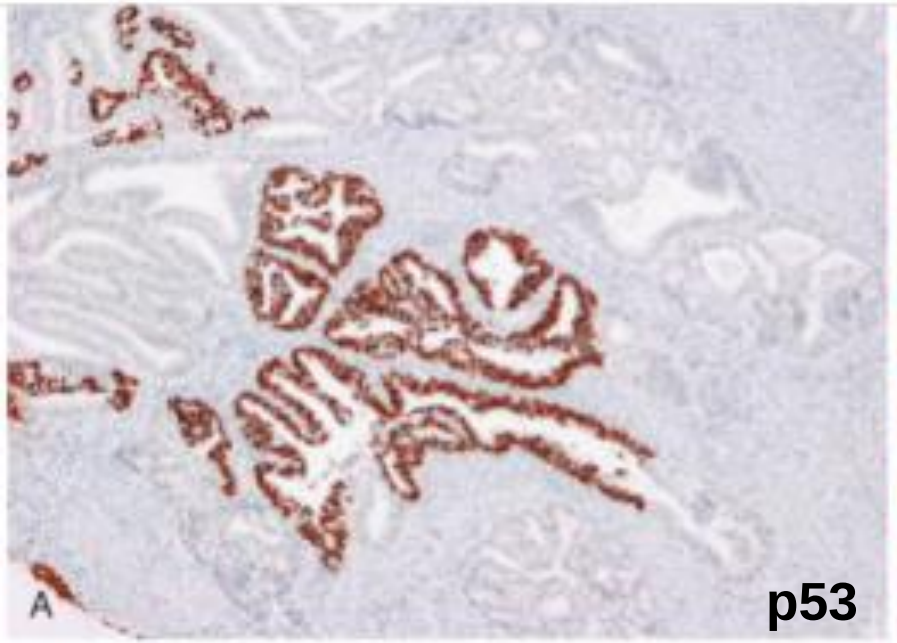


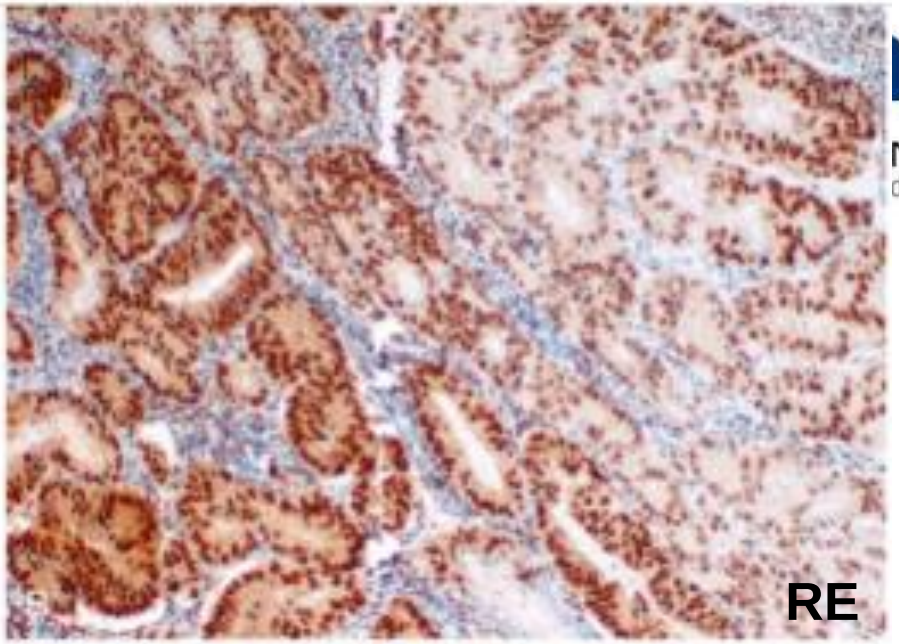
p53

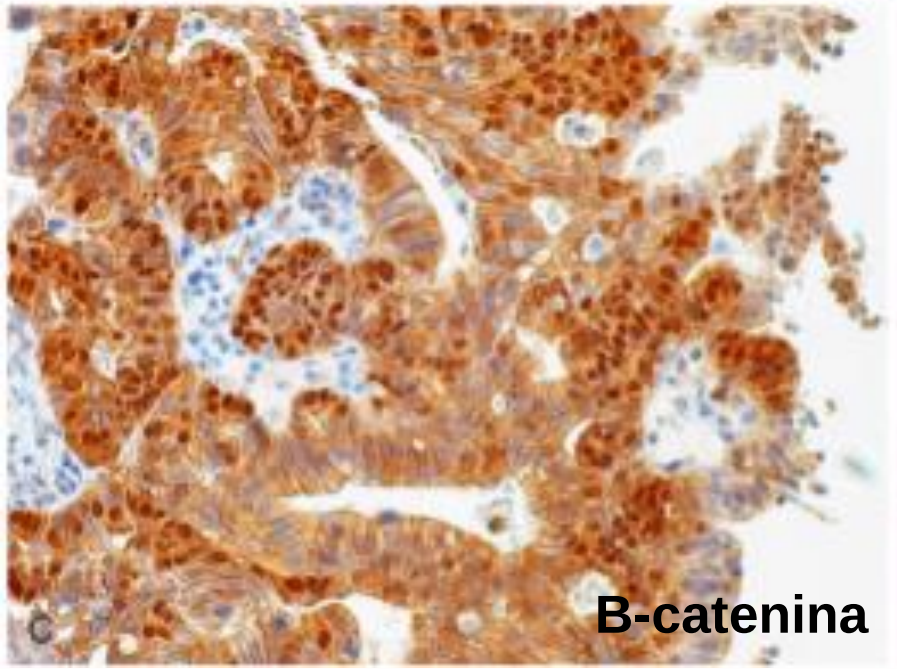
KEY DIAGNOSTIC POINTS: ENDOMETRIOID CARCINOMAS

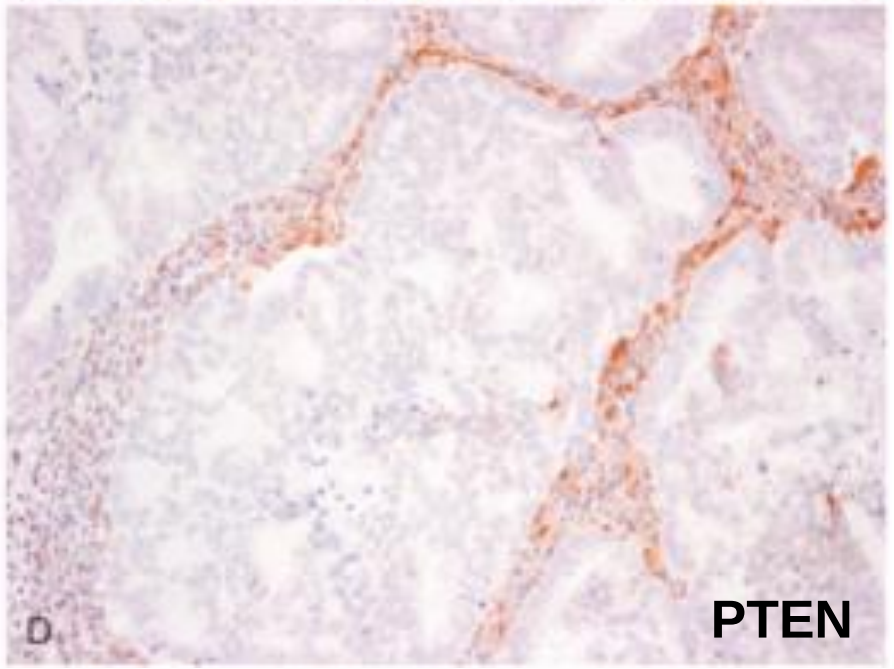
- Endometrioid carcinomas typically express CK7, CA 125, estrogen receptors, progesterone receptors, and vimentin, and they are usually negative for CK20.
- Overexpression of both p53 and p16 is only occasionally seen; however, a subset of FIGO grade 2/3 endometrioid carcinomas may strongly and diffusely express p53 and harbor *p53* mutations.
- Nuclear β-catenin expression and loss of PTEN and DNA MMR proteins are seen in significant minorities.

Dabbs









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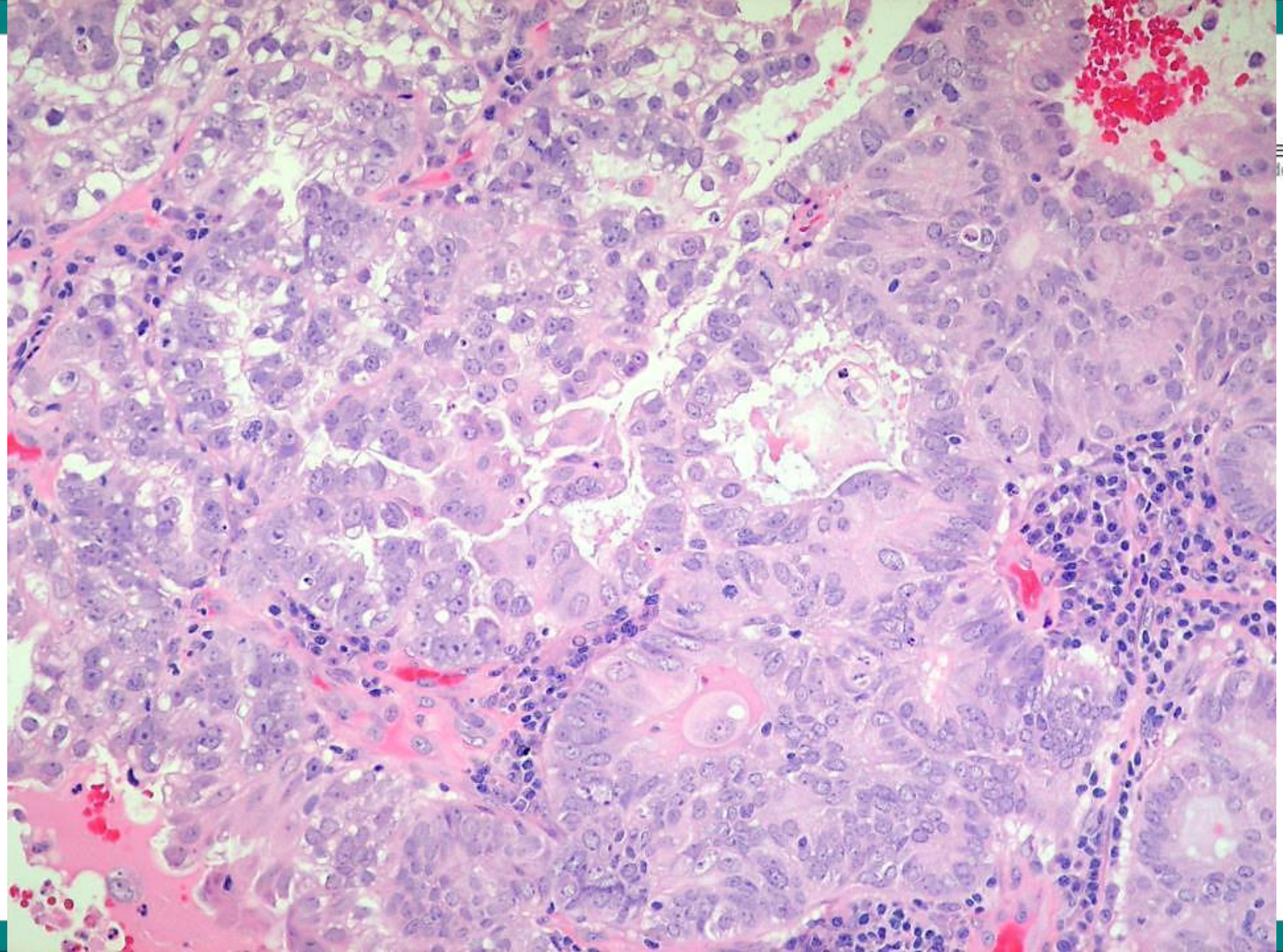

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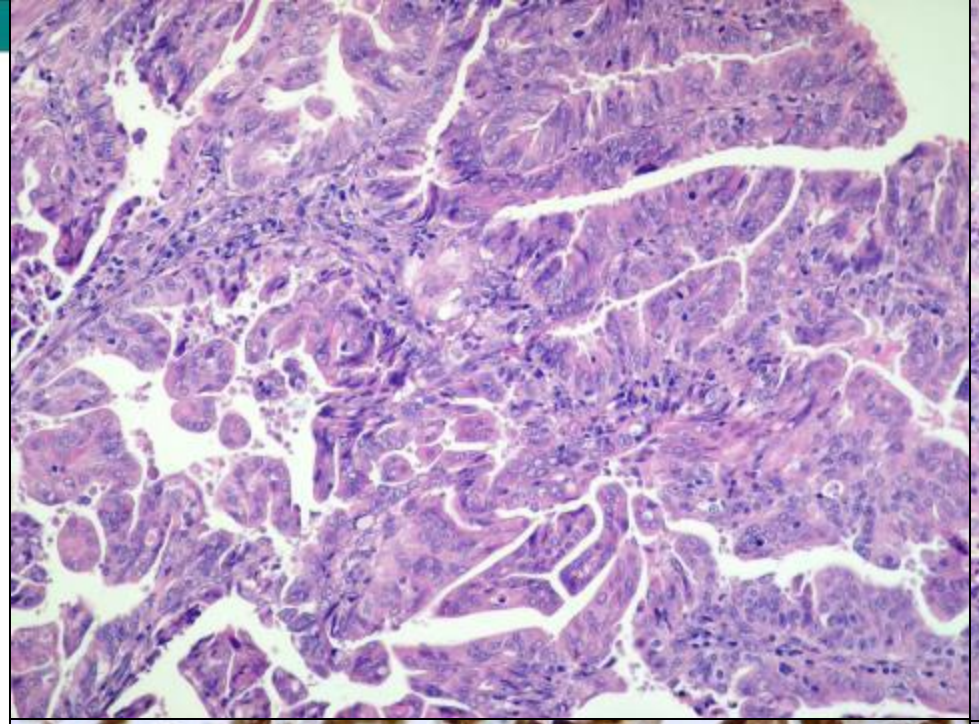
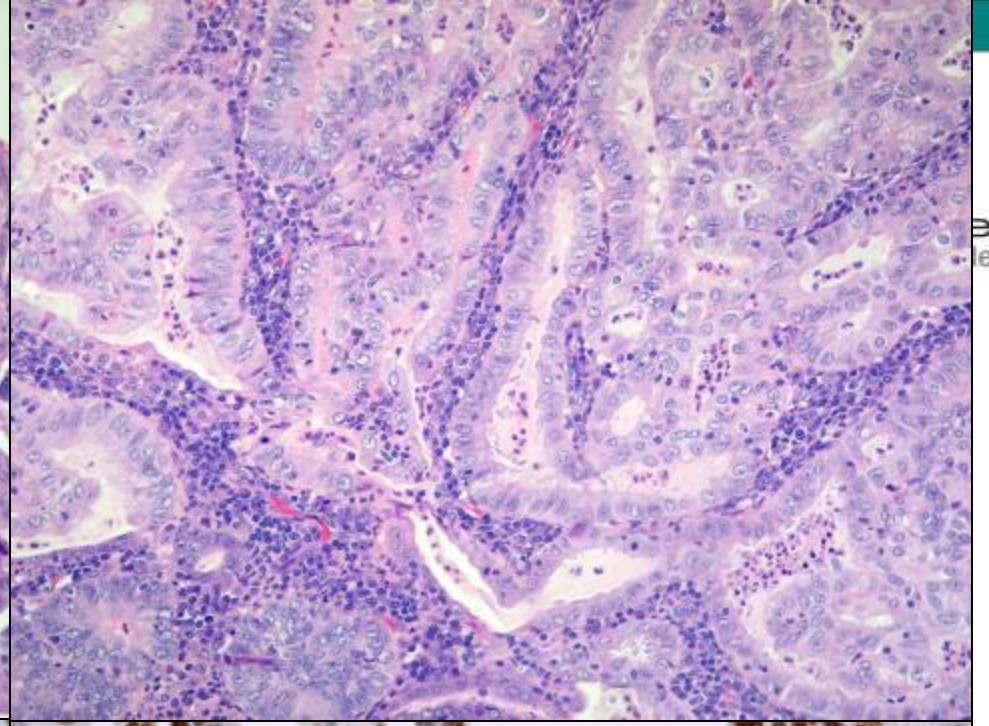
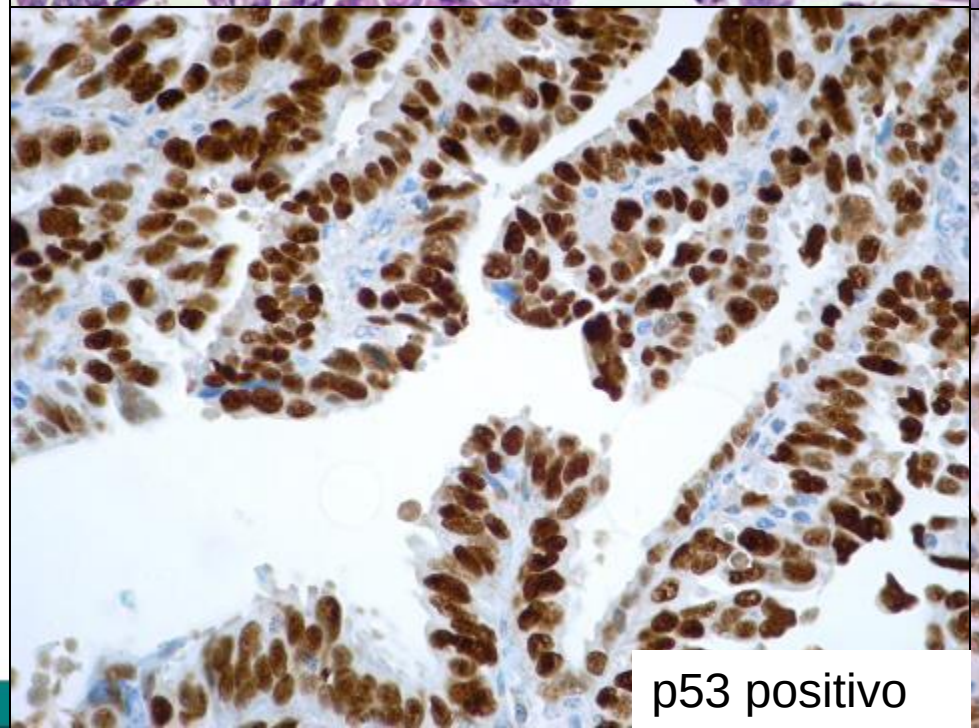
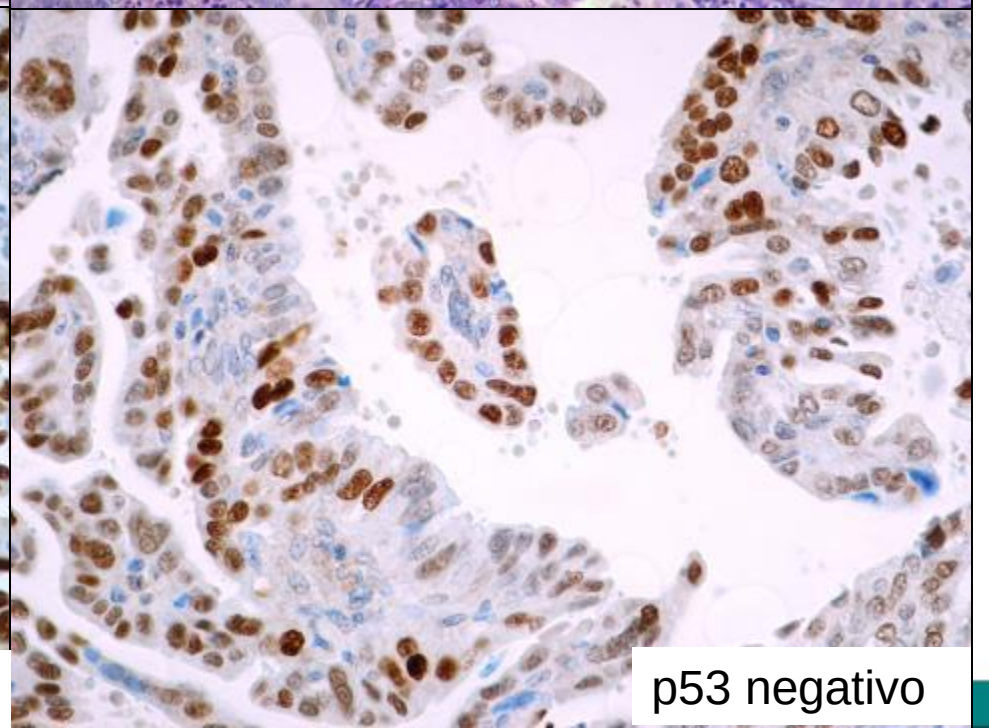


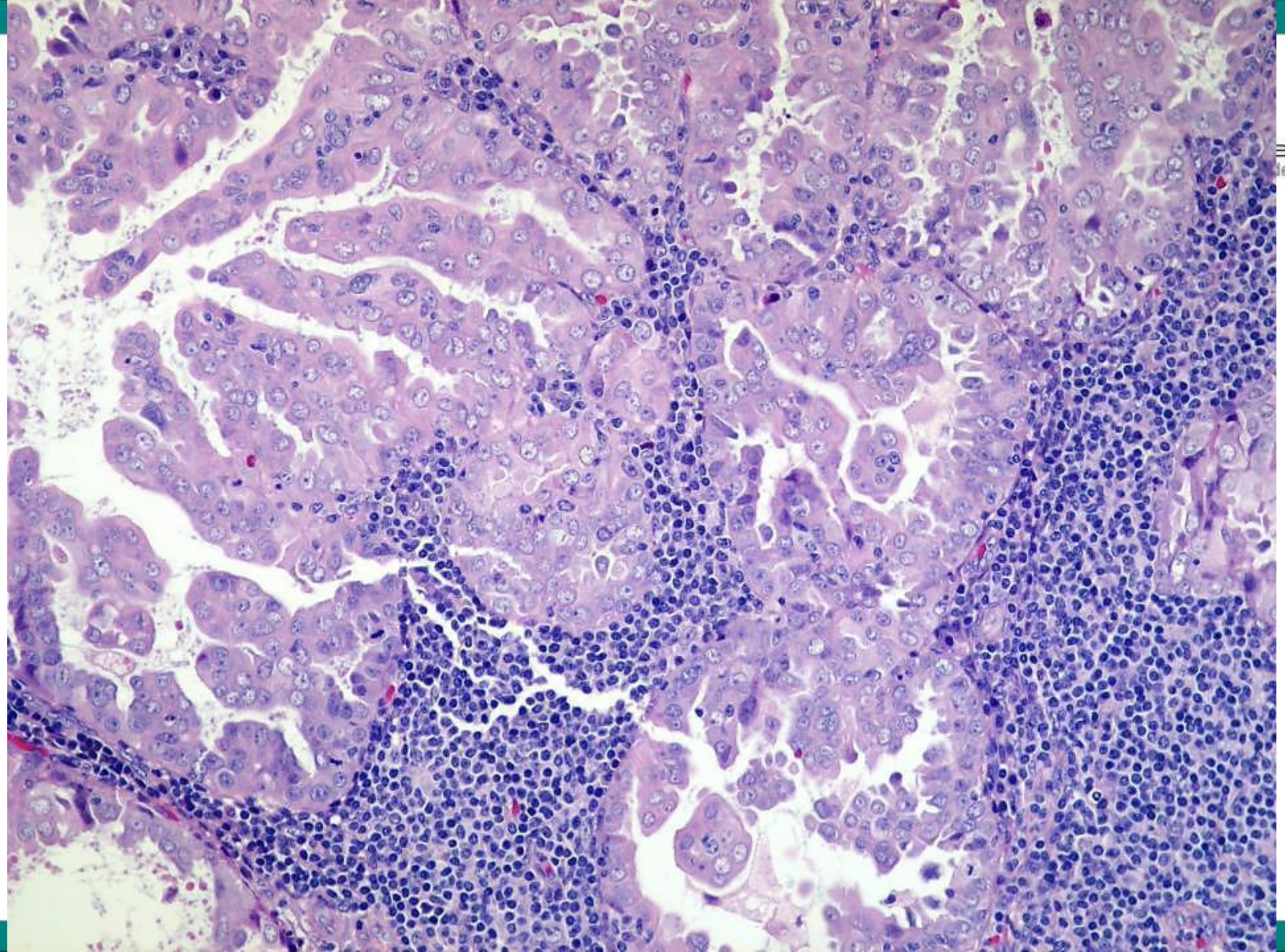




p53 positivo



p53 negativo



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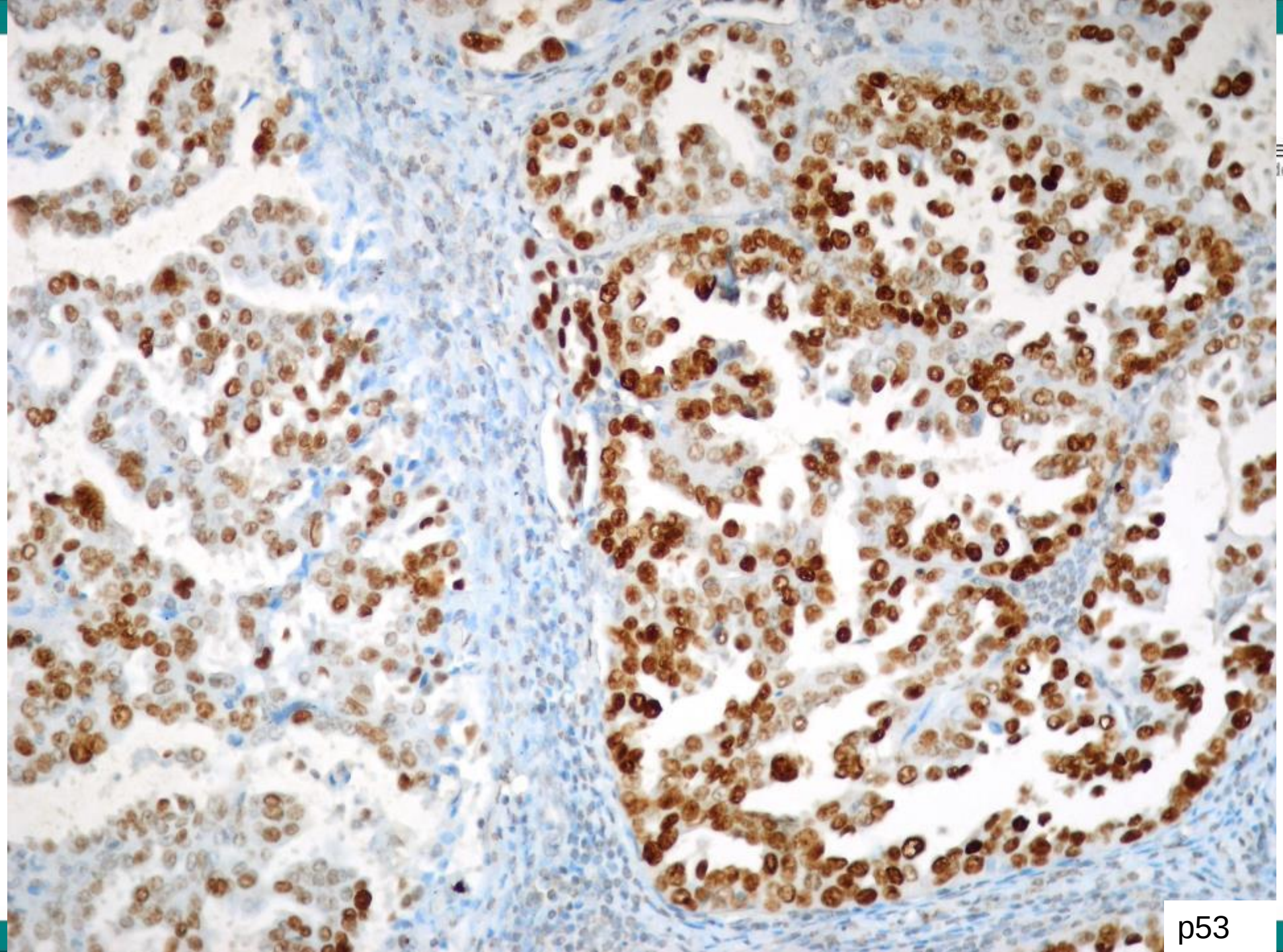

p53

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“CARCINOMAS AMBIGUOS”

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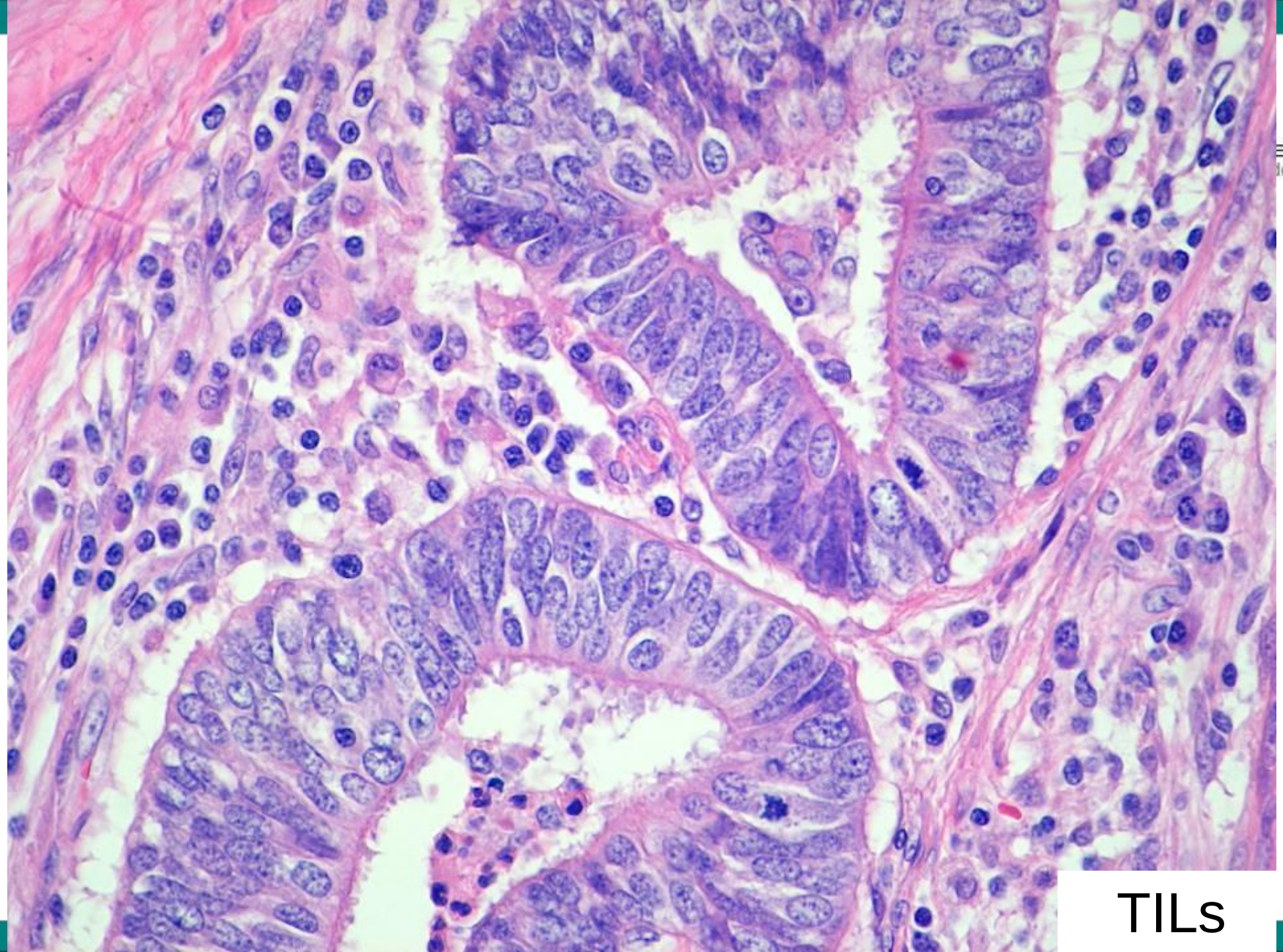
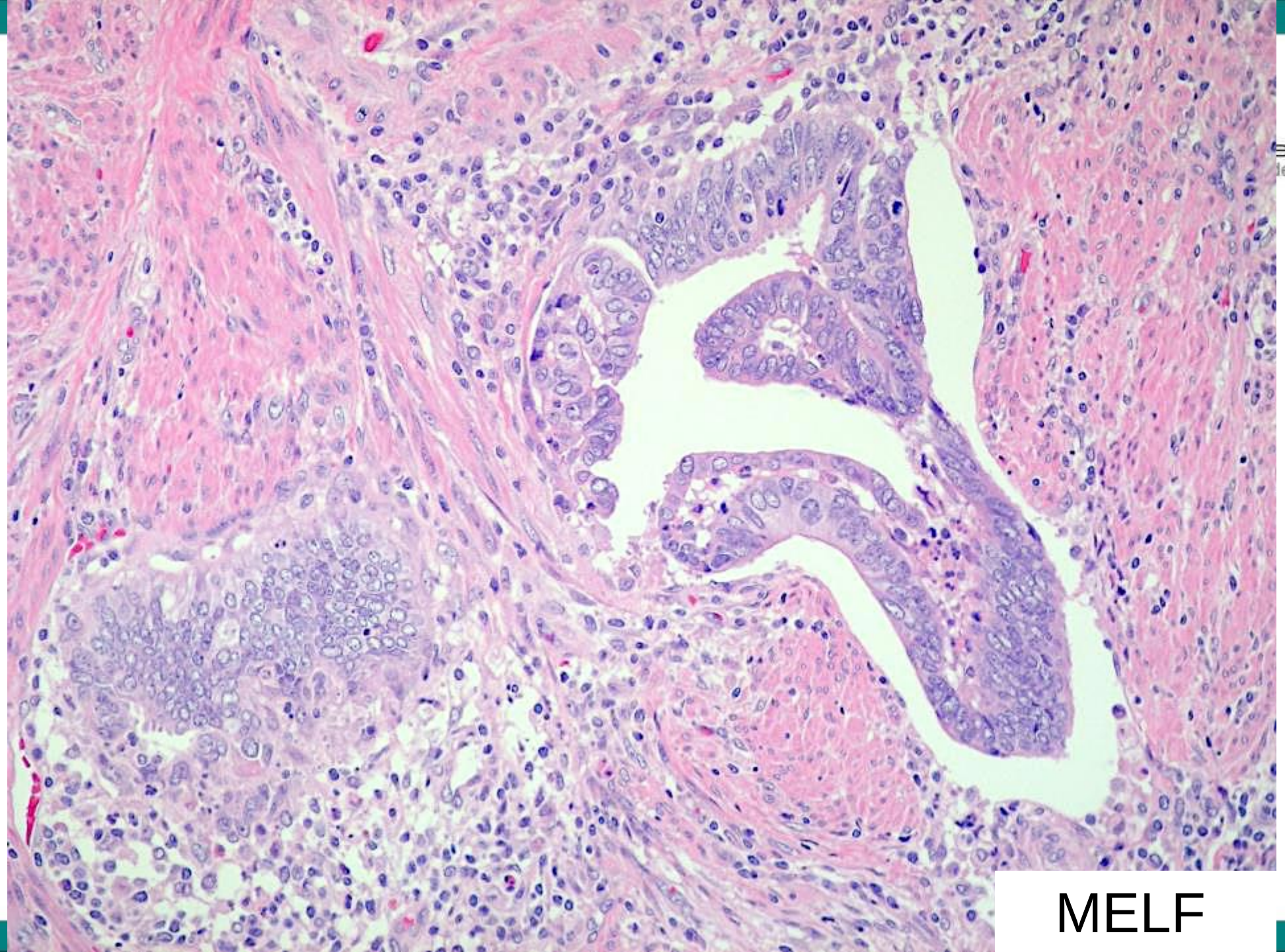
Variabilidad interobservador

Limitaciones en la clasificación histológica



TILs



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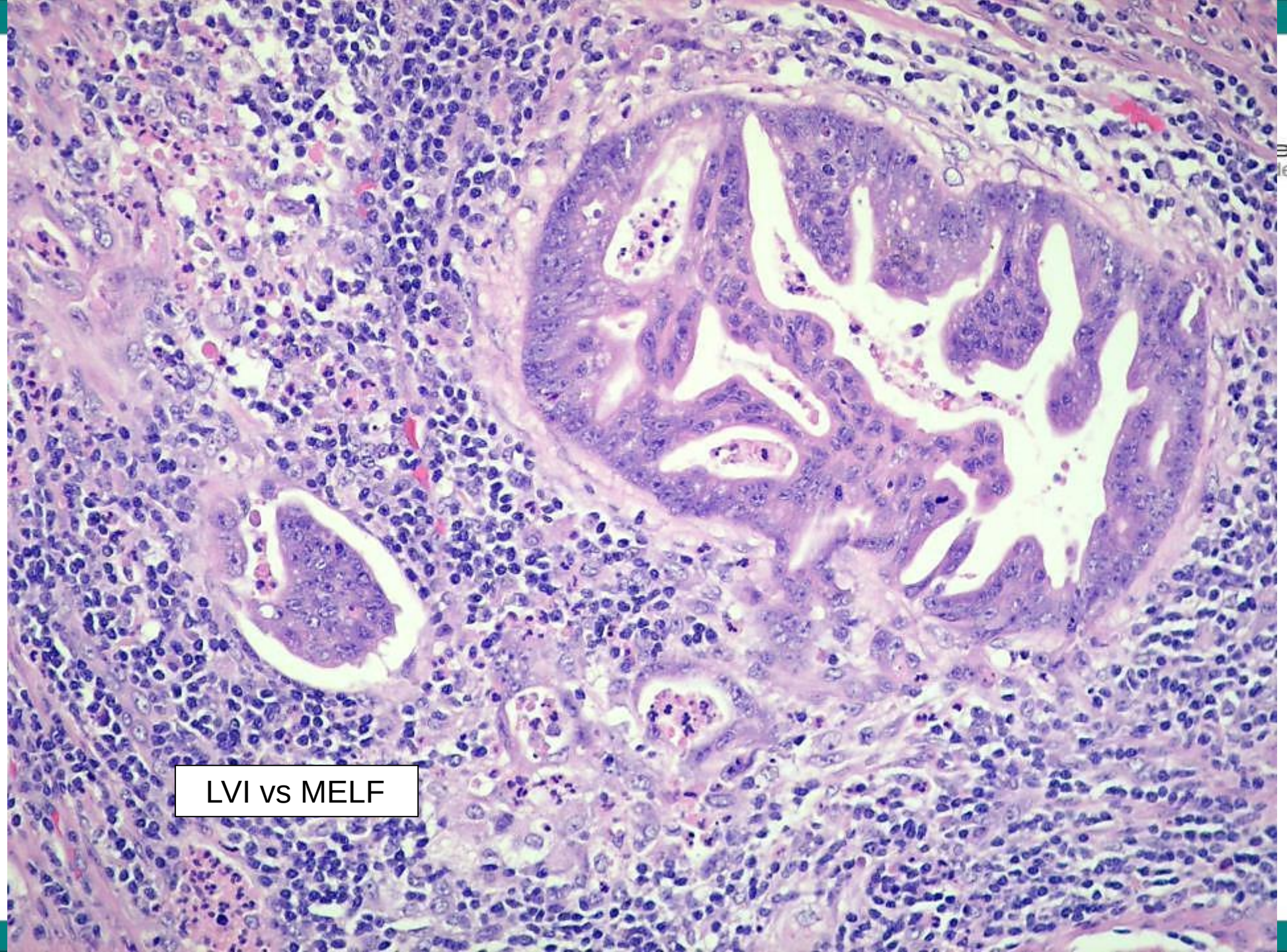
MELF


LVI vs MELF

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Cáncer de endometrio:

- Variabilidad en evolución clínica en tipos histológicos y grados similares
- Características clínico-patológicas son insuficientes para clasificar subgrupos tumorales con distintos pronósticos

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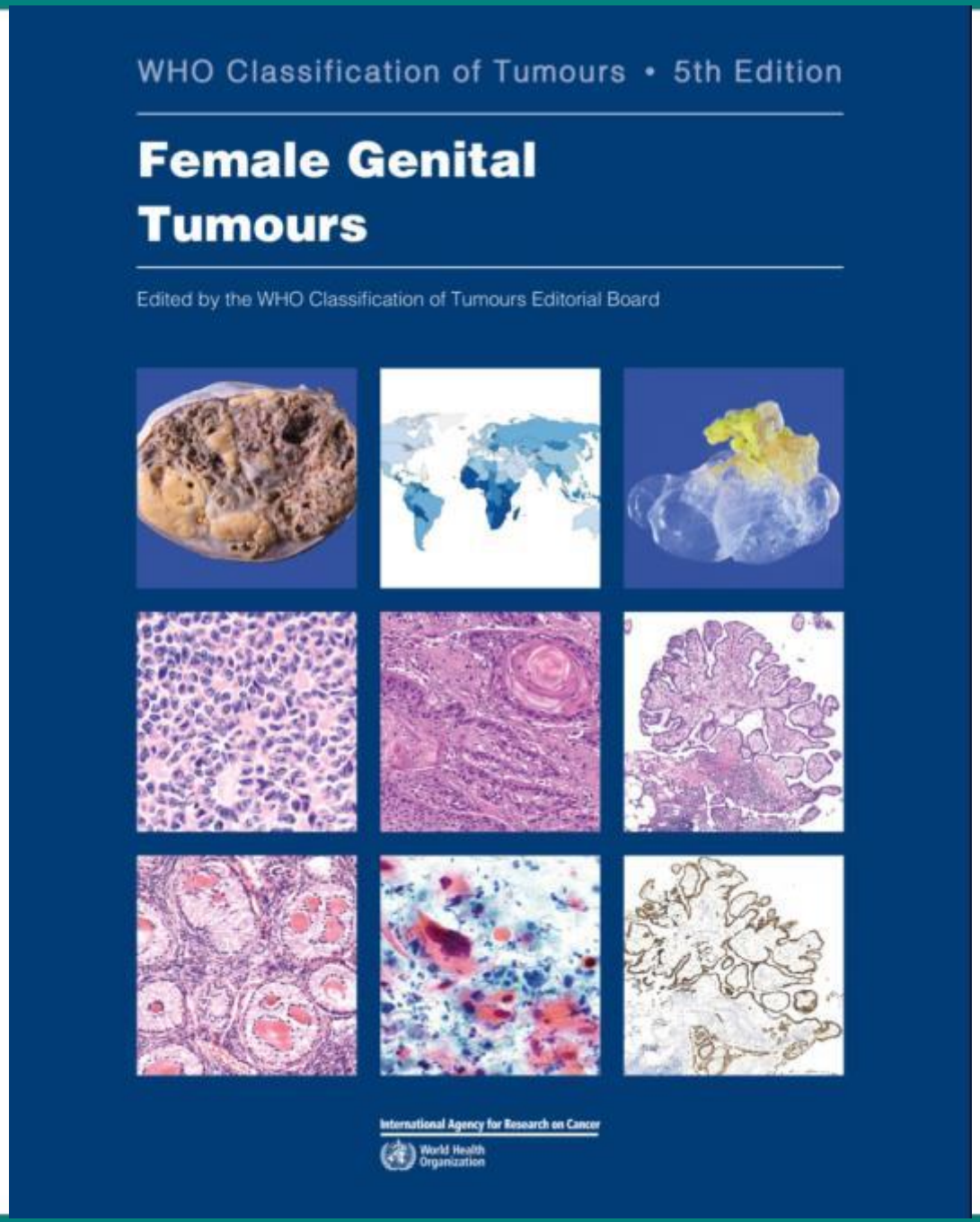
Cáncer de endometrio:

- Caracterización genómica y clasificación molecular
- Superposición de características clínico-patológicas y moleculares entre algunos de estos tumores



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Histologic Type (Note B)

___ Endometrioid carcinoma, NOS
___ Endometrioid carcinoma with squamous differentiation
___ Endometrioid carcinoma, villoglandular variant
___ Endometrioid carcinoma with secretory differentiation
___ Endometrioid carcinoma, other variant (specify): _____
___ Serous endometrial intraepithelial carcinoma
___ Serous carcinoma
___ Carcinosarcoma (malignant mixed Müllerian tumor)
___ Mucinous carcinoma
___ Clear cell carcinoma
___ Small cell neuroendocrine carcinoma
___ Large cell neuroendocrine carcinoma
___ Mixed cell carcinoma (specify types and percentages): _____
___ Undifferentiated carcinoma
___ Dedifferentiated carcinoma
___ Other histologic type not listed (specify): _____

WHO 5° edición

Histologic Type (Note C)

___ Endometrioid carcinoma, NOS
___ POLE-ultramutated endometrioid carcinoma
___ Mismatch repair–deficient endometrioid carcinoma
___ p53-mutant endometrioid carcinoma
___ No specific molecular profile (NSMP) endometrioid carcinoma
___ Serous carcinoma
___ Carcinosarcoma
___ Mucinous carcinoma, intestinal type
___ Clear cell adenocarcinoma, NOS
___ Small cell neuroendocrine carcinoma
___ Large cell neuroendocrine carcinoma
___ Mixed neuroendocrine non-neuroendocrine carcinoma
___ Mixed cell adenocarcinoma (specify types and percentages): _____
___ Dedifferentiated carcinoma
___ Undifferentiated carcinoma, NOS
___ Mesonephric adenocarcinoma
___ Squamous cell carcinoma, NOS
___ Mesonephric-like adenocarcinoma
___ Other histologic type not listed (specify): _____
+Histologic Type Comment: _____

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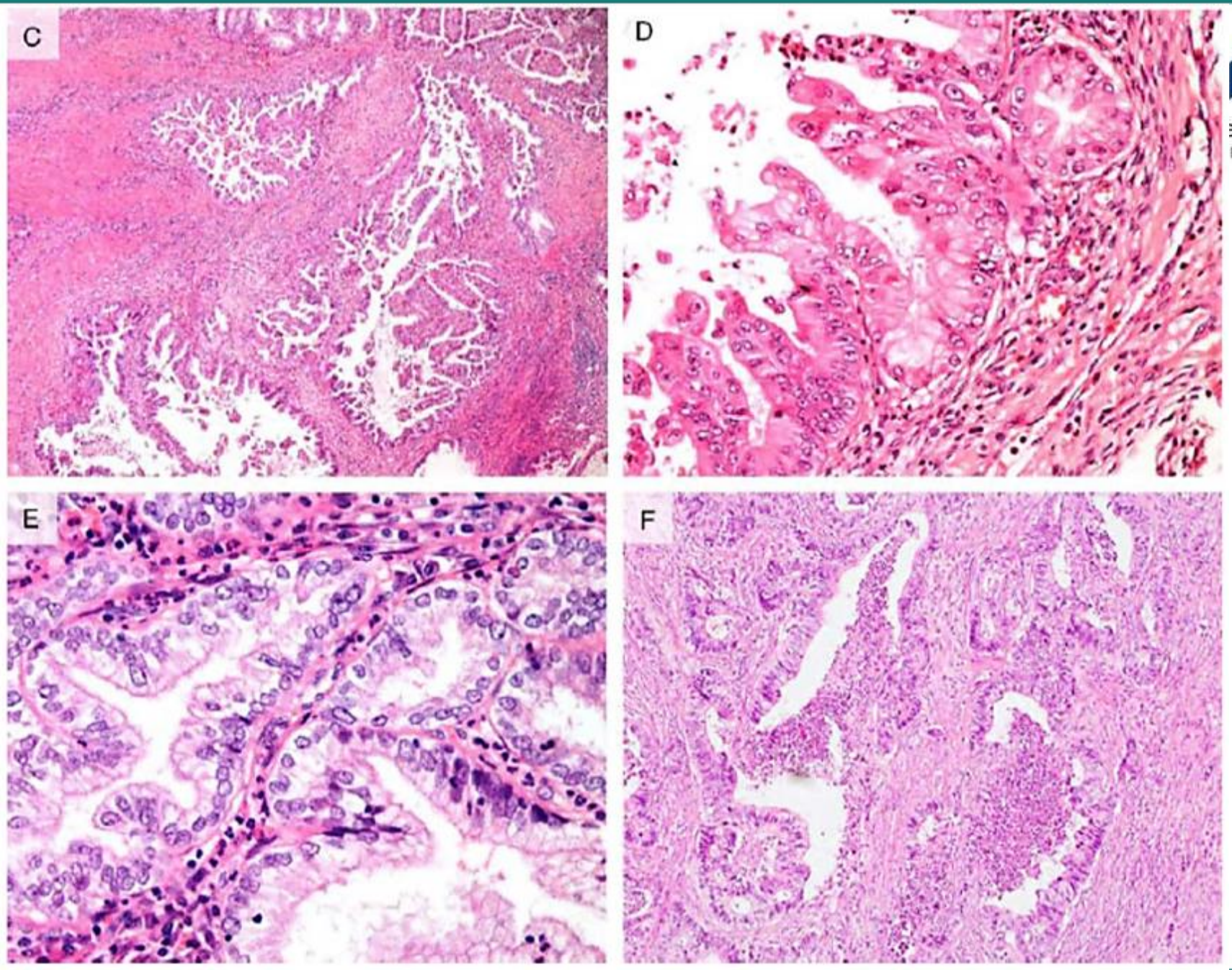
ORIGINAL ARTICLE

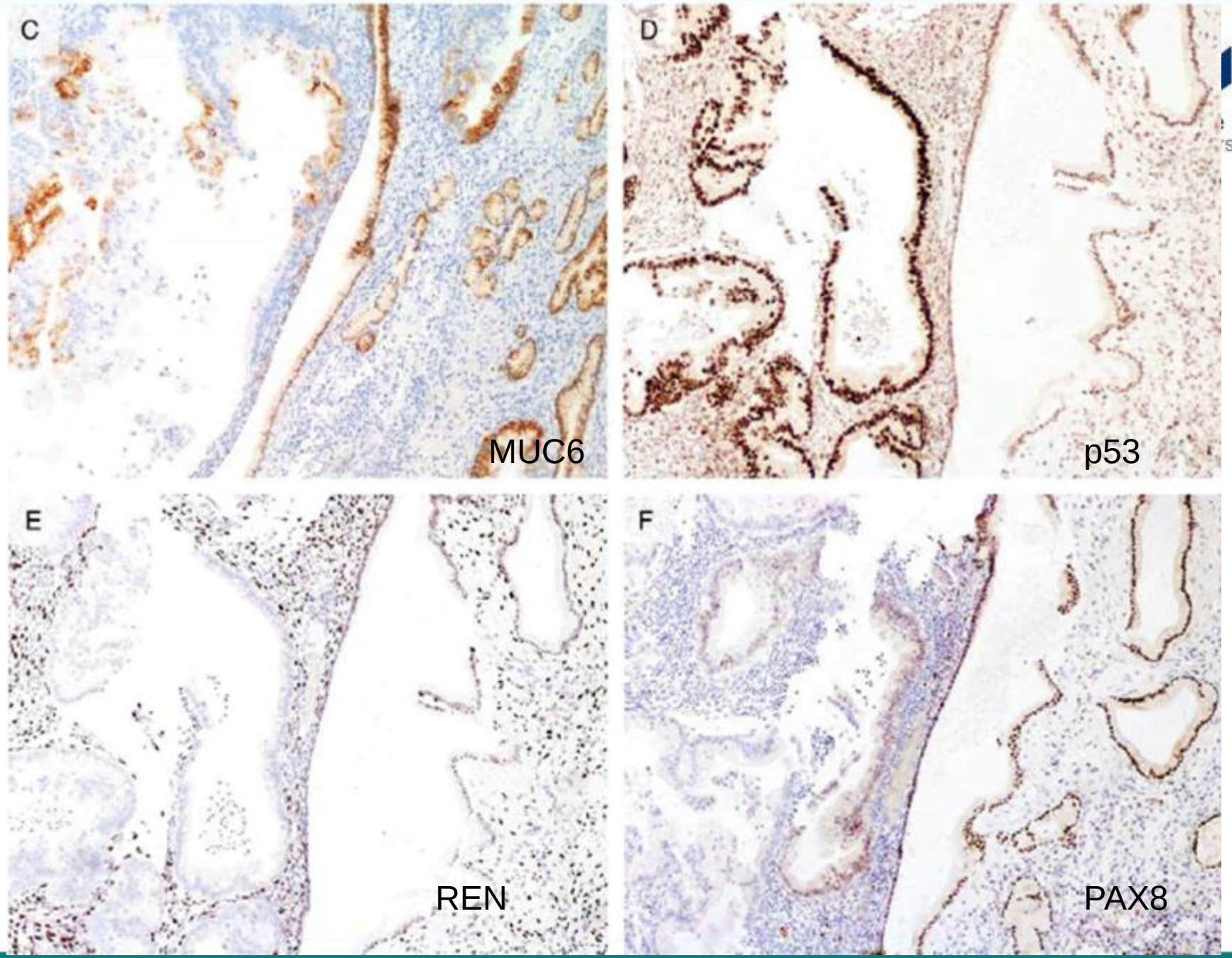
Endometrial Gastric (Gastrointestinal)-type Mucinous Lesions

Report of a Series Illustrating the Spectrum of Benign and Malignant Lesions

Richard Wing-Cheuk Wong, FRCPA, Angela Ralte, FRCPath,† Katherine Grondin, MD, PhD,‡ Karen L. Talia, FRCPA,§ and W. Glenn McCluggage, FRCPath‖*

Am J Surg Pathol 2019





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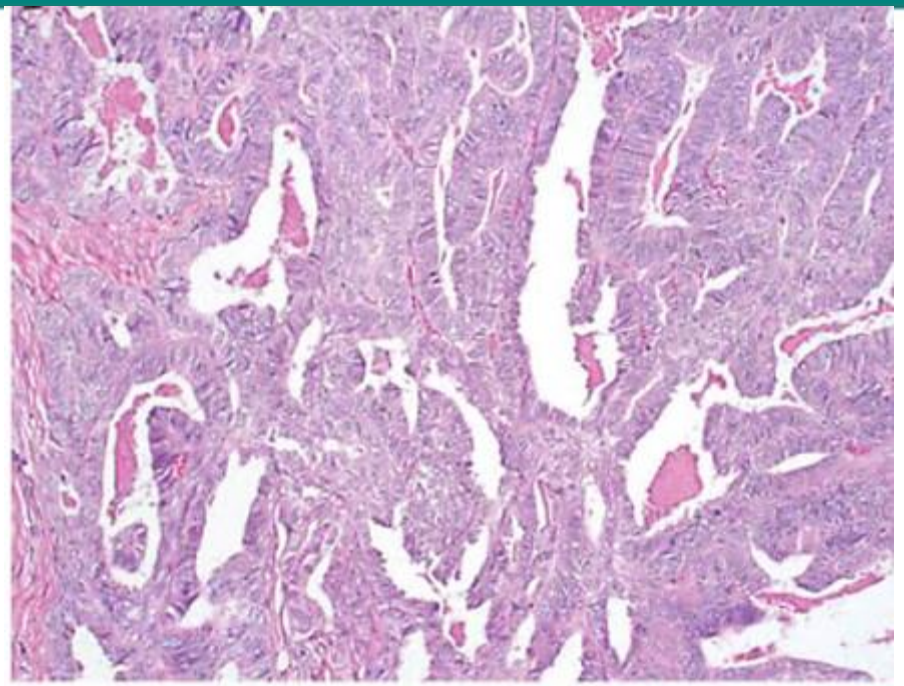
ORIGINAL ARTICLE

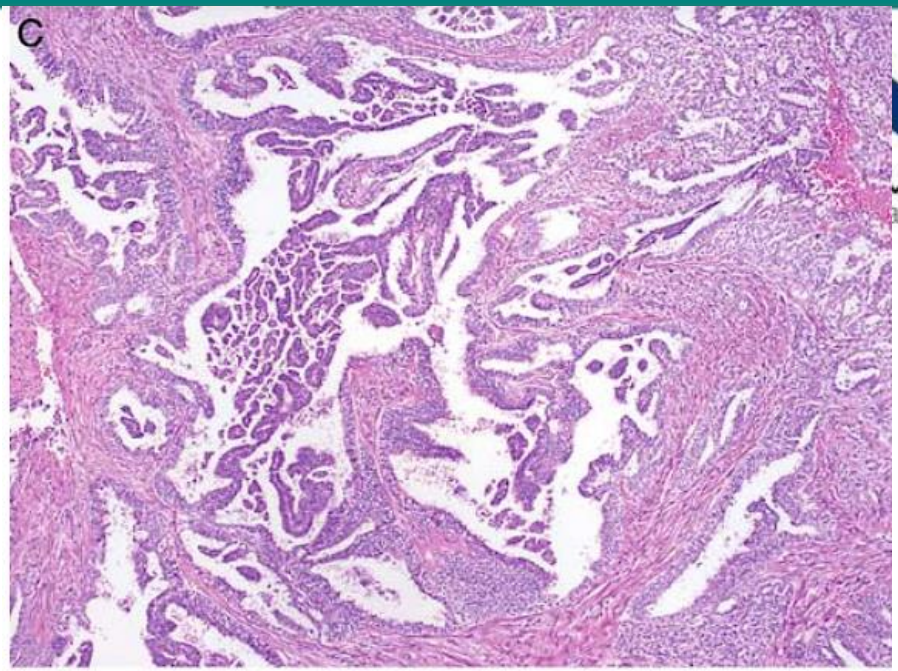
Mesonephric-like Carcinoma of the Endometrium

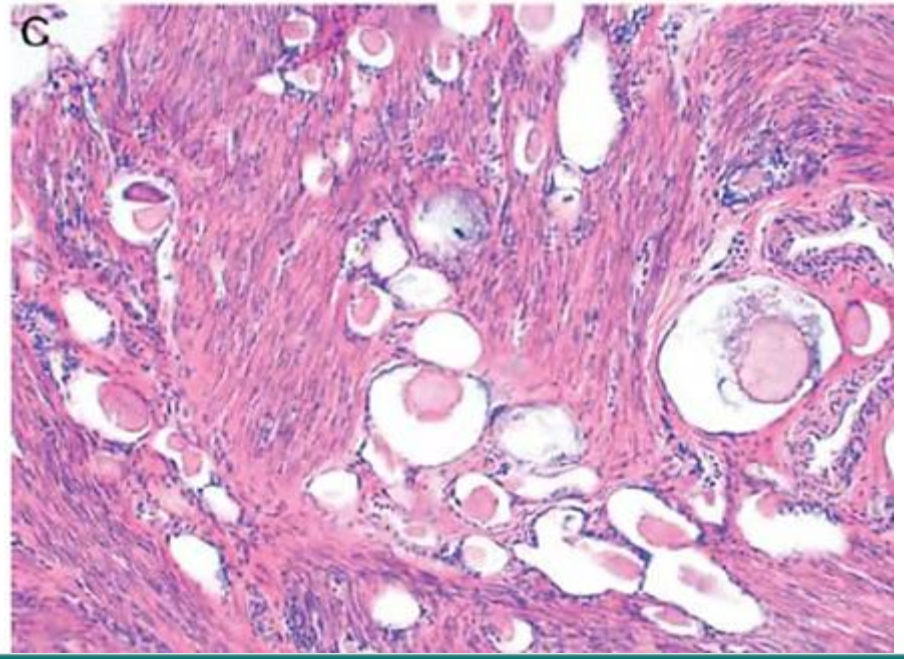
A Subset of Endometrial Carcinoma With an Aggressive Behavior

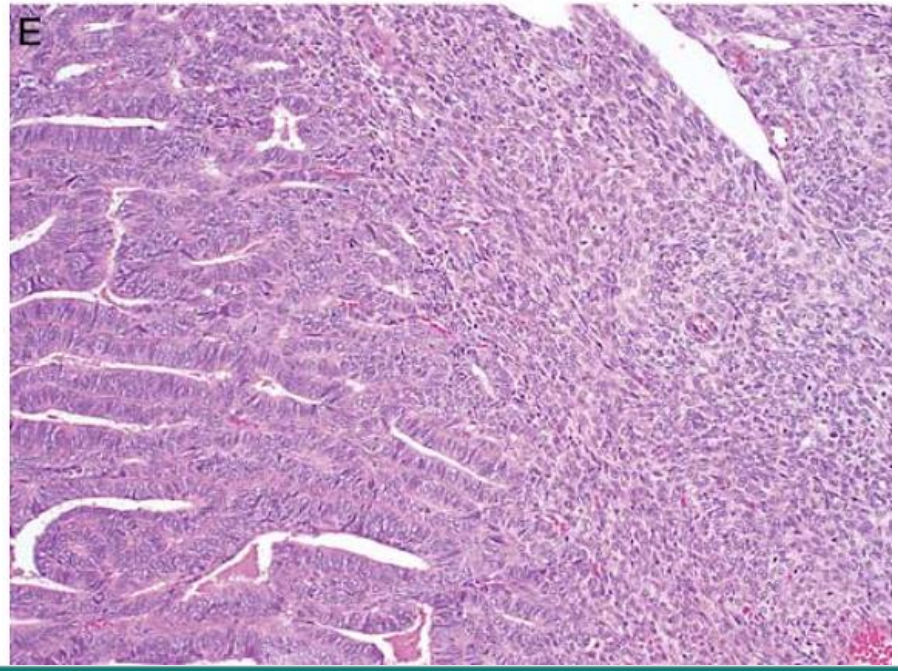
Elizabeth D. Euscher, MD, Roland Bassett,† Dzifa Y. Duose, PhD,* Chieh Lan,* Ignacio Wistuba, MD,* Lois Ramondetta, MD,‡ Preetha Ramalingam, MD,* and Anais Malpica, MD**

Am J Surg Pathol 2019









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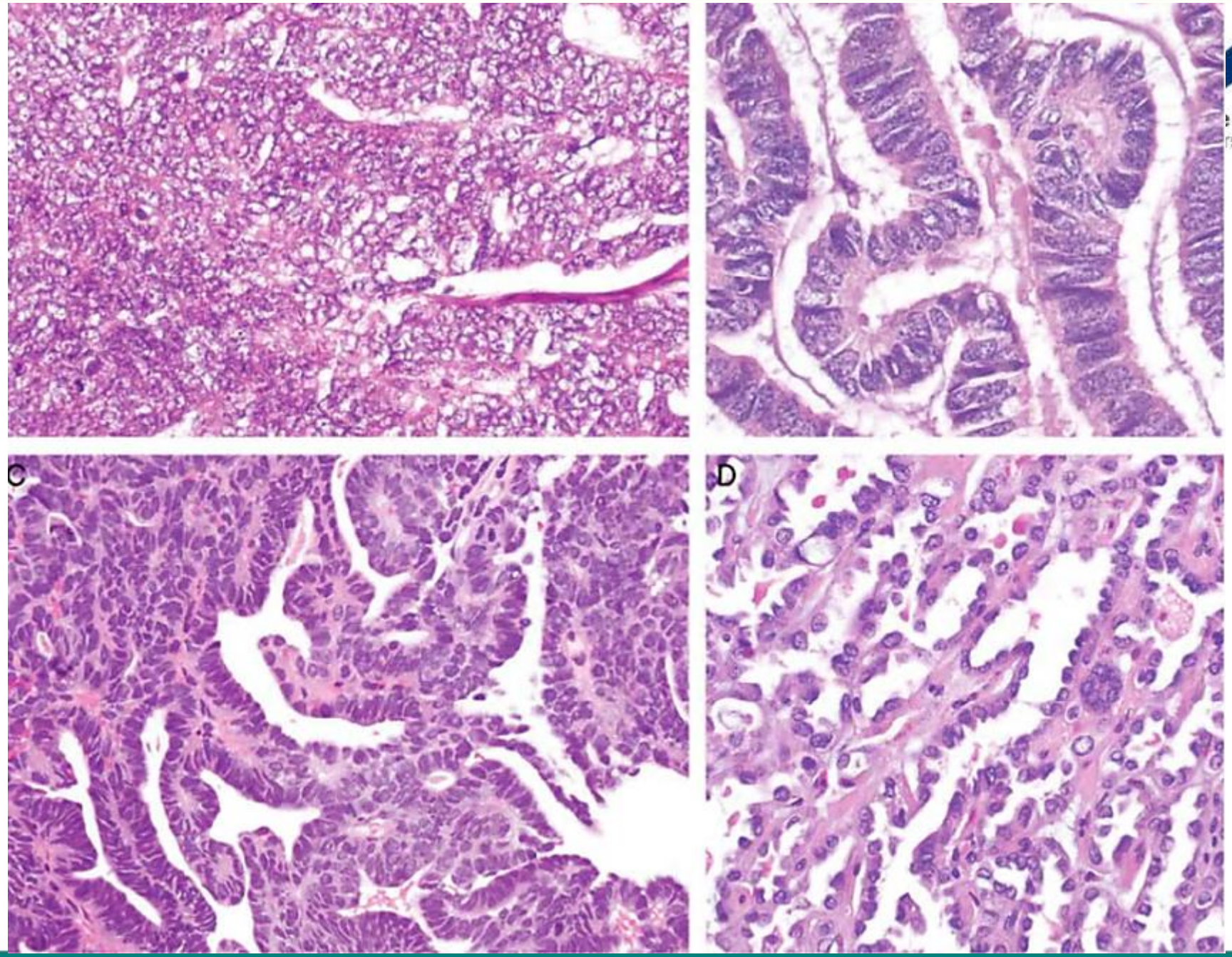

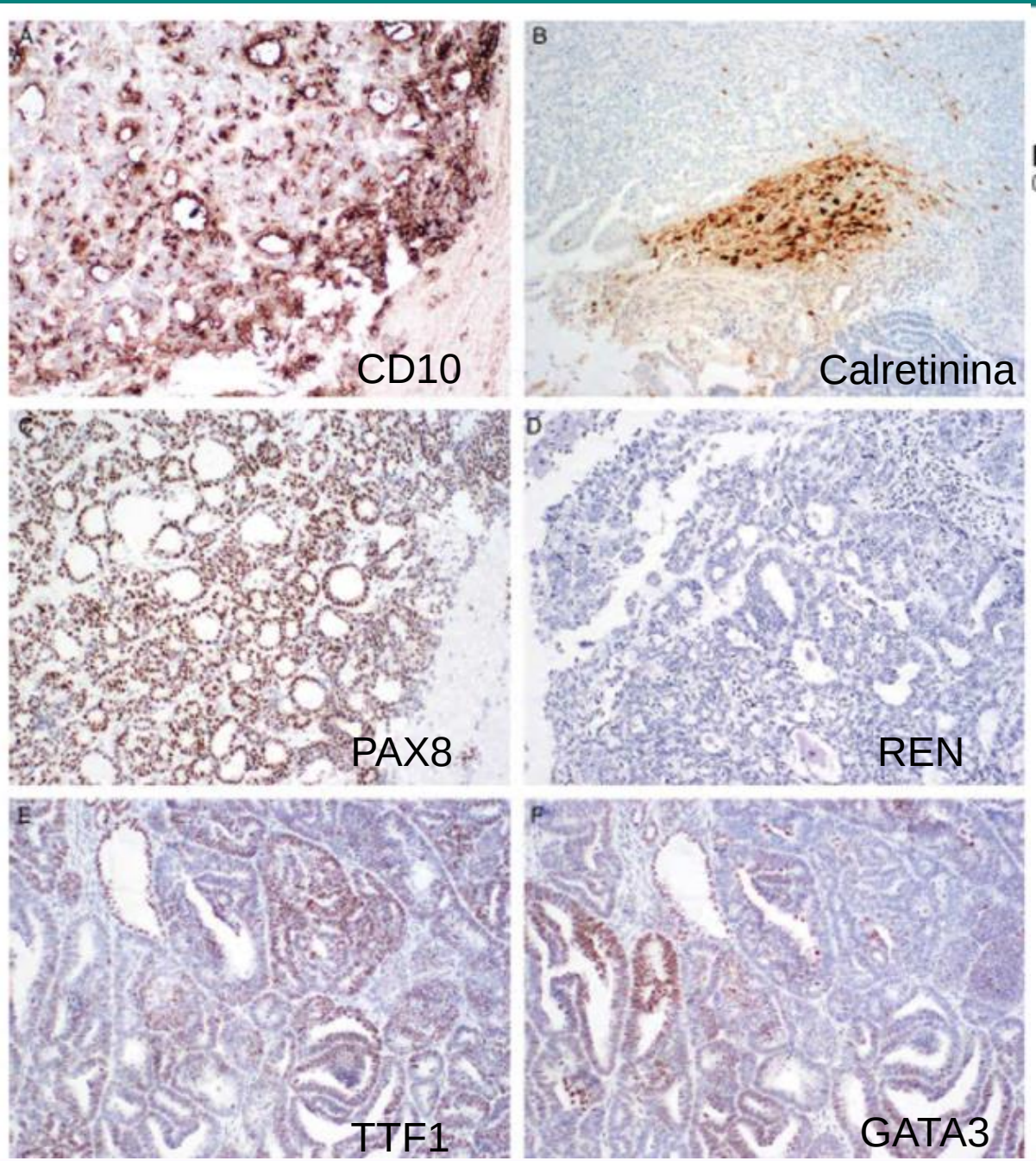

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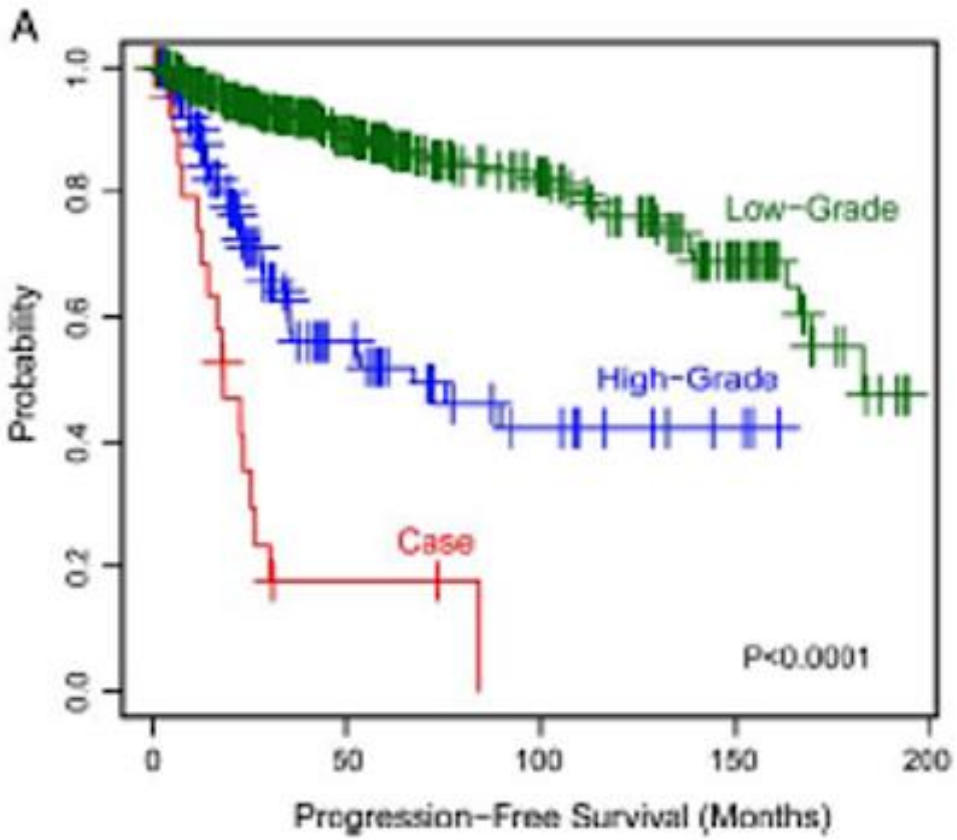
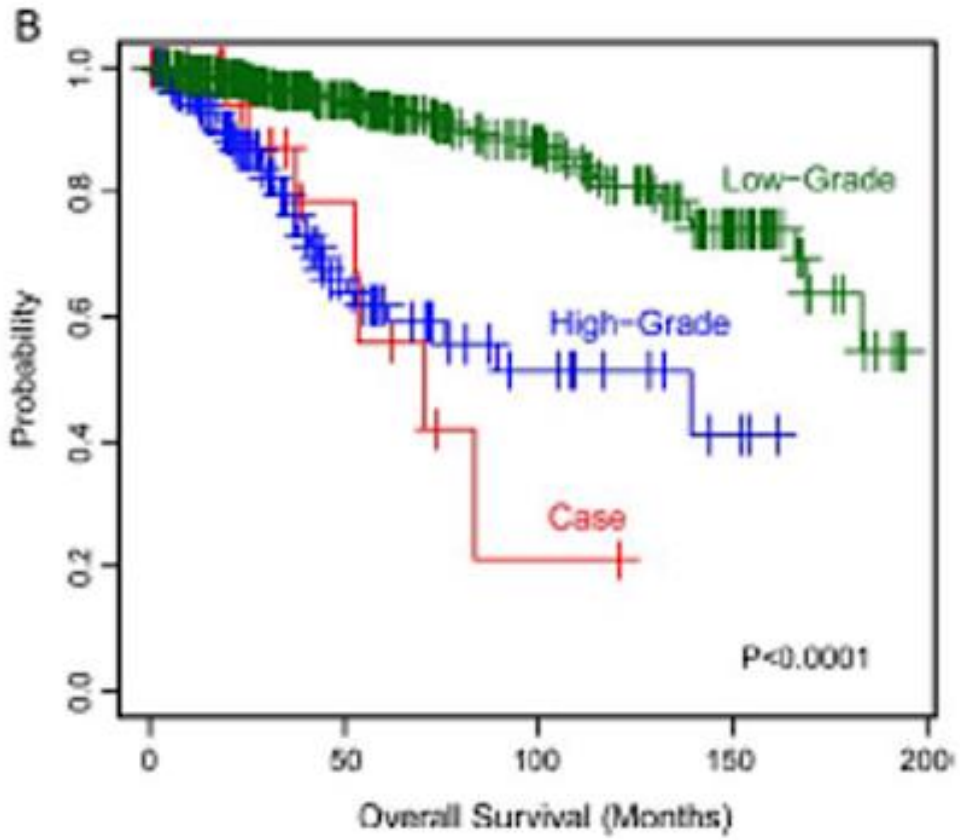

A
Probability
1.0
0.8
0.6
0.4
0.2
0.0
Low-Grade
High-Grade
Case
P<0.0001
0
50
100
150
200
Progression-Free Survival (Months)


B
Probability
1.0
0.8
0.6
0.4
0.2
0.0
Low-Grade
High-Grade
Case
P<0.0001
0
50
100
150
200
Overall Survival (Months)

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Histologic Type (Note B)

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___ Endometrioid carcinoma with squamous differentiation
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WHO 5° edición

Histologic Type (Note C)

___ Endometrioid carcinoma, NOS
  ___ POLE-ultramutated endometrioid carcinoma
  ___ Mismatch repair–deficient endometrioid carcinoma
  ___ p53-mutant endometrioid carcinoma
  ___ No specific molecular profile (NSMP) endometrioid carcinoma
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___ Mucinous carcinoma, intestinal type
___ Clear cell adenocarcinoma, NOS
___ Small cell neuroendocrine carcinoma
___ Large cell neuroendocrine carcinoma
___ Mixed neuroendocrine non-neuroendocrine carcinoma
___ Mixed cell adenocarcinoma (specify types and percentages): _____
___ Dedifferentiated carcinoma
___ Undifferentiated carcinoma, NOS
___ Mesonephric adenocarcinoma
___ Squamous cell carcinoma, NOS
___ Mesonephric-like adenocarcinoma
___ Other histologic type not listed (specify): _____
+Histologic Type Comment: _____

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ARTICLE

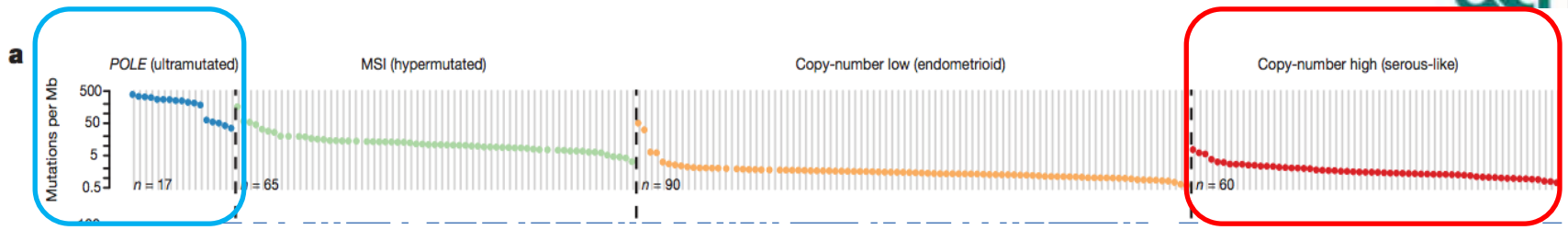
OPEN

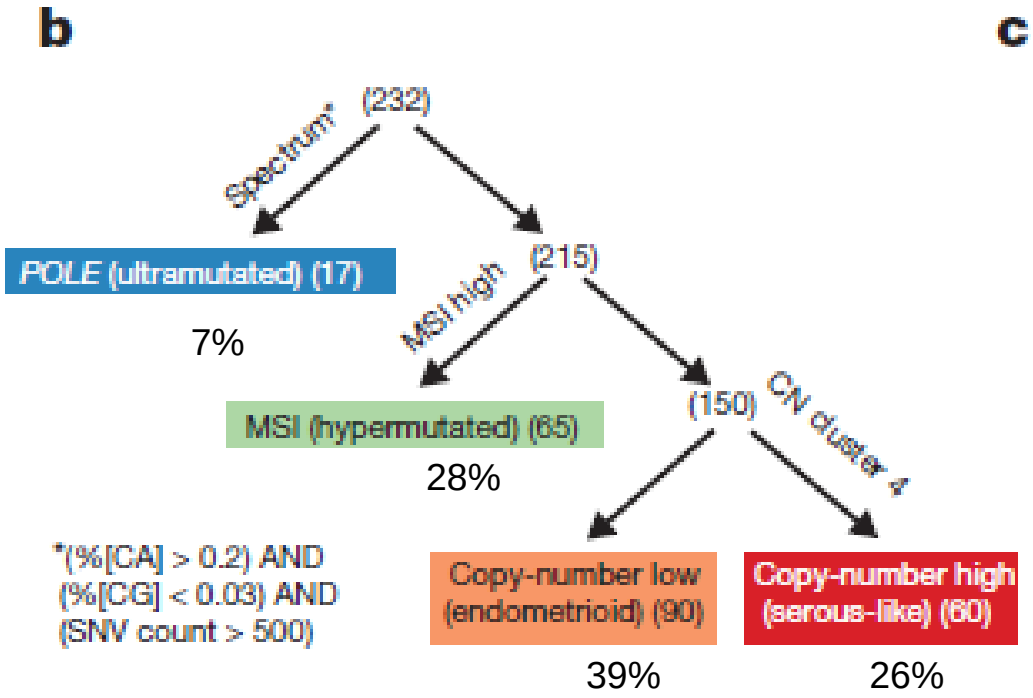
doi:10.1038/nature12113

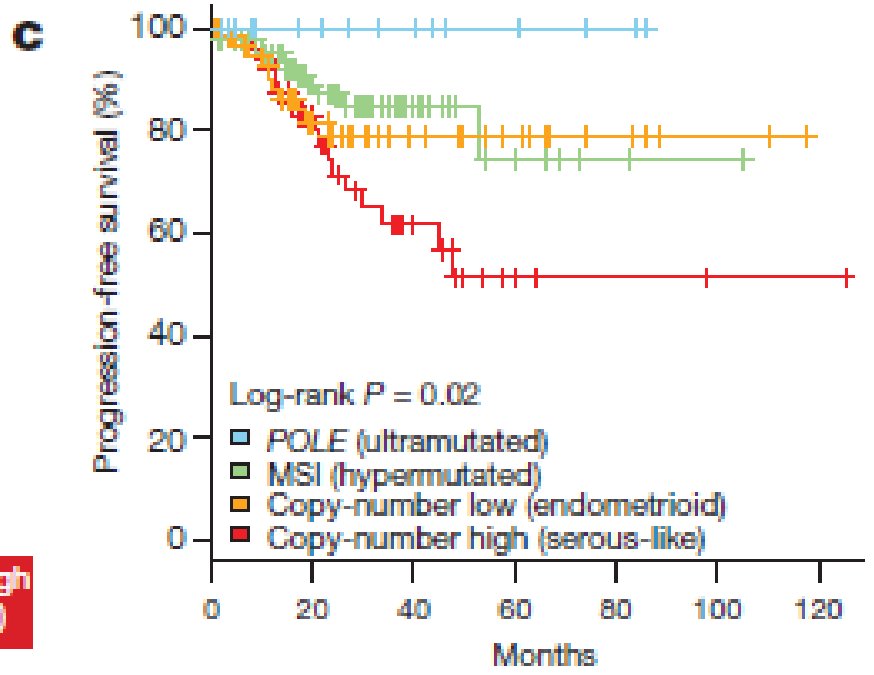
Integrated genomic characterization of endometrial carcinoma

The Cancer Genome Atlas Research Network*

Análisis multiplataforma
Ca endometrioides bajo y alto grado
Ca serosos







Ca. Serosos
25% Ca Endometrioide G3

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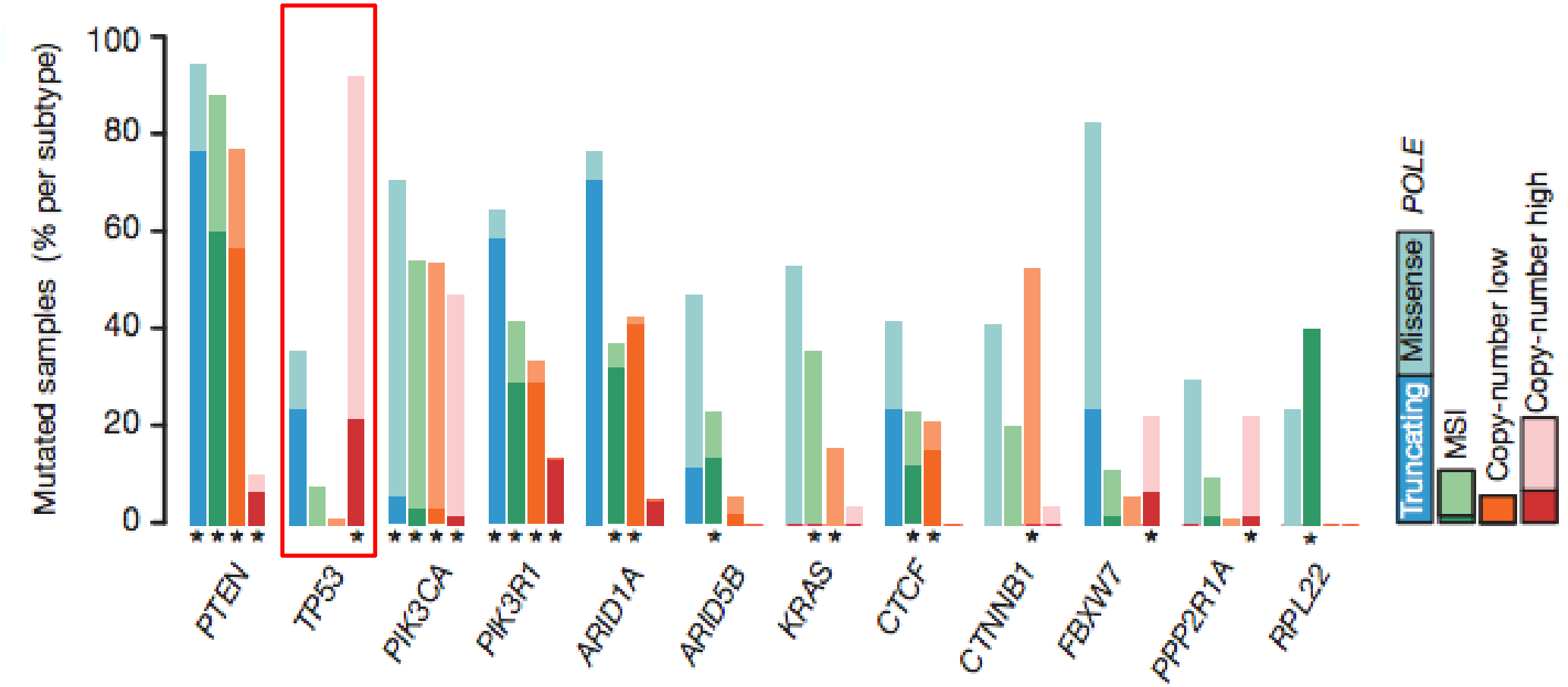

OMS (2021)

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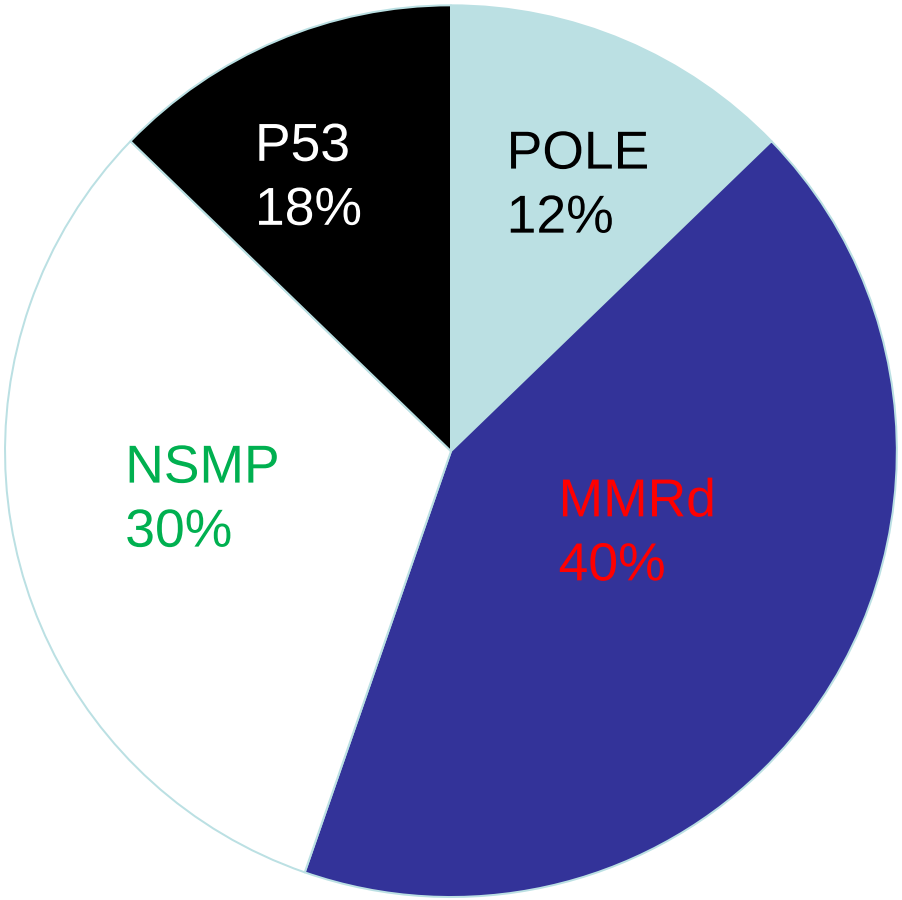

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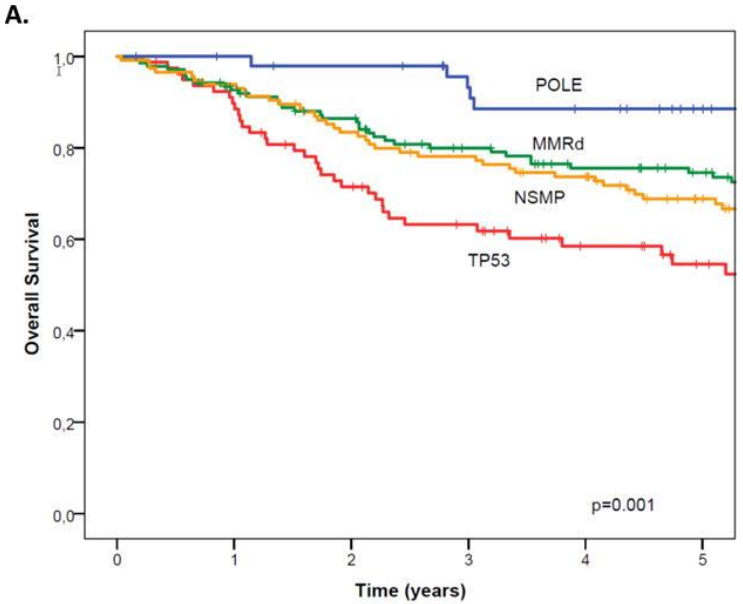
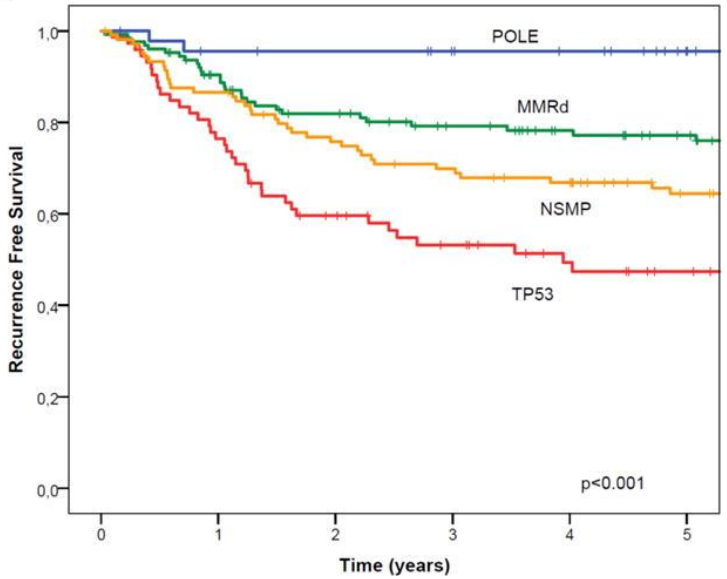
A.



B.



Bosse et al. AJSP 2018

Molecular subtypes of endometrial carcinoma: Molecular, pathologic, and clinical features[1-19]

TCGA category	Molecular classification	Molecular features (diagnostic tests)	Pathology features	Clinical features	Outcomes	Treatment options
***POLE* "ultramutated"** (approximately 7% of TCGA)	***POLE*mut** (approximately 7 to 9% of all ECs)	▪ Markedly high TMB ▪ >100 mut/Mb ▪ SCNA very low ▪ *PTEN* mutations (94%) ▪ (*POLE* EDM or hotspot sequencing)	Commonly high grade, LVSI, aggressive features, "ambiguous morphology" prominent TIL, EEC G3-2-1* but can be any	Presents in younger, often thinner women	Highly favorable (>96% five-year survival)	▪ Observation only may be reasonable, even if high-risk features. Clinical trials are needed to establish safety and efficacy. ▪ Checkpoint inhibitors for rare advanced/recurrent
MSI "hypermutated" (approximately 28% of TCGA)	**MMRd** (26 to 30% of all ECs)	▪ 10 to 100 mut/Mb ▪ SCNA low ▪ *PTEN* (88%), *PIK3CA* (54%), *ARID1A* (37%) mutations ▪ (MMR IHC: PMS2, MSH6, ±MSH2, and MLH1; or MSI assay)	LVSI and higher grade, prominent TIL, MELF, EEC G2/3-1* but can be any	Lynch syndrome association	Intermediate	▪ Radiation ▪ Checkpoint inhibitors if advanced/recurrent
Copy-number low (approximately 39% of TCGA)	**p53wt/NSMP** (45 to 50% of all ECs)	▪ Low TMB (<10 mut/Mb) ▪ SCNA low ▪ *PTEN* (77%), *PIK3CA* (53%), *CTNNB1* (52%), *ARID1A* (42%) mutations ▪ ER+ PR+ ▪ (p53 IHC: wt [normal expression] and absence of *POLE*mut or MMRd)	Squamous differentiation, low TIL, mostly low-grade EEC G1-2-3*	Often presents in younger individuals with higher BMI or exogenous estrogen	Intermediate-favorable	▪ Hormonal therapy ▪ PI3K/mTOR inhibitors?
Copy-number high (approximately 26% of TCGA)	**p53abn** (13 to 18% of all ECs)	▪ Low TMB (<10 mut/Mb) ▪ SCNA high ▪ *PIK3CA* (47%), *PPP2R1A* (22%), *FBXW7* (22%) mutations ▪ (p53 IHC: abnormal or *TP53* mutation)	LVSI, high cytonuclear atypia, mostly high grade, mostly serous but approximately 25% EEC G3	Presents in older, thinner, women; commonly advanced stage	Poor (approximately 50% five-year survival)	▪ Chemotherapy ▪ *HER2*-targeted or *HRD*-targeted therapy?

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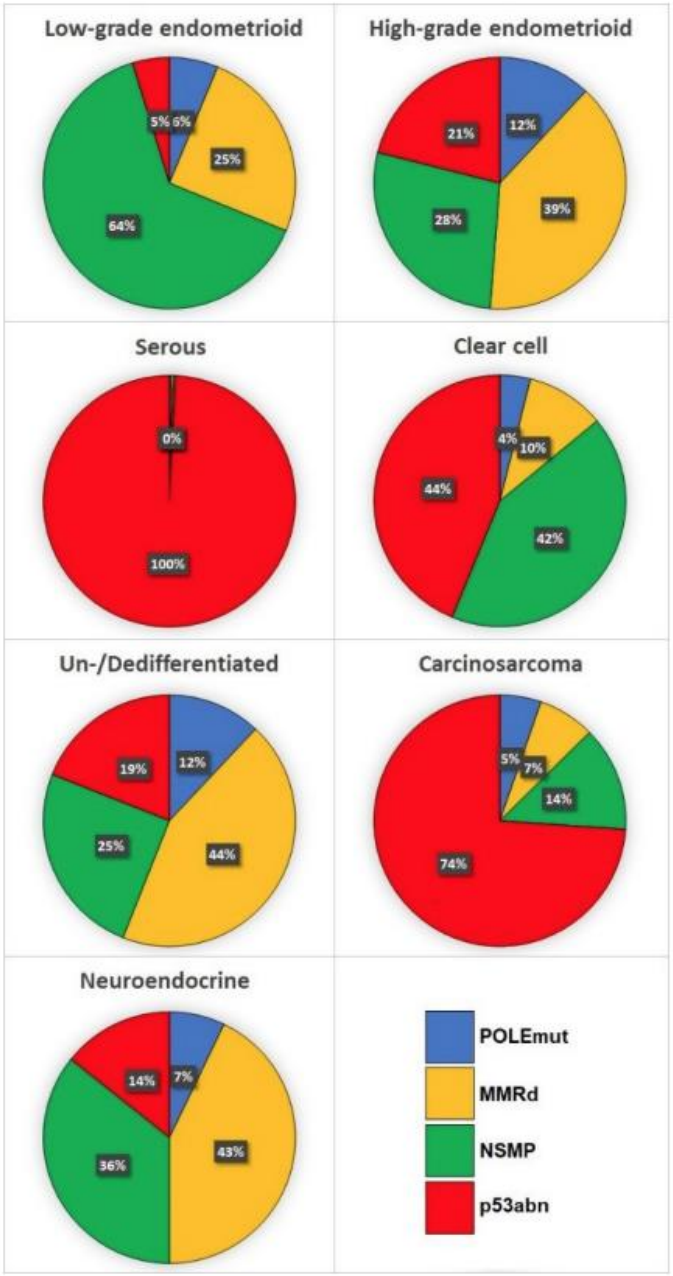

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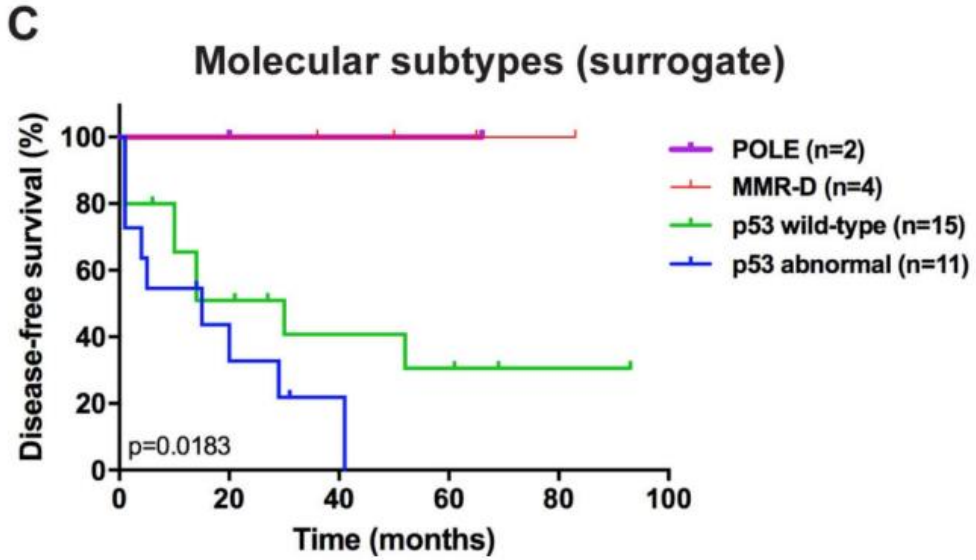
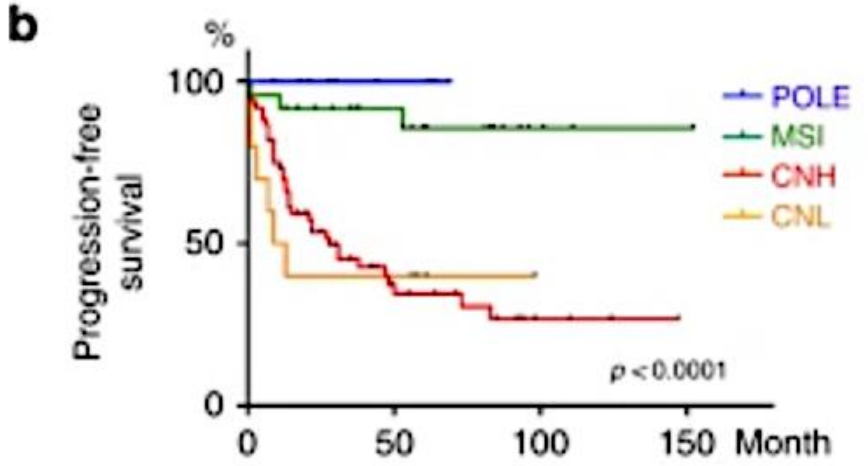
A. Santoro et al. Cancers 2021



Carcinoma de células claras
Delair et al. J Pathol 2017



Carcinosarcoma
Gotoh et al. Nature Comm 2019

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¿Cómo hacer una clasificación molecular más accesible para cáncer de endometrio?

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FULL PAPER

BJC

British Journal of Cancer (2015) 113, 299–310 | doi: 10.1038/bjc.2015.190

Keywords: endometrial cancer; mismatch repair; risk stratification; prognostic; *POLE*; molecular classification; p53

A clinically applicable molecular-based classification for endometrial cancers

A Talhouk[1], M K McConechy[1], S Leung[2], H H Li-Chang[1,3], J S Kwon[4], N Melnyk[1], W Yang[1], J Senz[1], N Boyd[1], A N Karnezis[1], D G Huntsman[1], C B Gilks[1] and J N McAlpine[*,4]

"PROMISE"

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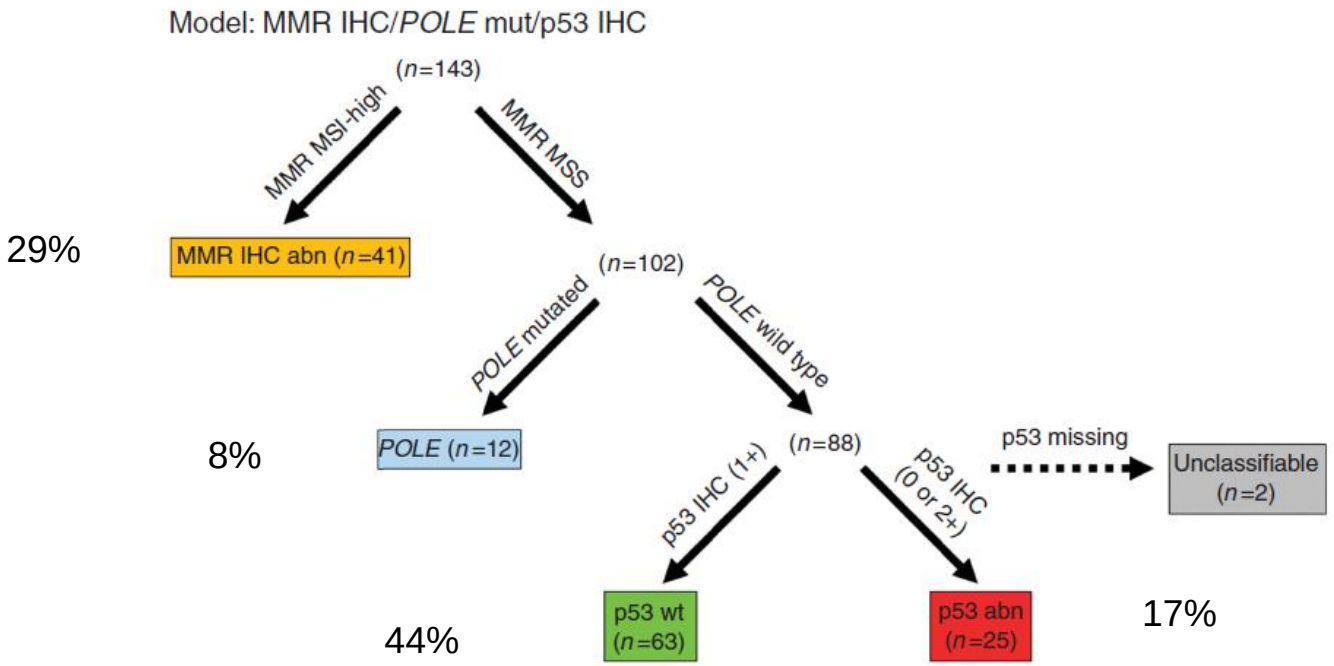

29%

8%

44%

17%

Figure 3. Favoured pragmatic model for molecular classification of endometrial cancers (Model 8 in Figures 1 and 2). Selection was based on survival analyses, C-index, anticipated clinical benefit in order of testing, and cost and accessibility of methods.

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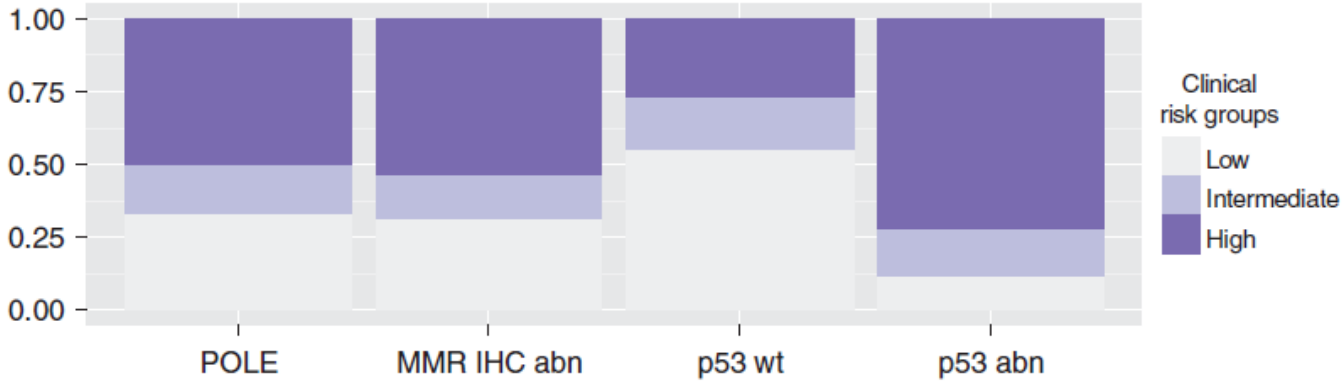
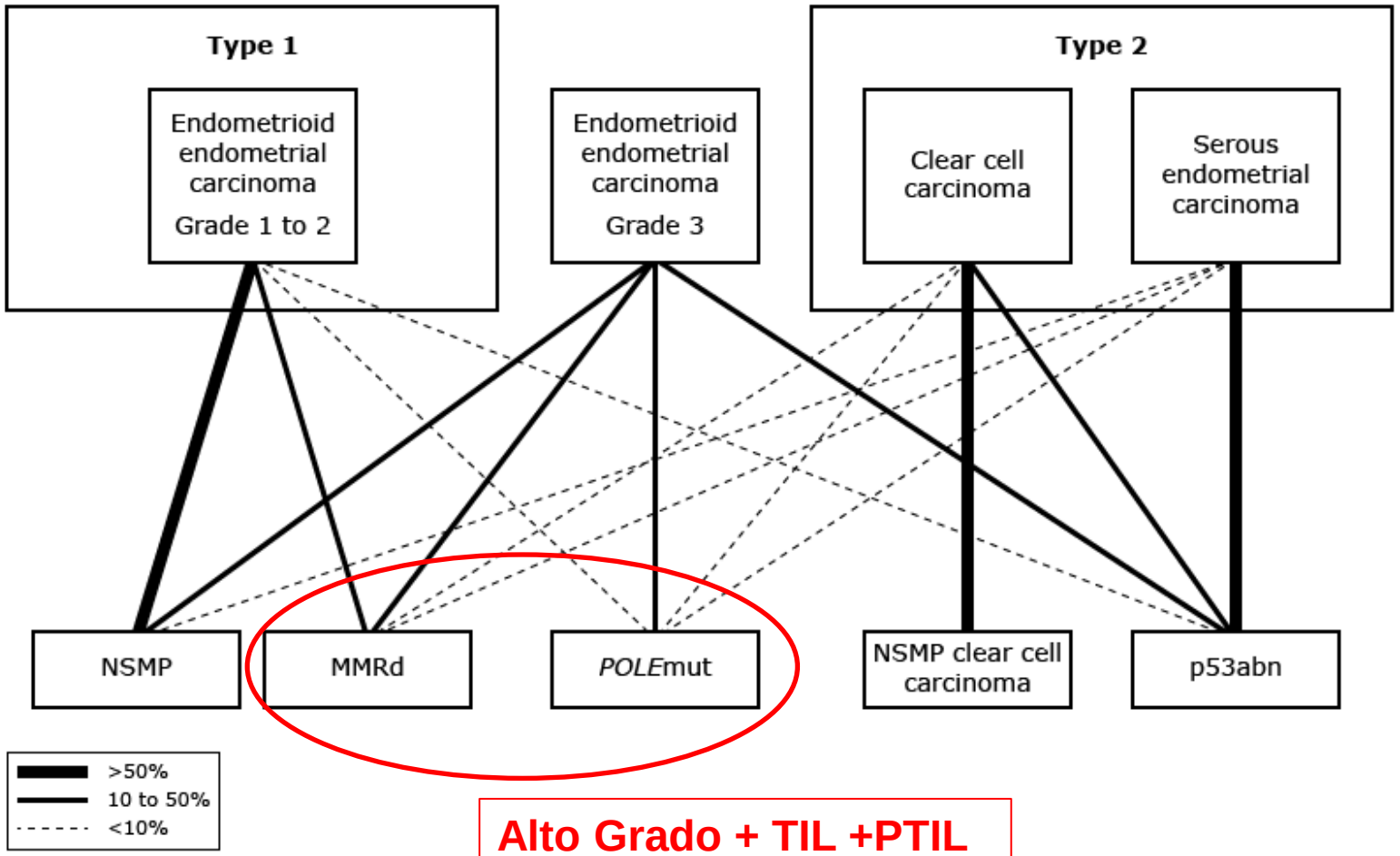


- Tipo histológico
- Grado
- Estadío

Figure 4. Cross-tabulation of clinicopathologic risk groups (ESMO) with molecular classification by proposed model: MMR IHC/*POLE* mut/p53

Type 1 and 2 classification and relationship to histomorphologic and molecular endometrial carcinoma classification



Alto Grado + TIL +PTIL

- En material de legrado / Pipelle / quirúrgico

- Mutación en POLE
- Inmunohistoquímica de MMR / MSI PCR
- Inmunohistoquímica de p53

- Algoritmos

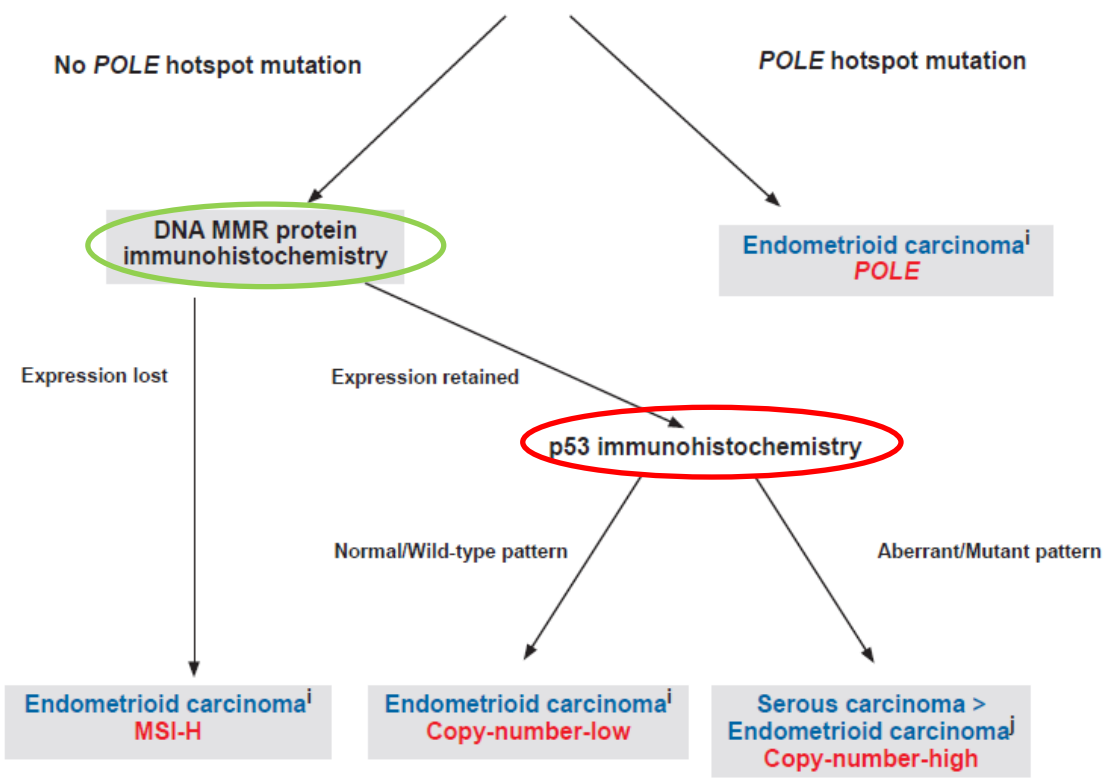
National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2021
Endometrial Carcinoma
NCCN Evidence Blocks™

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF MOLECULAR ANALYSIS

FIGURE 1: PATHOLOGY AND GENOMICS IN ENDOMETRIAL CARCINOMA[f,g]



[f]Adapted with permission from Murali R, Delair DF, Bean SM, et al. Evolving roles of histologic evaluation and molecular/genomic profiling in the management of endometrial cancer. J Nat Compr Canc Netw 2018;16:201-209.
[g]Diagnostic algorithm for integrated genomic-pathologic classification of endometrial carcinomas (blue represents histotype; red represents TCGA genomic class).
[h]*POLE* sequencing made by mutational analysis may not be available at all institutions.
[i]May also apply to clear cell carcinomas.
[j]This algorithm does not distinguish between high-grade tumors that cannot otherwise be classified (ie, high-grade carcinoma, serous carcinoma, clear cell carcinoma).

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¿Cuándo hacerla?

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Joint statement

ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma

Nicole Concin ,[1,2] Xavier Matias-Guiu,[3,4] Ignace Vergote,[5] David Cibula,[6] Mansoor Raza Mirza,[7] Simone Marnitz,[8] Jonathan Ledermann ,[9] Tjalling Bosse,[10] Cyrus Chargari,[11] Anna Fagotti,[12] Christina Fotopoulou ,[13] Antonio Gonzalez Martin,[14] Sigurd Lax,[15,16] Domenica Lorusso,[12] Christian Marth,[17] Philippe Morice,[18] Remi A Nout,[19] Dearbhaile O'Donnell,[20] Denis Querleu ,[12,21] Maria Rosaria Raspollini,[22] Jalid Sehouli,[23] Alina Sturdza,[24] Alexandra Taylor,[25] Anneke Westermann,[26] Pauline Wimberger,[27] Nicoletta Colombo,[28] François Planchamp,[29] Carien L Creutzberg[30]

Int J Gynecol Cancer: first published as 10.

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- En todos los cánceres de endometrio
  (con recursos)

- En carcinomas endometrioides de alto grado/alto riesgo
  (con recursos limitados)

- Evaluar POLE, MSI, p53

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Journal of Pathology
J Pathol 2020; **250:** 312–322
Published online 12 January 2020 in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/path.5373

ORIGINAL PAPER

Clinicopathological and molecular characterisation of 'multiple-classifier' endometrial carcinomas

Alicia León-Castillo[1], Ester Gilvazquez[2,3], Remi Nout[4], Vincent THBM Smit[1], Jessica N McAlpine[5], Melissa McConechy[6], Stefan Kommoss[7], Sara Y Brucker[7], Joseph W Carlson[8], Elisabeth Epstein[9], Tilman T Rau[10], Robert A Soslow[11], Raji Ganesan[12], Xavier Matias-Guiu[13], Esther Oliva[14], Beth T Harrison[15], David N Church[2,3], C Blake Gilks[16] and Tjalling Bosse[1]*

Multiple-classifier endometrial carcinoma

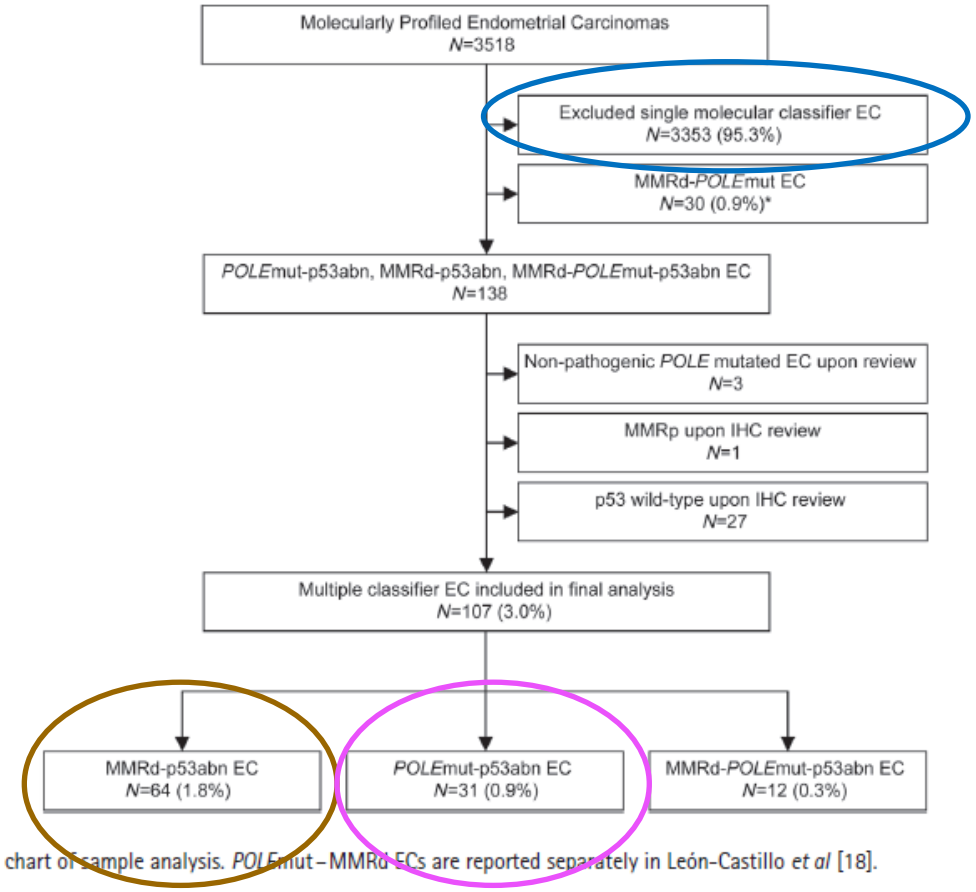
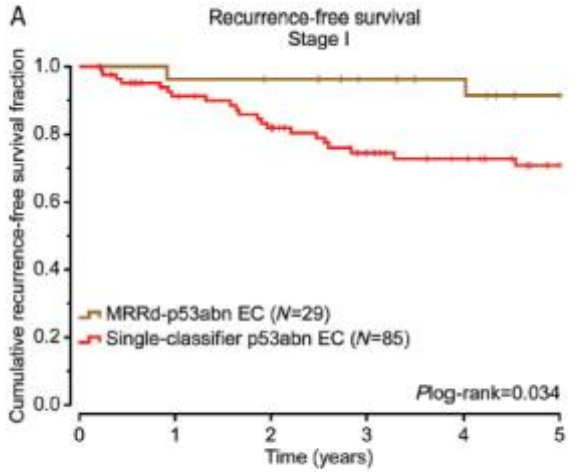
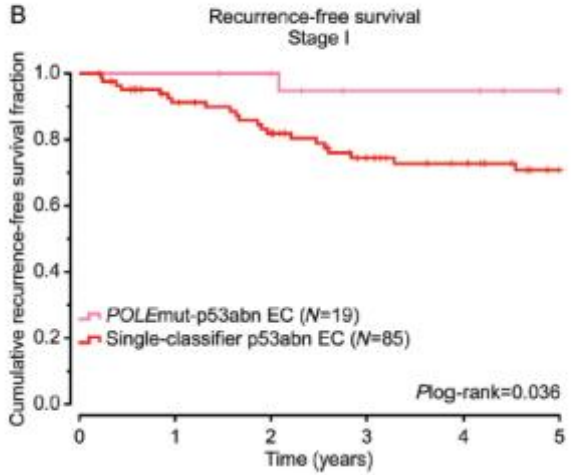


Figure 1. Flow chart of sample analysis. *POLE*mut–MMRd ECs are reported separately in León-Castillo *et al* [18].





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Integrar información histopatológica y molecular

Table 2 Definition of prognostic risk groups

Risk group	Molecular classification unknown	Molecular classification known*†
Low	► Stage IA endometrioid + low-grade‡ + LVSI negative or focal	► Stage I–II ***POLEmut*** endometrial carcinoma, no residual disease ► Stage IA **MMRd/NSMP** endometrioid carcinoma + low-grade‡ + LVSI negative or focal
Intermediate	► Stage IB endometrioid + low-grade‡ + LVSI negative or focal ► Stage IA endometrioid + high-grade‡ + LVSI negative or focal ► Stage IA non-endometrioid (serous, clear cell, undifferentiared carcinoma, carcinosarcoma, mixed) without myometrial invasion	► Stage IB **MMRd/NSMP** endometrioid carcinoma + low-grade‡ + LVSI negative or focal ► Stage IA **MMRd/NSMP** endometrioid carcinoma + high-grade‡ + LVSI negative or focal ► Stage IA **p53abn** and/or non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) without myometrial invasion
High–intermediate	► Stage I endometrioid + substantial LVSI regardless of grade and depth of invasion ► Stage IB endometrioid high-grade‡ regardless of LVSI status ► Stage II	► Stage I **MMRd/NSMP** endometrioid carcinoma + substantial LVSI regardless of grade and depth of invasion ► Stage IB **MMRd/NSMP** endometrioid carcinoma high-grade‡ regardless of LVSI status ► Stage II **MMRd/NSMP** endometrioid carcinoma
High	► Stage III–IVA with no residual disease ► Stage I–IVA non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) with myometrial invasion, and with no residual disease	► Stage III–IVA **MMRd/NSMP** endometrioid carcinoma with no residual disease ► Stage I–IVA **p53abn** endometrial carcinoma with myometrial invasion, with no residual disease ► Stage I–IVA **NSMP/MMRd** serous, undifferentiated carcinoma, carcinosarcoma with myometrial invasion, with no residual disease
Advanced metastatic	► Stage III–IVA with residual disease ► Stage IVB	► Stage III–IVA with residual disease of any molecular type ► Stage IVB of any molecular type

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Técnicas disponibles en CAS

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Panel ONCO-161

- Estudio de mutaciones en sectores "hotspots" de genes (detalle en primera columna).
- Estudio de mutaciones en genes completos (detalle en segunda columna).
- Estudio de alteraciones en el número de copias de genes (detalle en tercera columna).
- Estudio de fusiones de genes (detalle en cuarta columna).

Hotspot genes				Full-length genes			Copy number genes		Gene fusions (inter- and intragenic)		
AKT1	ESR1	KIT	PDGFRB	ARID1A	FBXW7	PTEN	AKT1	FGFR4	AKT2	FGFR2	NUTM1
AKT2	EZH2	KNSTRN	PIK3CB	ATM	MLH1	RAD50	AKT2	FLT3	ALK	FGFR3	PDGFRA
AKT3	FGFR1	KRAS	PIK3CA	ATR	MRE11	RAD51	AKT3	IGF1R	AR	FGR	PDGFRB
ALK	FGFR2	MAGOH	PPP2R1A	ATRX	MSH6	RAD51B	ALK	KIT	AXL	FLT3	PIK3CA
AR	FGFR3	MAP2K1	PTPN11	BAP1	MSH2	RAD51C	AXL	KRAS	BRCA1	JAK2	PRKACA
ARAF	FGFR4	MAP2K2	RAC1	BRCA1	NBN	RAD51D	AR	MDM2	BRCA2	KRAS	PRKACB
AXL	FLT3	MAP2K4	RAF1	BRCA2	NF1	RNF43	BRAF	MDM4	BRAF	MDM4	PTEN
BRAF	FOXL2	MAPK1	RET	CDK12	NF2	RB1	CCND1	MET	CDKN2A	MET	PPARG
BTK	GATA2	MAX	RHEB	CDKN1B	NOTCH1	SETD2	CCND2	MYC	EGFR	MYB	RAD51B
CBL	GNA11	MDM4	RHOA	CDKN2A	NOTCH2	SLX4	CCND3	MYCL	ERBB2	MYBL1	RAF1
CCND1	GNAQ	MED12	ROS1	CDKN2B	NOTCH3	SMARCA4	CCNE1	MYCN	ERBB4	NF1	RB1
CDK4	GNAS	MET	SF3B1	CHEK1	PALB2	SMARCB1	CDK2	NTRK1	ERG	NOTCH1	RELA
CDK6	H3F3A	MTOR	SMAD4	CREBBP	PIK3R1	STK11	CDK4	NTRK2	ESR1	NOTCH4	RET
CHEK2	HIST1H3B	MYC	SMO	FANCA	PMS2	TP53	CDK6	NTRK3	ETV1	NRG1	ROS1
CSF1R	HNF1A	MYCN	SPOP	FANCD2	POLE	TSC1	EGFR	PDGFRA	ETV4	NTRK1	RSPO2
CTNNB1	HRAS	MYD88	SRC	FANCI	PTCH1	TSC2	ERBB2	PDGFRB	ETV5	NTRK2	RSPO3
DDR2	IDH1	NFE2L2	STAT3				ESR1	PIK3CB	FGFR1	NTRK3	TERT
EGFR	IDH2	NRAS	TERT				FGF19	PIK3CA			
ERBB2	JAK1	NTRK1	TOP1				FGF3	PPARG			
ERBB3	JAK2	NTRK2	U2AF1				FGFR1	RICTOR			
ERBB4	JAK3	NTRK3	XPO1				FGFR2	TERT			
ERCC2	KDR	PDGFRA					FGFR3				

Panel ONCO-161-IO

- Mismo estudio de alteraciones que el panel ONCO-161 y adicionalmente:
- Análisis de Inestabilidad microsatelital por PCR.
- Análisis de la expresión de PD-L1 por IHQ.

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Determinación de mutaciones del gen POLE

	Onco-161 (POLE secuencia completa)	Panel NGS hotspot (POLE exones 9-14)	Secuenciación Sanger POLE (exones 9-14)
Factibilidad Técnica	En uso clínico	Factible	Factible
Estado de validación	Validado	No validado	No validado
Ventajas	Información genómica altamente detallada (cobertura completa), requiere poco material, puede ser solicitado hoy en CAS	Información detallada a nivel de hotspot mutacional, capacidad de multiplex, requiere poco material	Bajo costo **($0,7 M)**, fácil de implementar (sin considerar la validación)
Desventajas	Alto costo **(1,5 a $3,4 M)**	Costo intermedio **($1,5 M)**	Requiere mayor cantidad de material

ONCO 161 CAS	Diagnóstico	Estadio FIGO	Grupo de riesgo histológico	Onco-161	Grupo de riesgo histomolecular
1	Ca. Seroso LVSI +	IIIC	Alto	Mut. P53 Amp. CCNE1 Del. PIK3	Alto
2 *	Ca. Endometrioide G3 + morfología ambigua LVSI (e)	IB	Intermedio-alto	Mut. P53 Mut. MSH2 Mut. MSH6 Mut. HER2 Mut. PIK3CA Del. PTEN	Intermedio-alto
3	Ca. Endometrioide G3 con TIL LVSI -	IA	Intermedio	Mut. POLE Mut. PIK3CA Mut. PTEN Mut. ARID1A Mut. BRCA2	Bajo
4	Ca. Endometrioide G3 LVSI – P53+	IA	Intermedio	Múltiples mut. Subclonales Mut. PIK3CA Mut. PTEN (NSMP)	Intermedio
5	Ca. Endometrioide G3 con morfología ambigua LVSI – P53+	IA	Intermedio	Mut. P53 Mut. KRAS	Intermedio
6	Ca Desdiferenciado	NA	Alto	Mut. PTEN Mut PIK3C Mut MSH6	Alto

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Caso 2

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ESTUDIO DE MUTACIONES PANEL CAS-ONCO161 B20-00879 DE LA MUESTRA H20-11307

Diagnóstico:

ALTERACIONES DETECTADAS (por orden de frecuencia):

-MUTACIÓN R273C EN GEN TP53 (Frecuencia: 32%; c.817C>T; p.Arg273Cys; rs121913343).
-MUTACIÓN G628* EN GEN MSH2 (Frecuencia: 30%; c.1882G>T; p.Gly628Ter; rs371776176).
-MUTACIÓN T306M EN GEN HER2 (Frecuencia: 28%; c.917C>T; p.Thr306Met).
-MUTACIÓN V344M EN GEN PIK3CA (Frecuencia: 27%; c.1030G>A; p.Val344Met; rs1057519942).
-DELECIÓN T319* EN GEN PTEN (Frecuencia: 26%; c.955_958delACTT; p.Thr319Ter; rs868257011).
-MUTACIÓN N671I EN GEN MSH2 (Frecuencia: 25%; c.2012A>T; p.Asn671Ile).
-MUTACIÓN T1284M EN GEN MSH6 (Frecuencia: 23%; c.3851C>T; p.Thr1284Met; rs63750836).
-MUTACIÓN S947G EN GEN PDGFRA (Frecuencia: 23%; c.2839A>G; p.Ser947Gly).
-MUTACIÓN R18H EN GEN RAD51B (Frecuencia: 20%; c.53G>A; p.Arg18His; rs768576952).
-MUTACIÓN C420R EN GEN PIK3CA (Frecuencia: 19%; c.1258T>C; p.Cys420Arg; rs121913272).
-MUTACIÓN S436L EN GEN ATR (Frecuencia: 16%; c.1307C>T; p.Ser436Leu; rs760248783).
-FUSIÓN DE GENES EIF3E-RSPO2

COMENTARIO: Los hallazgos genómicos sugieren un patrón de alteración de la reparación del ADN consistente con inestabilidad microsatelital. Las alteraciones detectadas en múltiples genes presentan probable o posible efecto deletéreo. Se identificó además las variantes R75W en NOTCH3, K416del en MYCN, R714W en FANCA, M1848T en BRCA1, R1335* en ARID1A y P986fs en FLT3 que presentan una frecuencia alélica menor a 10%. La muestra presenta una baja proporción estimada de células tumorales (~25%) lo que podría disminuir la sensibilidad del test. Este examen no permite distinguir entre variantes genéticas somáticas y germinales por lo que se recomienda evaluación de ADN no tumoral en caso de sospecha clínica. Los resultados de este informe deben ser evaluados por el médico tratante y se sugiere discusión en comité oncológico-molecular.

Determinación de MSI PCR

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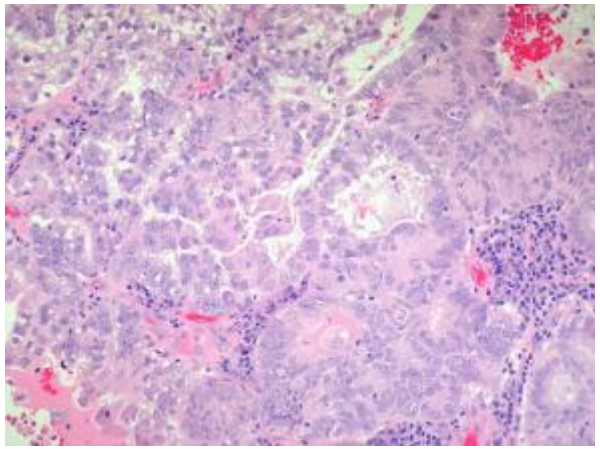
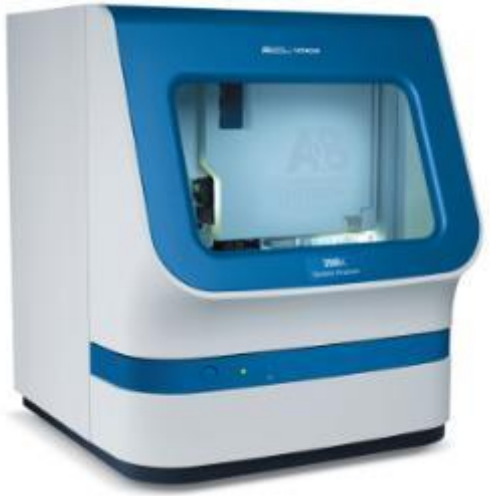
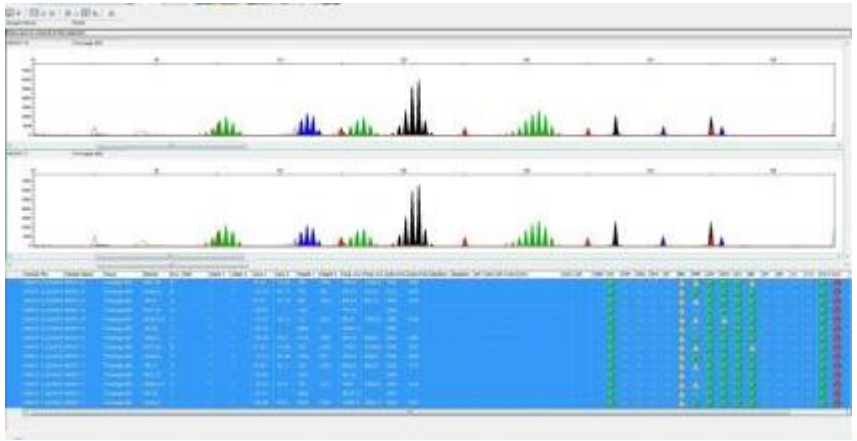


Promega





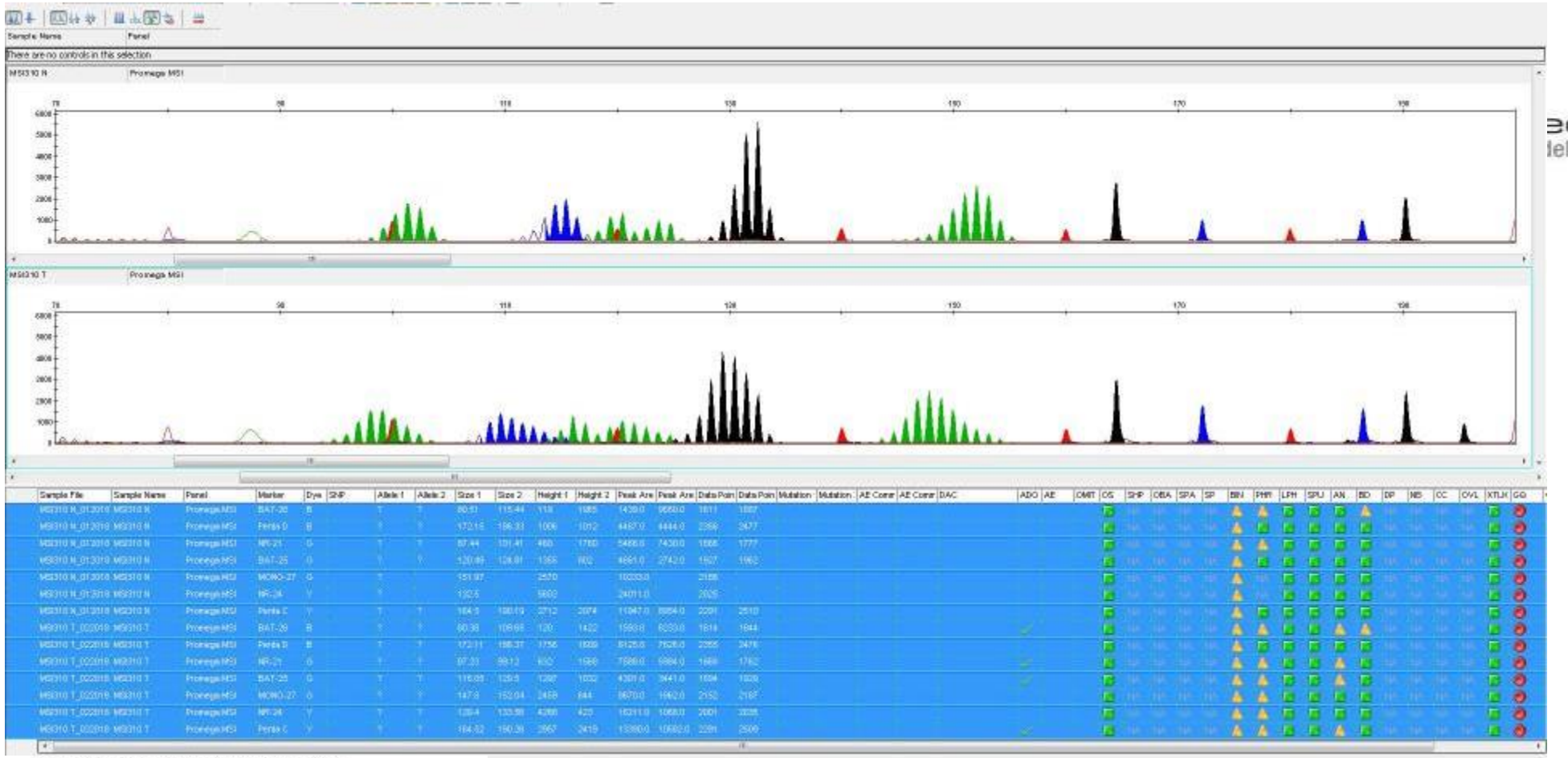


Table 1. The MSI Analysis System Locus Information.

Marker Name	GenBank® Number	Major Repeat Sequence	Size Range (bp)[1]	K562 Alleles (bp)	Primer Dye[2]
NR-21	XM_033393	$(A)_{21}$	94–101	101	JOE
BAT-26	U41210	$(A)_{26}$	103–115	113	FL
BAT-25	L04143	$(A)_{25}$	114–124	122	JOE
NR-24	X60152	$(A)_{24}$	130–133	130	TMR
MONO-27	AC007684	$(A)_{27}$	142–154	150	JOE
Penta C	AL138752	$(AAAAG)_{3-15}$	143–194	164, 174	TMR
Penta D	AC000014	$(AAAAG)_{2-17}$	135–201	168, 187	FL

[1]Allele sizes were determined using the ABI PRISM® 3100 Genetic Analyzer with POP-4™ polymer and a 36cm capillary. Rare alleles outside these size ranges may exist. Allele sizes may vary when using different polymers or instrument configurations.

[2]TMR = carboxy-tetramethylrhodamine; FL = fluorescein; JOE = 6-carboxy-4',5'-dichloro-2',7'-dimethoxyfluorescein

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ESTUDIO DE INESTABILIDAD DE MICROSATELITES B20-00881 DE LA MUESTRA H20-11307.

Se estudió inestabilidad de microsatélites a partir del análisis comparativo de ADN extraído de tejido fijado en formalina e incluido en parafina. Se disecó zonas de la preparación con tejido no tumoral (muestra 3A) y con carcinoma (muestra 1E). Se extrajo ADN con método basado en proteinasa K. Para el análisis de microsatélites se utilizó kit Promega MSI Analysis System, basado en reacción de polimerasa en cadena (PCR) múltiple utilizando partidores fluorescentes para 5 marcadores microsatelitales mononucleotídicos (NR-21, BAT-26, BAT-25, NR-24 y MONO-27); y 2 marcadores pentanucleotídicos de identificación de muestra (PENTA-C y PENTA-D). Los productos de PCR fueron resueltos mediante electroforésis capilar en un secuenciador automático ABI PRISM 3100 (Applied Biosystems) y evaluados con el programa GeneMapper. Se utilizó controles positivos y negativos. **RESULTADO MARCADORES MICROSATELITES: NR-21: CON INESTABILIDAD; BAT-26: CON INESTABILIDAD; BAT-25: CON INESTABILIDAD; NR-24: CON INESTABILIDAD; MONO-27: CON INESTABILIDAD.**

Diagnóstico:

CONCLUSIÓN: POSITIVO, INESTABILIDAD DETECTADA EN 5 DE 5 MARCADORES ESTUDIADOS, LO QUE CORRESPONDE A INESTABILIDAD MICROSATELITAL ALTA (MSI-H).

- Recomendación NCCN evaluar MSI en todos los carcinomas de endometrio

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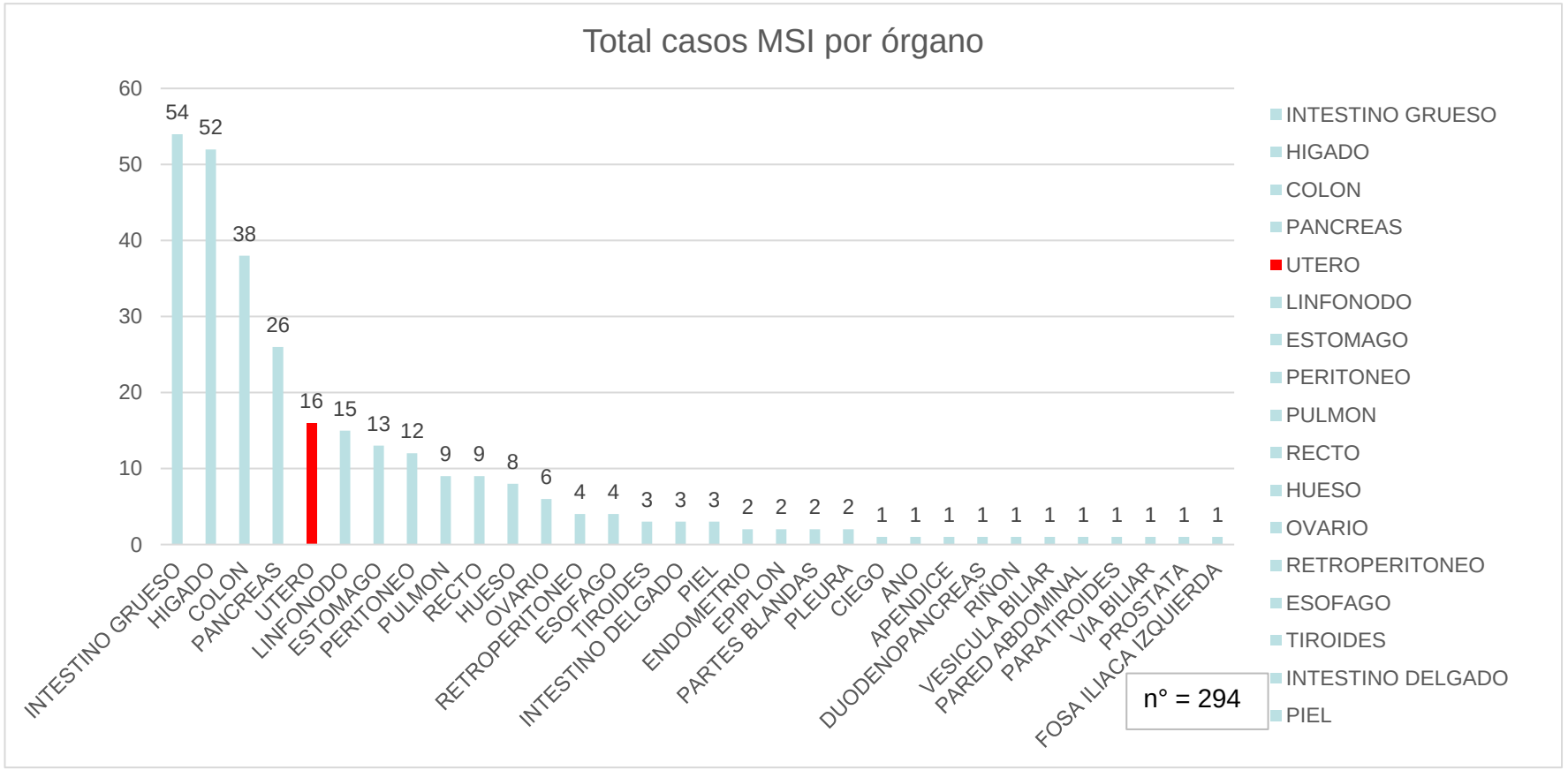

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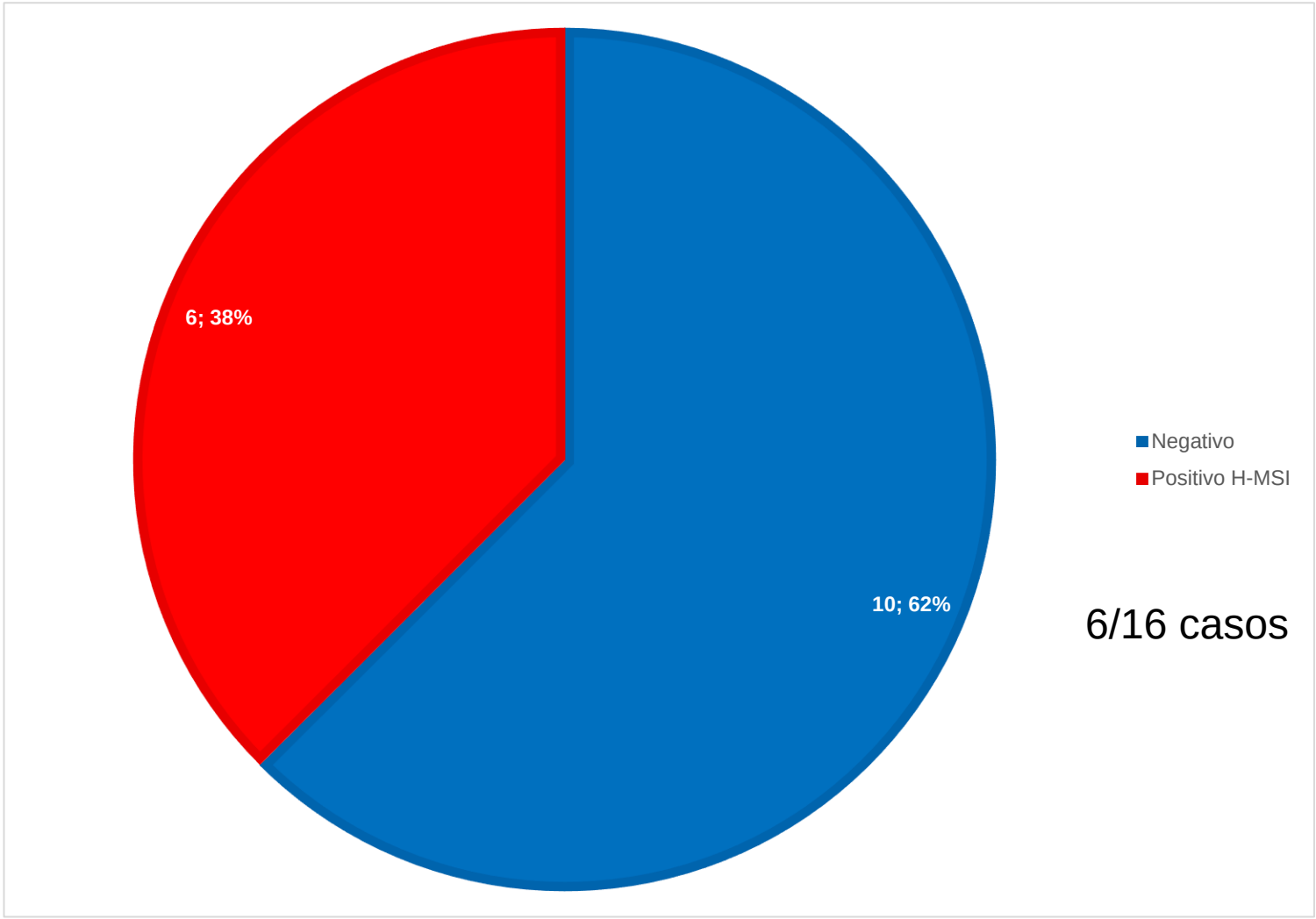
CASOS MSI EN CÁNCER DE ENDOMETRIO



6/16 casos

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M.P.Y.C.
59 años

Carcinoma endometrioide, NOS.

FIGO grado 1 (bajo grado).

pTNM AJCC 8 edición: pT1bN0 FIGO 2018 IB

Risgo histopatológico intermedio-alto

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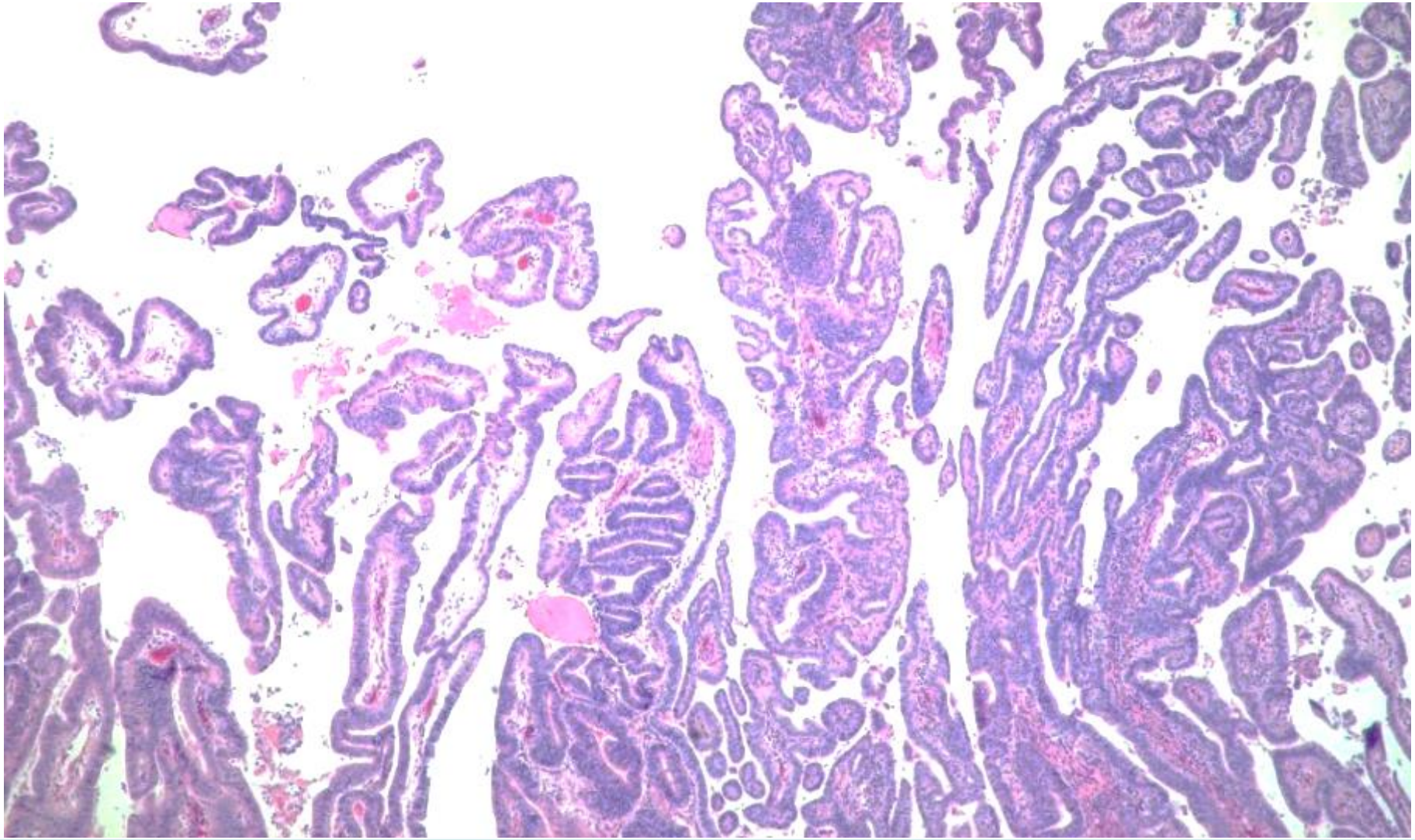

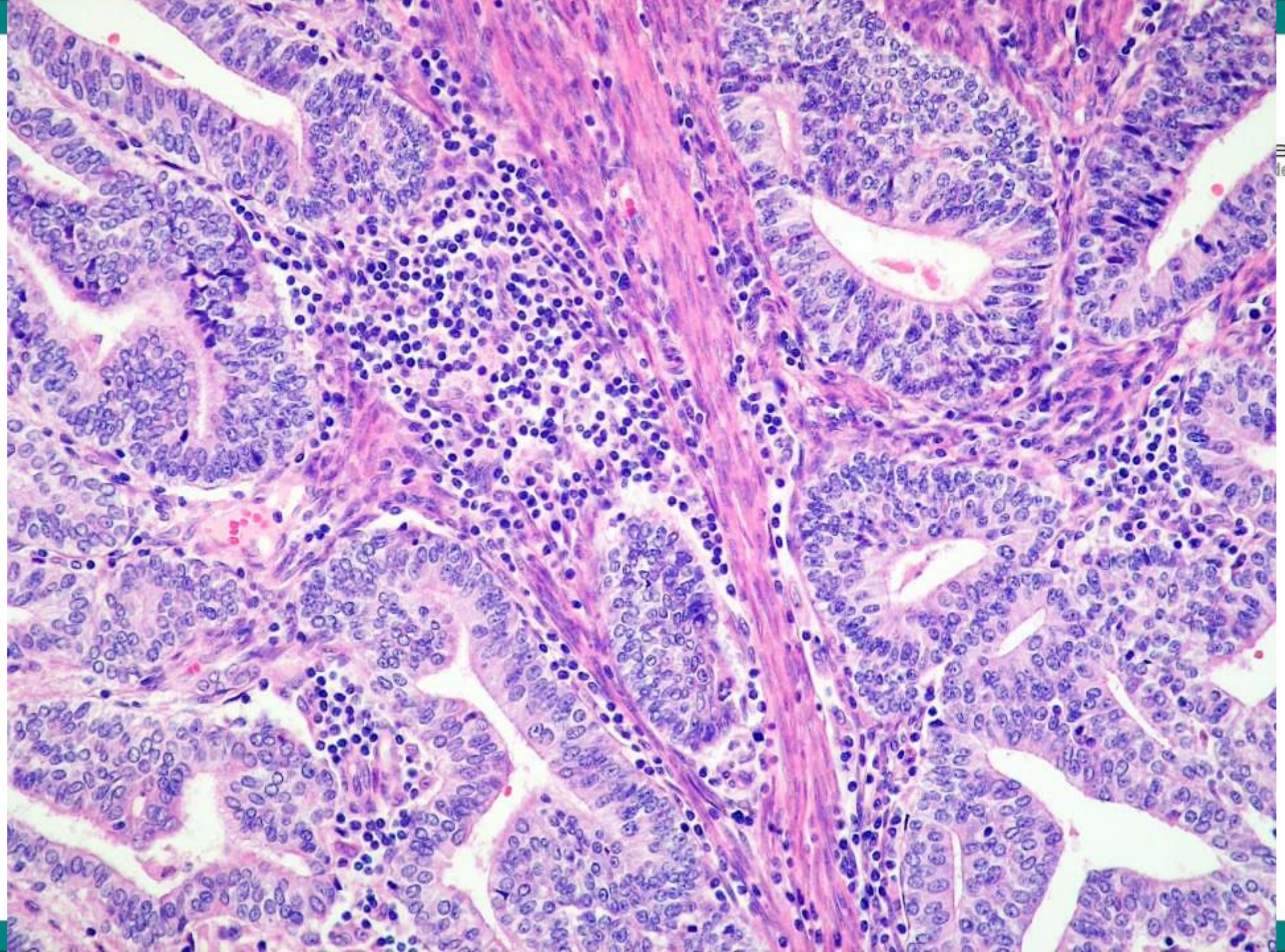

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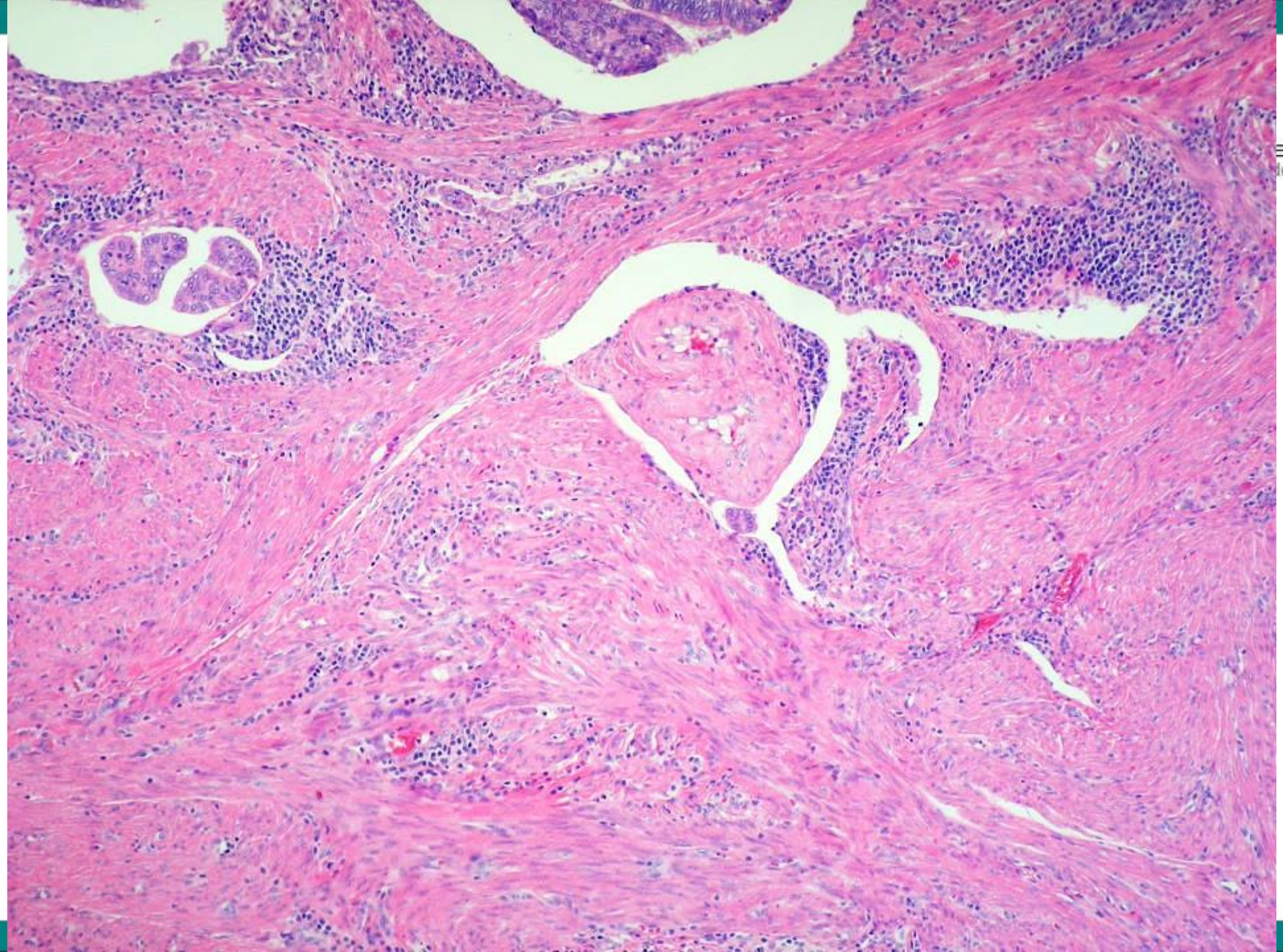

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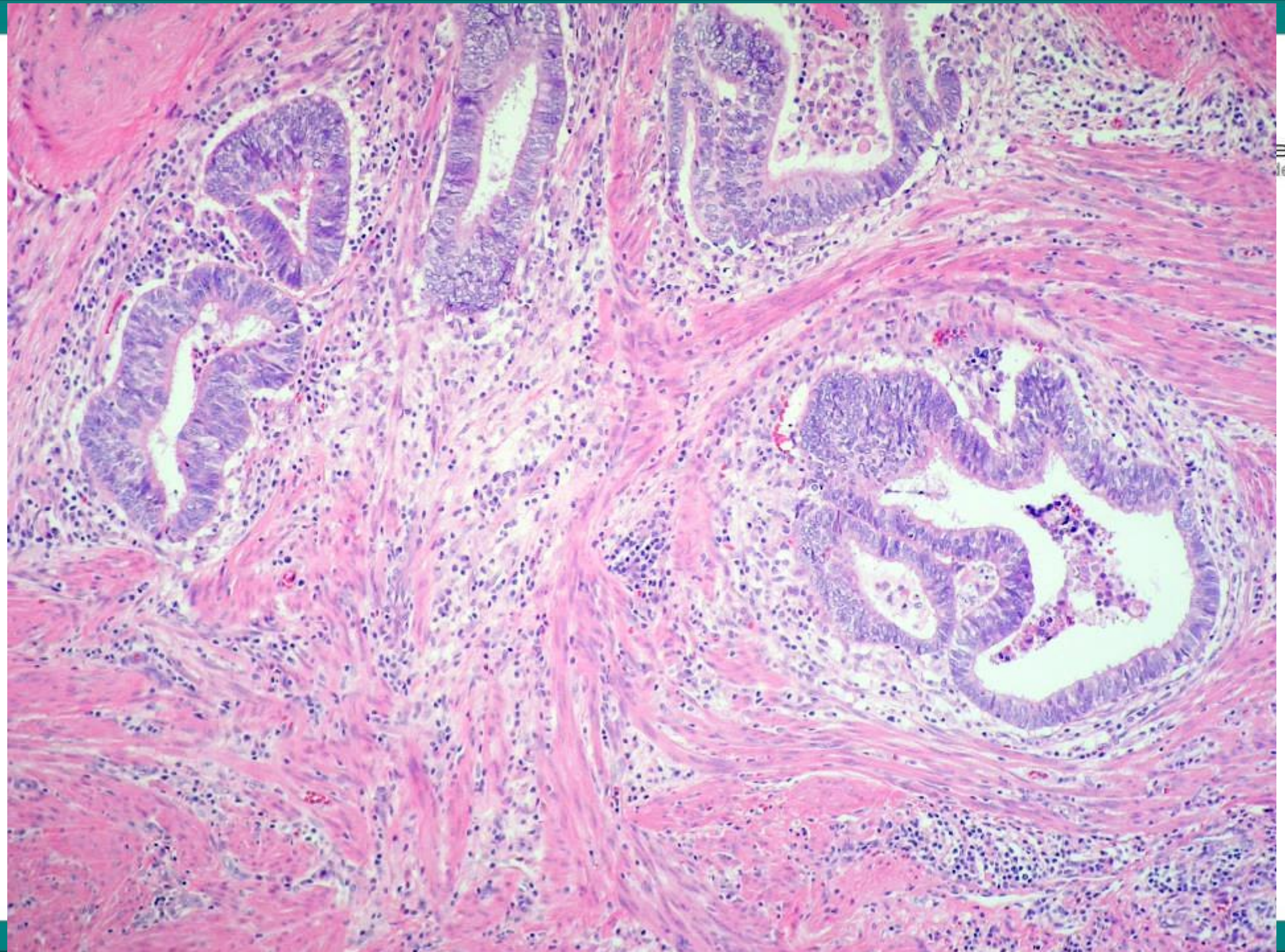

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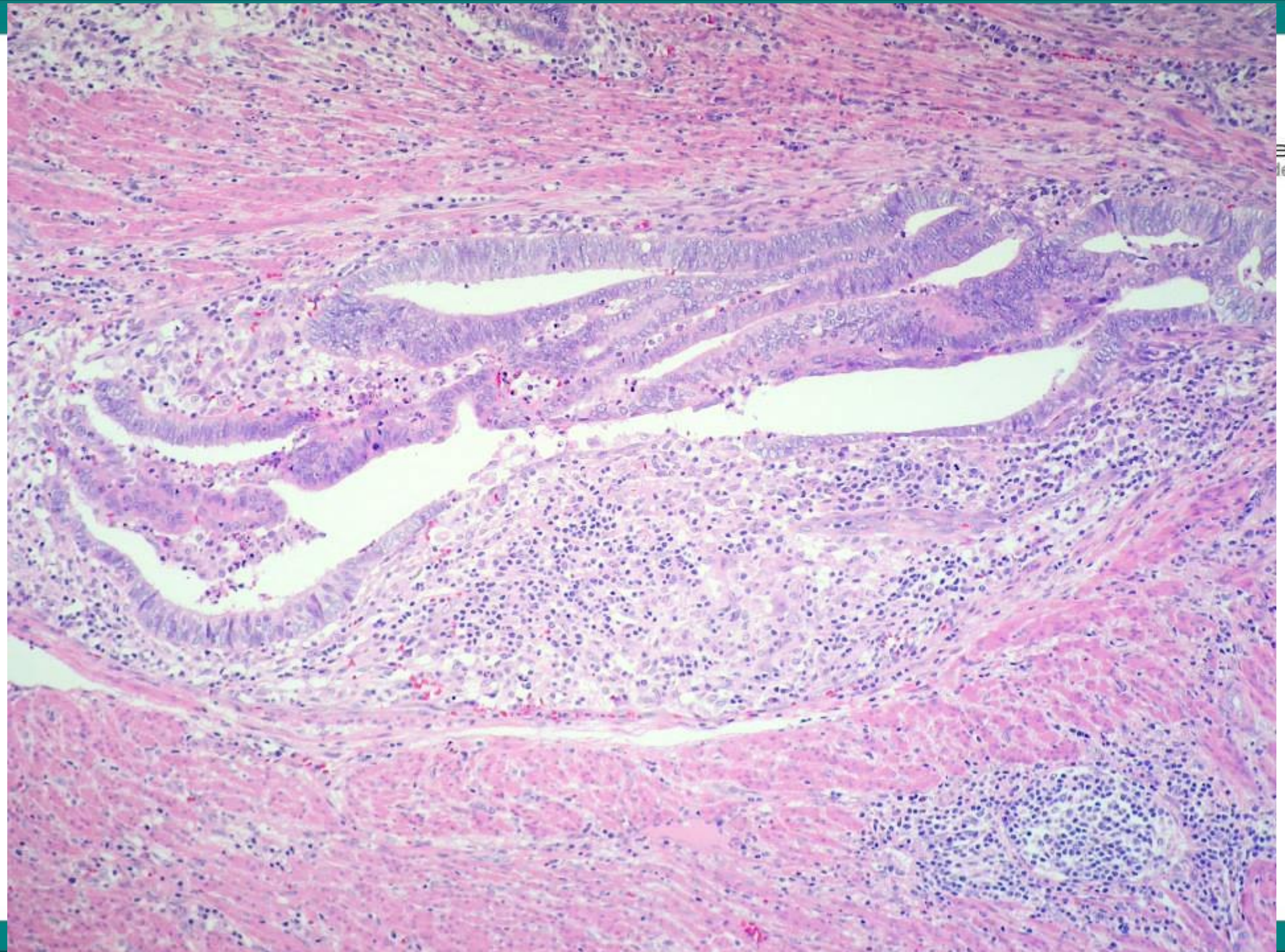

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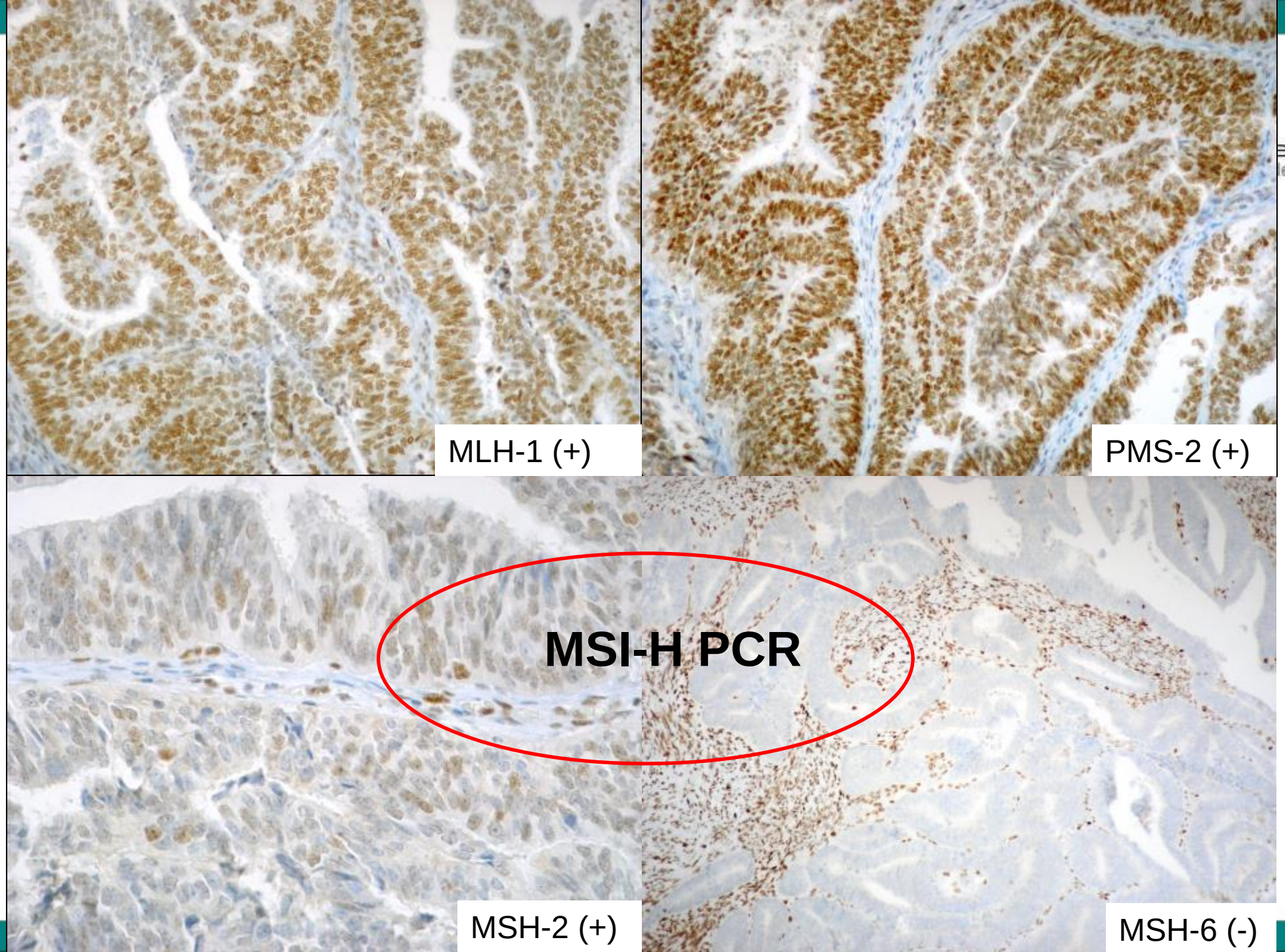
MLH-1 (+)
PMS-2 (+)
MSI-H PCR
MSH-2 (+)
MSH-6 (-)

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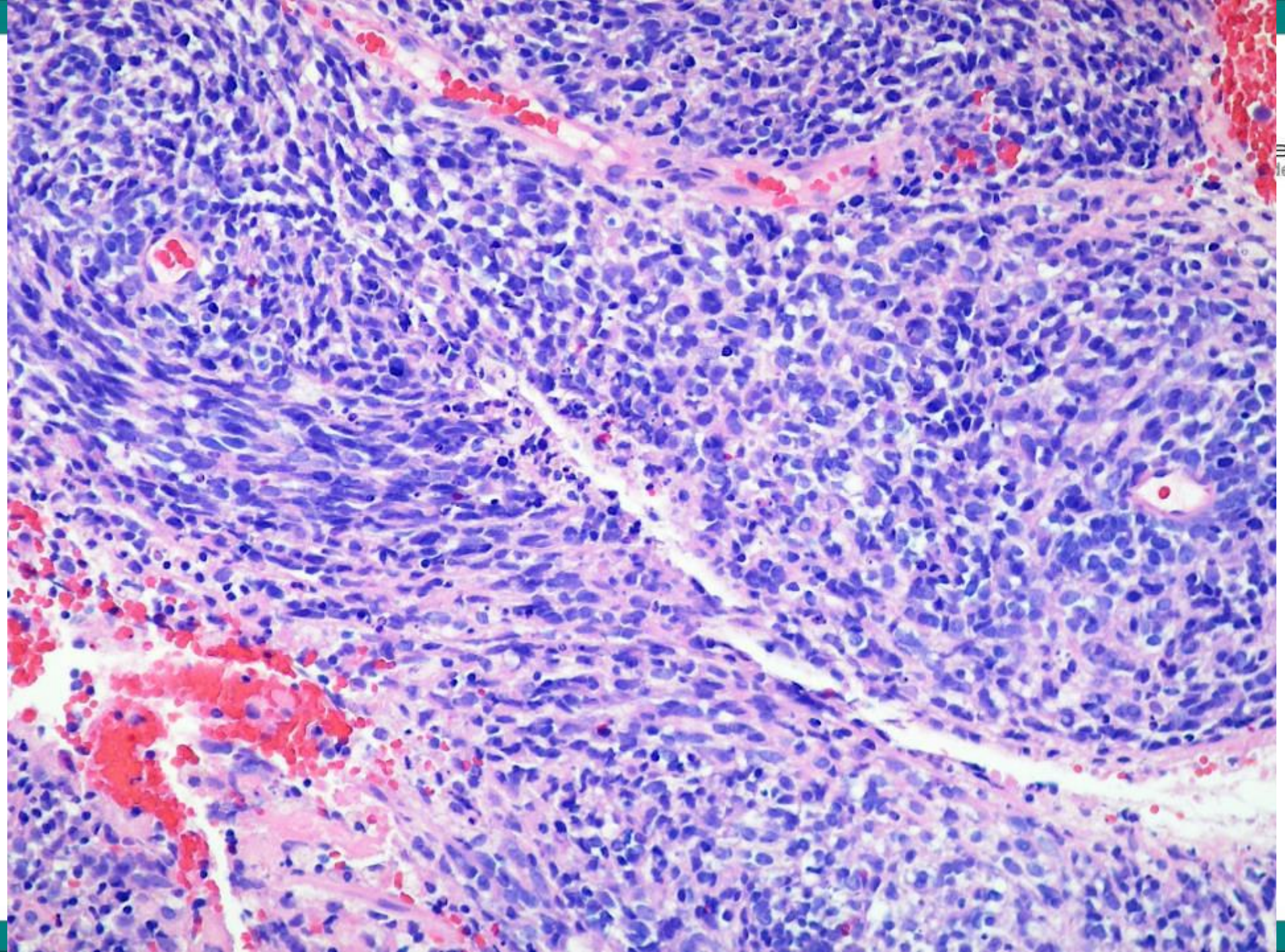
L.V.B.B.
89 años

Legrado uterino



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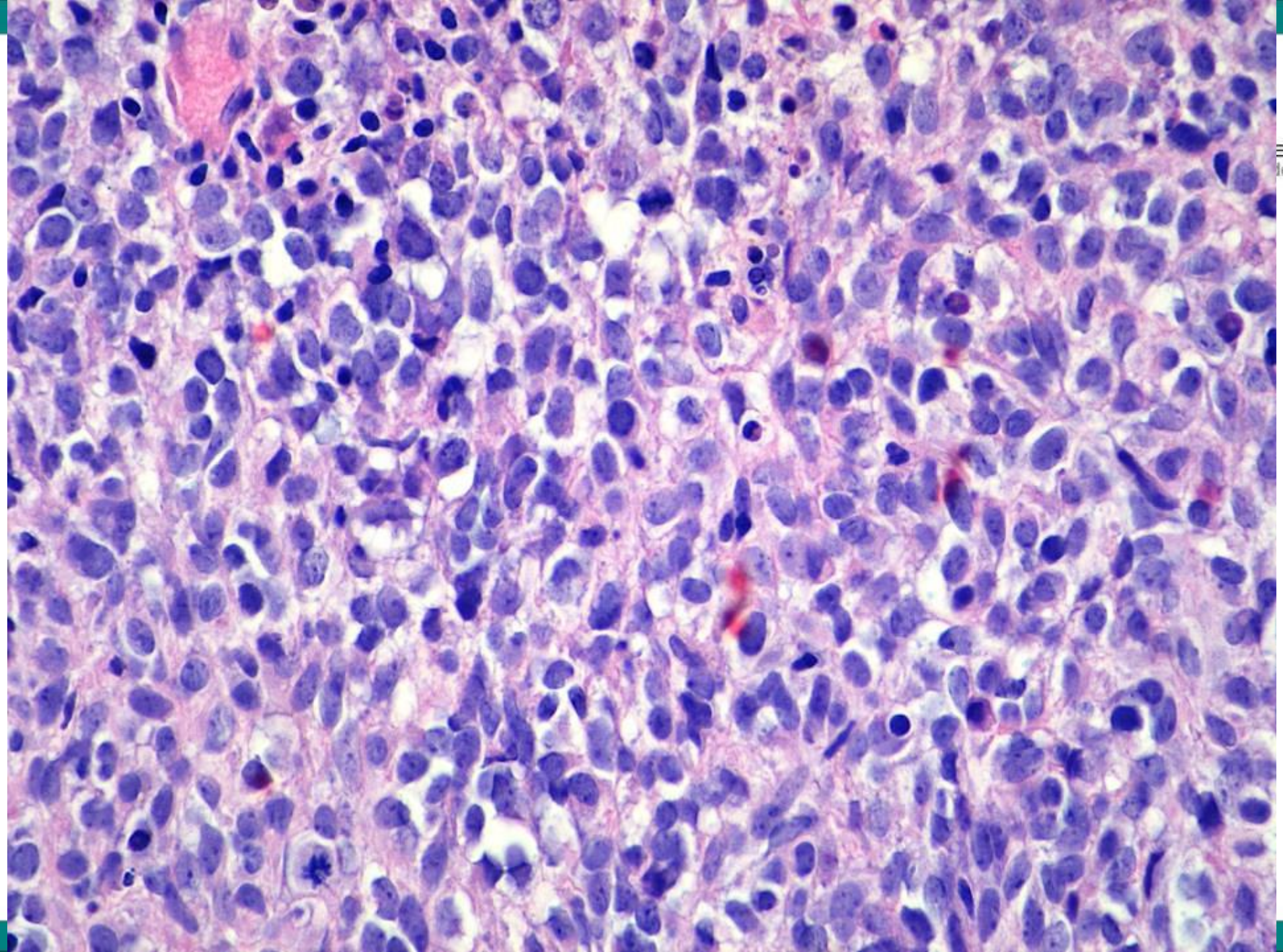

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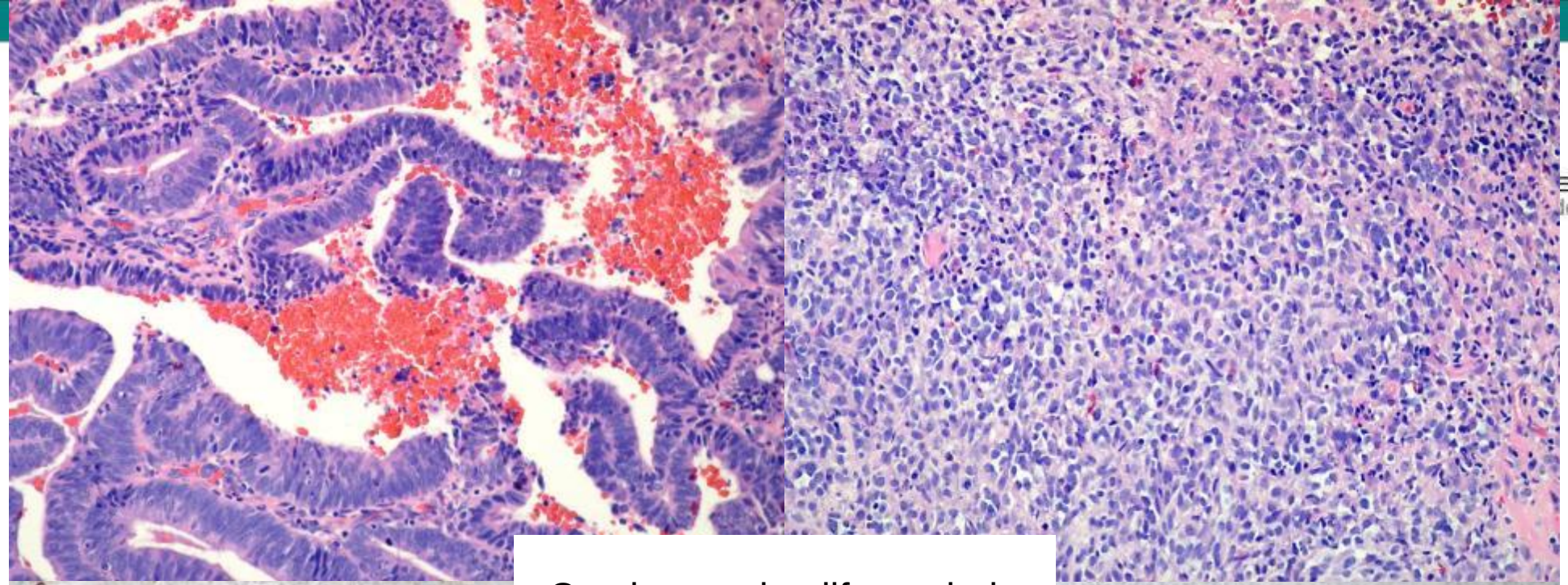
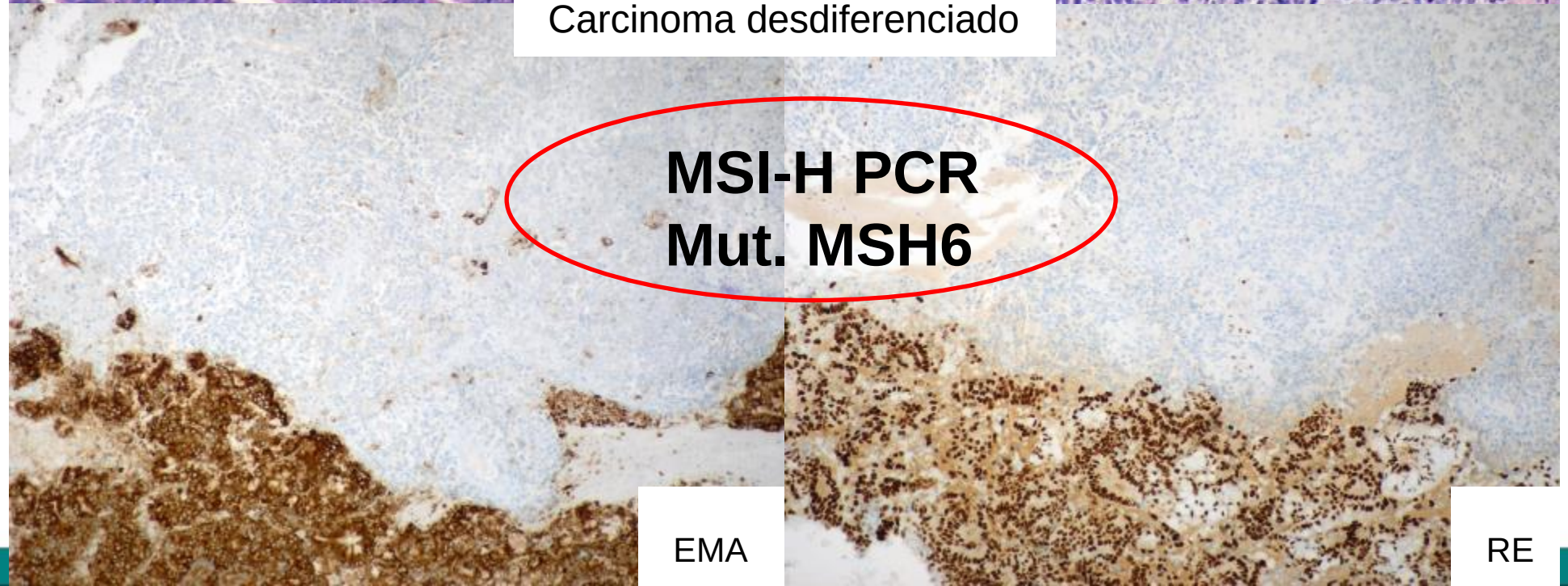


Carcinoma desdiferenciado

MSI-H PCR
Mut. MSH6



EMA

RE

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Objetivos

Conocer los principales cambios en cáncer de endometrio relacionados con:

- Tipos histológicos y clasificación tumoral 
- Sistema de graduación
- Permeaciones tumorales linfáticas
- Linfonodo centinela

Histologic Grade (required only if applicable) (Note C)#

___ FIGO grade 1
___ FIGO grade 2
___ FIGO grade 3
___ Other (specify): _____
___ Cannot be assessed (explain): _____

+Two-Tier Grading System (for endometrioid carcinomas only)

___ Low grade (encompassing FIGO 1 and 2)
___ High grade (FIGO 3)
___ Other (specify): _____
___ Cannot be assessed: _____
___ Not applicable

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Substantial lymph-vascular space invasion (LVSI) is a significant risk factor for recurrence in endometrial cancer – A pooled analysis of PORTEC 1 and 2 trials

Tjalling Bosse [a,1], Elke E.M. Peters [a,1], Carien L. Creutzberg [b], Ina M. Jürgenliemk-Schulz [c], Jan J. Jobsen [d], Jan Willem M. Mens [e], Ludy C.H.W. Lutgens [f], Elzbieta M. van der Steen-Banasik [g], Vincent T.H.B.M. Smit [a], Remi A. Nout [b,*]

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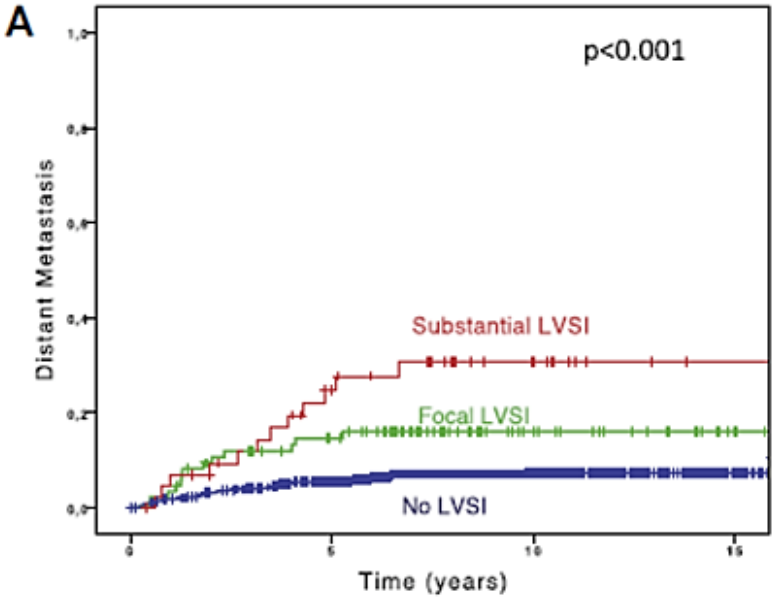

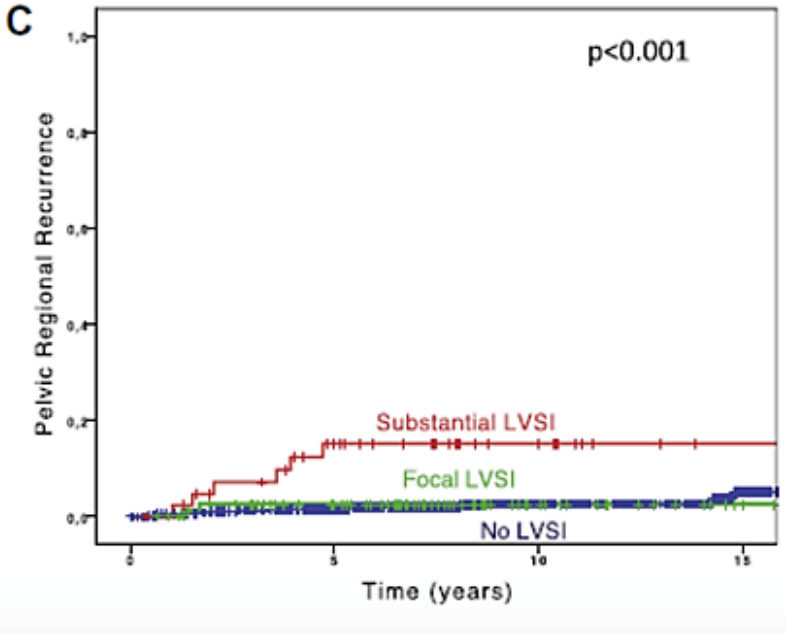

Lymphovascular Invasion (LVI) (Note I)
___ Not identified
___ Present
___ Low (less than 3 vessel involvement) (specify location, if possible): _____
___ Extensive (greater than or equal to 3 vessel involvement) (specify location, if possible): _____
___ Equivocal (explain): _____
___ Cannot be determined: _____

CAP 2021

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Objetivos

Conocer los principales cambios en cáncer de endometrio relacionados con:

- Tipos histológicos y clasificación tumoral ☑
- Sistema de graduación ☑
- Permeaciones tumorales linfáticas ☑
- Linfonodo centinela

Multicenter Study

Detection rate and diagnostic accuracy of sentinel-node biopsy in early stage endometrial cancer: a prospective multicentre study (SENTI-ENDO)

Marcos Ballester et al. Lancet Oncol. 2011 May.

Multicenter Study

A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial): a multicentre, prospective, cohort study

Emma C Rossi et al. Lancet Oncol. 2017 Mar.

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Centinela

RENDIMIENTO

Detection rate and diagnostic accuracy of sentinel-node biopsy in early stage endometrial cancer: a prospective multicentre study (SENTI-ENDO)

Marcos Ballester, Gil Dubernard, Fabrice Lécuru, Denis Heitz, Patrice Mathevet, Henri Marret, Denis Querleu, François Golfier, Eric Leblanc, Roman Rouzier, Emile Daraï

Lancet Oncol 2011; 12: 469-76

prospectivo multicéntrico No-randomizado

125 pacientes analizadas **(18 tipo II)**

89% Detección

17% pn1

Se 84%, VPN 97%

3 FN (tipo II)

Riesgo bajo/intermedio ✓

Alto riesgo= **Linfa Sistemática**

Alto Riesgo

European Journal of Cancer 116 (2019) 77–85

Pelvic Sentinel lymph node detection in High-Risk Endometrial Cancer (SHREC-trial)—the final step towards a paradigm shift in surgical staging

Jan Persson [a,b,*], Sahar Salehi [c], Michele Bollino [a,b], Celine Lönnerfors [a,b], Henrik Falconer [c], Barbara Geppert [a,b]

Conclusion: With a complete sensitivity to detect pelvic LNMs, the described pelvic SLN algorithm can, in the hands of experienced surgeons, exclude overall nodal involvement in 99% and thereby safely replace a full lymphadenectomy in HREC.

The Oncologist 2019;24:e1381–e1387

The Oncologist®

Gynecologic Oncology

A Prospective Study of Sentinel Lymph Node Mapping for Endometrial Cancer: Is It Effective in High-Risk Subtypes?

Conclusion: cervical injections of ICG and SLN mapping yield a low sensitivity and high FN rate for the identification of node metastasis in endometrial cancer with high-risk histologies. ***The Oncologist 2019;24:e1381-e1387***

Johnson & Johnson

centinela

ALTO RIESGO

Múltiples series de casos: tasas de detección, falsos negativos, comparables con grupos de bajo riesgo

Series de sobrevida limitadas, seguimiento corto y múltiples sesgos (retrospectiva), pero no hay evidencia de inferioridad

Tipo de linfadenectomía no se asoció a recurrencia global, linfática ni mortalidad

Detección a nivel paraaoórtico es limitada pero...

metástasis aislada son raras

comparaciones no muestran beneficio en sobrevida

Pacientes reciben adyuvancia casi sistemáticamente lo que limita la interpretación de datos

En espera de información de mayor calidad es útil evaluar los resultados locales antes de hacer un cambio

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2022
Endometrial Carcinoma

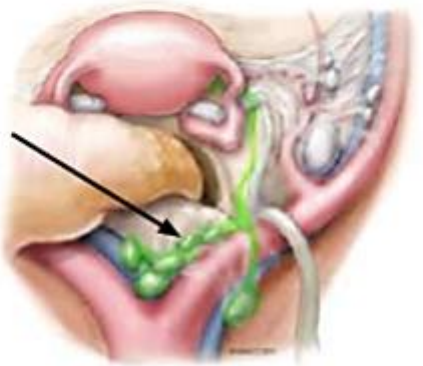
NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF EVALUATION AND SURGICAL STAGING WHEN SLN MAPPING IS USED

Figure 1: Common cervical injection sites for mapping uterine cancer[a]

Figure 2: Most common location of SLNs (blue, arrow) following a cervical injection[a]

Figure 3: Less common location of SLNs (green, arrow) usually seen when lymphatic trunks are not crossing over the umbilical ligament but following the mesoureter cephalad to common iliac and presacral region[a]



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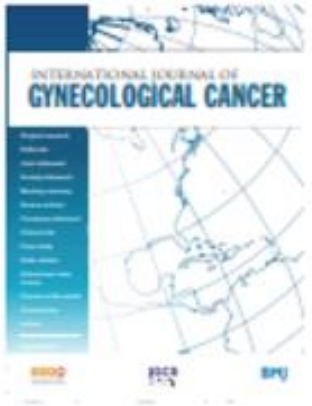
Memorial Sloan Kettering Cancer Center Protocol:
If the initial H&E-stained slide is negative for carcinoma and the endometrial cancer is myo-invasive or associated with vascular/lymphatic invasion, 2 additional levels at 50 µm apart are examined, at each level 2 slides are obtained, one for H&E and the second for keratin cocktail IHC if the H&E-stained slide is negative.

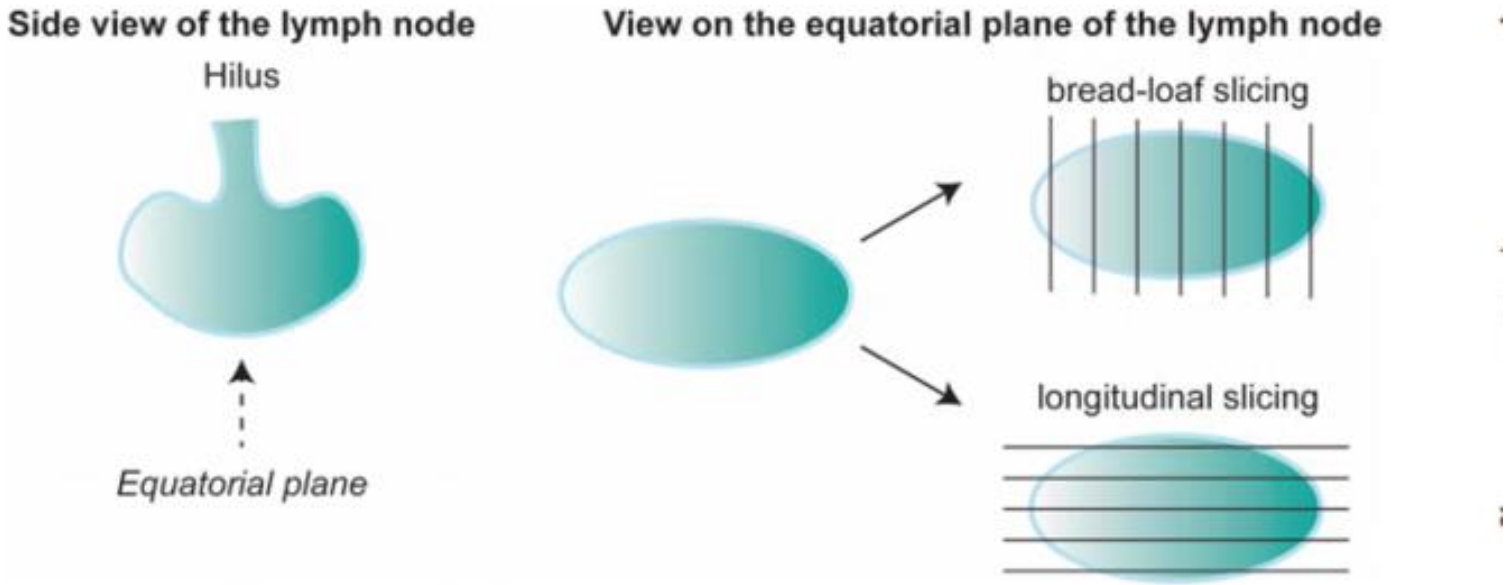
The University of Texas M.D. Anderson Cancer Center Protocol:
If the H&E-stained slide is negative for tumor, 3 consecutive sections at 250 µm into the paraffin block are obtained (one for H&E and one of the remaining 2 is to be used for keratin cocktail IHC if the additional H&E stained slide is negative).

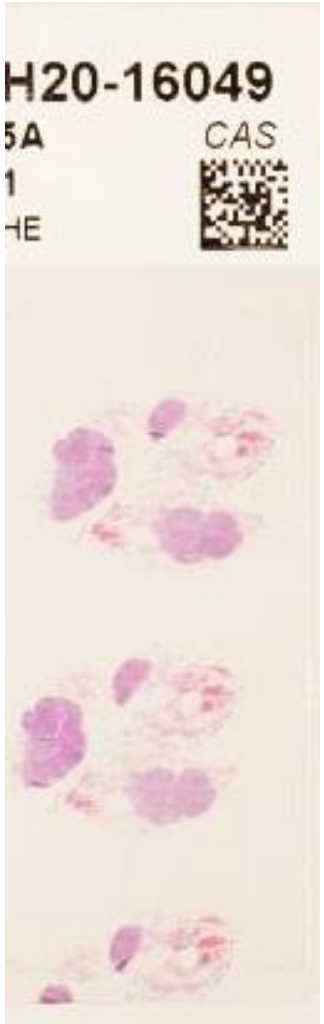
CAP 2021



Ultrastaging methods of sentinel lymph nodes in endometrial cancer – a systematic review

Lara C Burg,[1] Ellen M Hengeveld,[1] Joanna in 't Hout,[2] Johan Bulten,[3] Peter Bult,[3] Petra L M Zusterzeel[1]

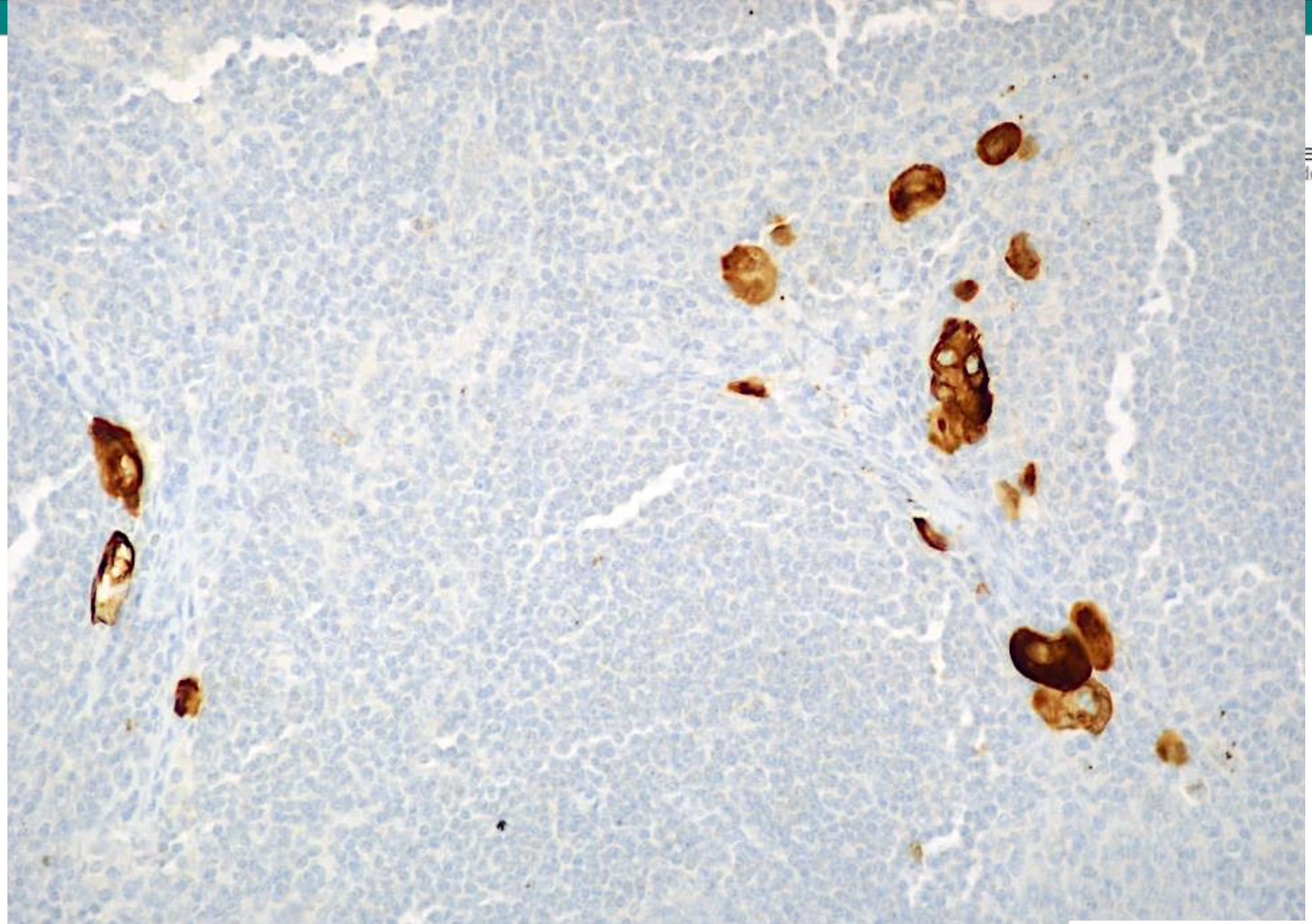



H20-16049
5A
CAS
1
HE

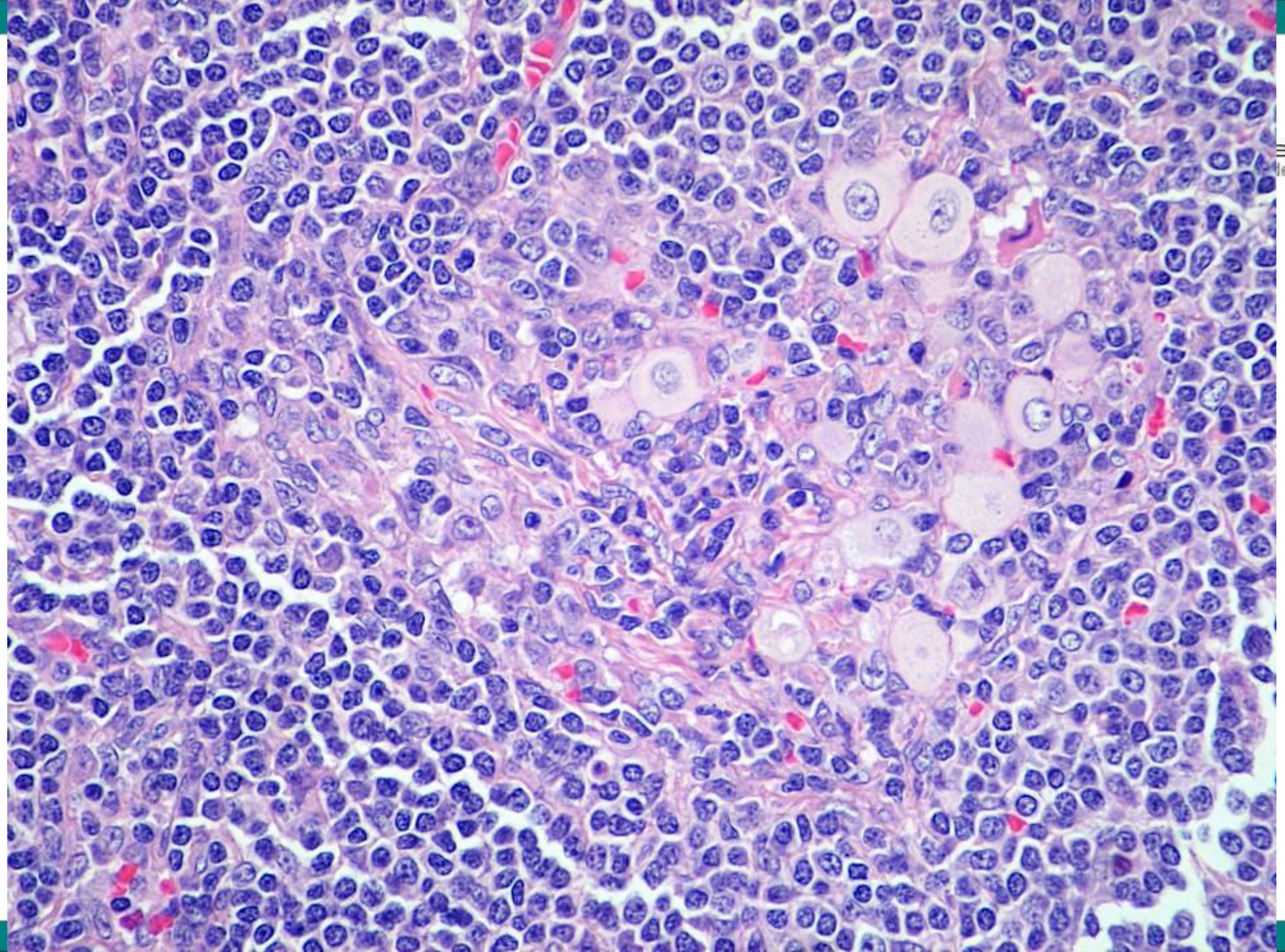

U36 CK AE1/AE3
H20-16049-5-A
15/12/20
CAS
LOT 40407


H20-16049
5A
CAS
3
HE

- Linfonodo centinela
- N° total (pélvicos / lumboaórticos)
- N° con macrometástasis (tamaño)
- N° con micrometástasis
- N° con células tumorales aisladas



AE1/AE3



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del Desarrollo

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Objetivos

Conocer los principales cambios en cáncer de endometrio relacionados con:

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- Sistema de graduación ☑
- Permeaciones tumorales linfáticas ☑
- Linfonodo centinela ☑

Conclusiones

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- El cáncer de endometrio es un grupo de tumores morfológicamente y genéticamente heterogéneo
- Con mutaciones recurrentes, patrones genómicos y subtipos moleculares en los distintos tipos histológicos
- Sin mutaciones patognomónicas

Conclusiones

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- La nueva clasificación molecular es un complemento a los criterios histopatológicos y clínicos
- Permite reclasificar y/o precisar categorías de riesgo con mayor objetividad
- Aporta mayor reproducibilidad en el diagnóstico, información pronóstica y predictiva
- A futuro redefinir enfoques terapéuticos y reducir sobre y subtratamiento

Conclusiones

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- Aplicación depende de recursos disponibles
- Requiere definir criterios de inclusión de casos
- Emplear tests validados, reproducibles
- Evaluar costo-beneficio

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