

Human Papillomavirus-independent Endocervical Adenocarcinoma

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- **Classification of endocervical adenocarcinoma (EAC)**
 - 2018 International Endocervical Adenocarcinoma Criteria and Classification (IECC)
 - 2020 World Health Organization (WHO) Classification

- **Human papillomavirus (HPV)-independent EAC**
 - Gastric type
 - Clear cell type
 - Mesonephric type

- Squamous cell carcinoma (SCC): 75-80%
 - HPV-associated SCC: Almost all cases
- EAC: 20-25%
 - HPV-associated EAC: 80-85%
 - HPV-independent EAC: 15-20%
 - A heterogeneous group of tumors
 - Various etiology, morphology, and prognosis

- WHO 2003

- Mucinous
 - Endocervical
 - Intestinal
 - Signet-ring cell
 - Minimal deviation
 - Villoglandular
- Endometrioid
- Clear cell
- Serous
- Mesonephric

- WHO 2014

- Usual
- Mucinous
 - Gastric
 - Intestinal
 - Signet-ring cell
- Villoglandular
- Endometrioid
- Clear cell
- Serous
- Mesonephric

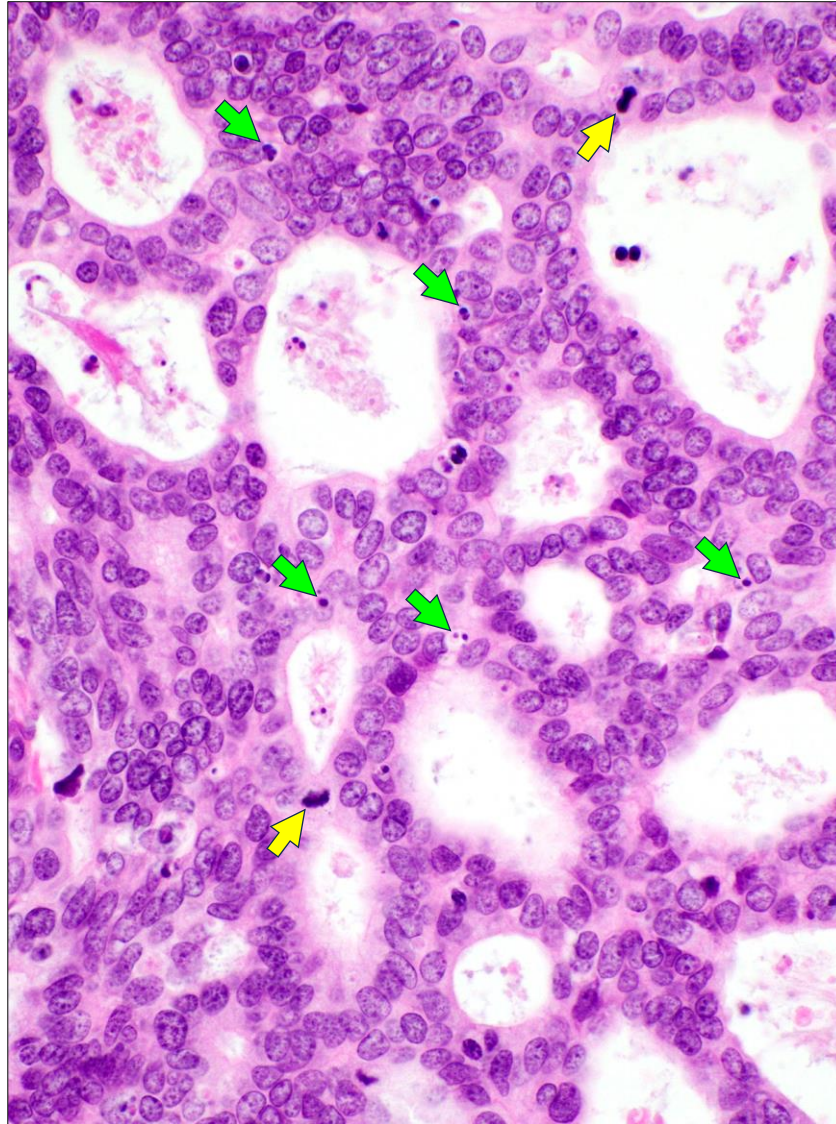
- The former WHO Classifications
 - Based on descriptive histology and subjective definitions
 - Does not fully reflect pathogenesis and clinical behavior
- Necessity for a new classification system
 - Linked to etiology, treatment, and prognosis

- A novel pathological classification system for EAC
 - An international multi-institutional study evaluating
 - HPV status and immunophenotype
 - Molecular profile and prognosis
 - Two categories
 - HPV-associated EAC
 - HPV-independent EAC

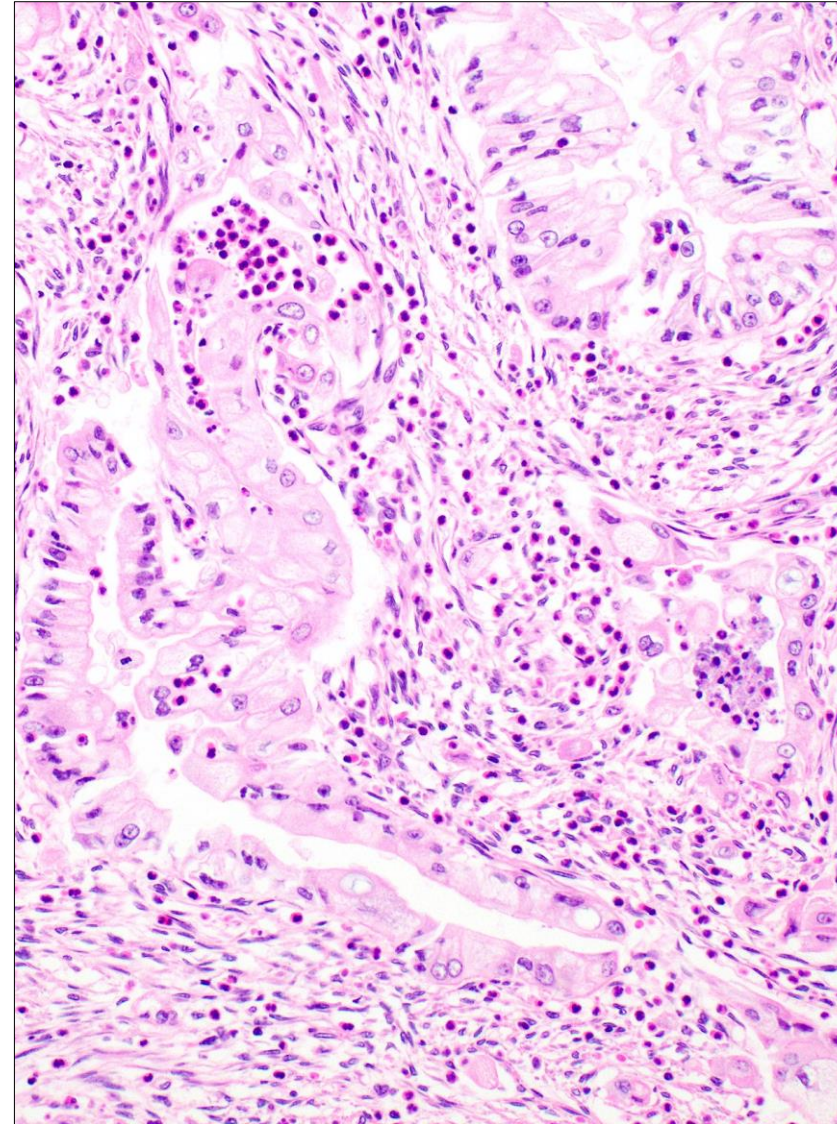
- Based on the presence of HPV-related morphology
 - Apical mitotic figures and basal apoptotic bodies
 - Readily identifiable at scanning or low-power magnification

- Without immunostaining or molecular testing

HPV-associated



HPV-independent



2018 IECC: Proportion of histological types

Type	Subtype	Proportion (%)	
HPV-associated (82.7%)	Usual	73.8	
	NOS	3.0	
	Mucinous	Intestinal	3.0
	Invasive stratified mucin-producing	2.4	
	Signet-ring cell	0.3	
HPV-independent (17.3%)	Gastric	10.0	
	Clear cell	3.0	
	Mesonephric	0.3	
	Endometrioid	1.1	
	Serous	0.5	
	NOS	2.4	

2018 IECC: Clinical characteristics

Characteristic	Type	
	HPV-associated	HPV-independent
Proportion (%)	80-85	15-20
Age	Fourth decade	Fifth decade or higher
Tumor size	Smaller	Larger
Stage	Lower	Higher
Propensity for resection margin	Negative	Positive
Prognosis	Better	Worse

- HPV-associated EAC

- Usual
- Mucinous
 - NOS
 - Intestinal
 - Signet-ring cell
 - Invasive stratified mucin-producing

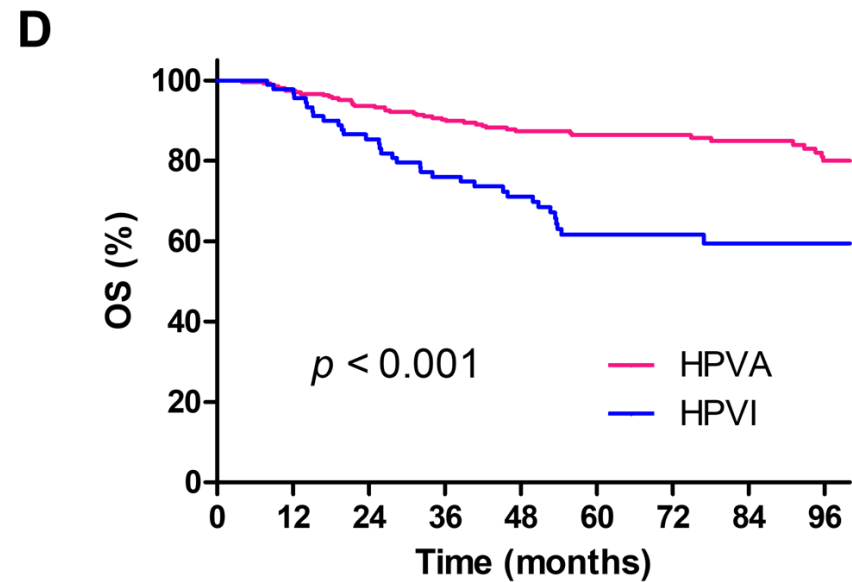
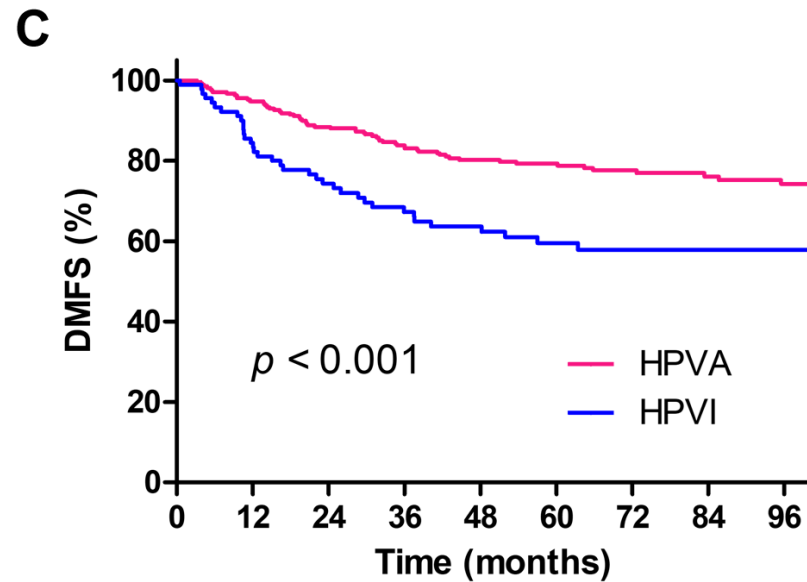
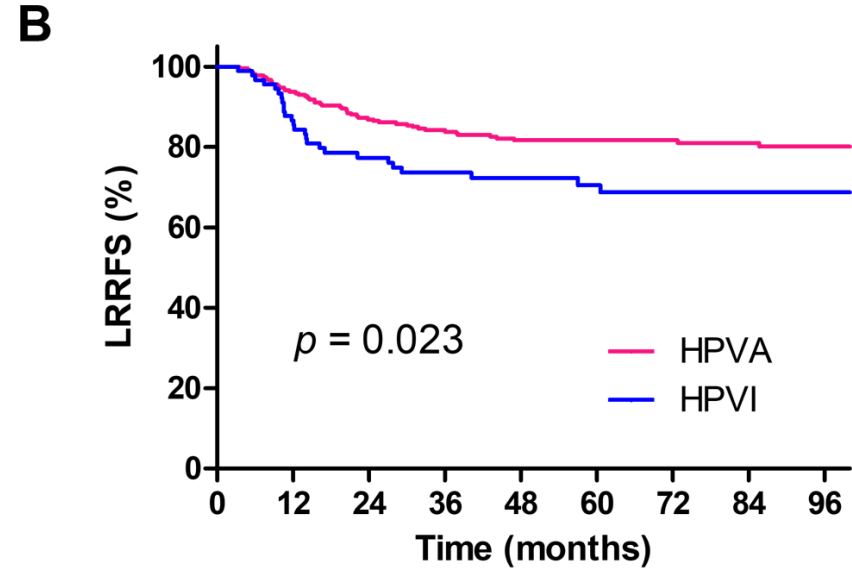
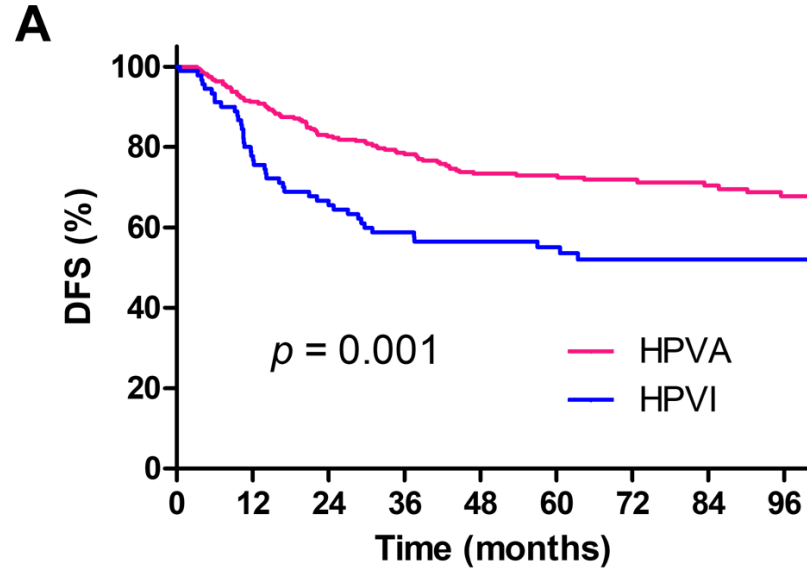
- HPV-independent EAC

- Gastric type
- Clear cell type
- Mesonephric type

2020 WHO: A multi-institutional study from Korea

Type	Subtype	Proportion (%)	
HPV-associated (75.4%)	Usual	59.5	
	NOS	6.3	
	Mucinous	Intestinal	5.2
	Invasive stratified mucin-producing	3.6	
	Signet-ring cell	0.8	
HPV-independent (24.6%)	Gastric	15.6	
	Clear cell	2.5	
	Mesonephric	1.1	
	Serous	1.6	
	NOS	3.8	

2020 WHO: A multi-institutional study from Korea



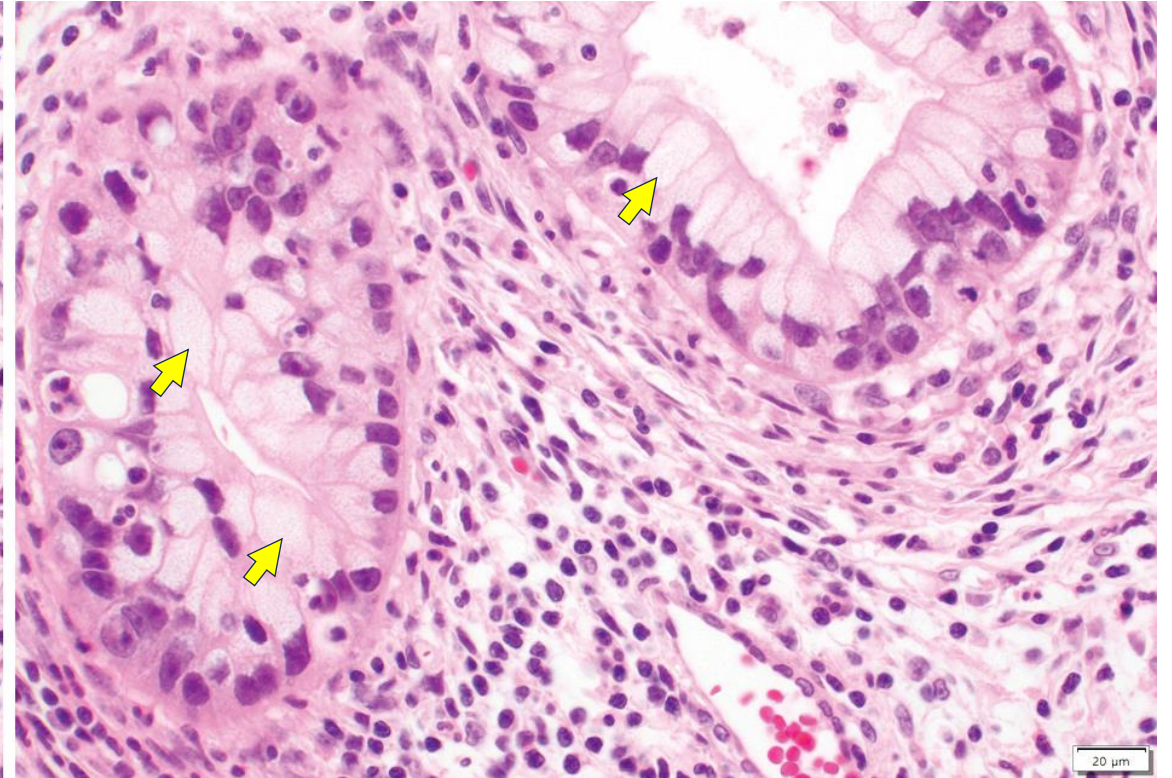
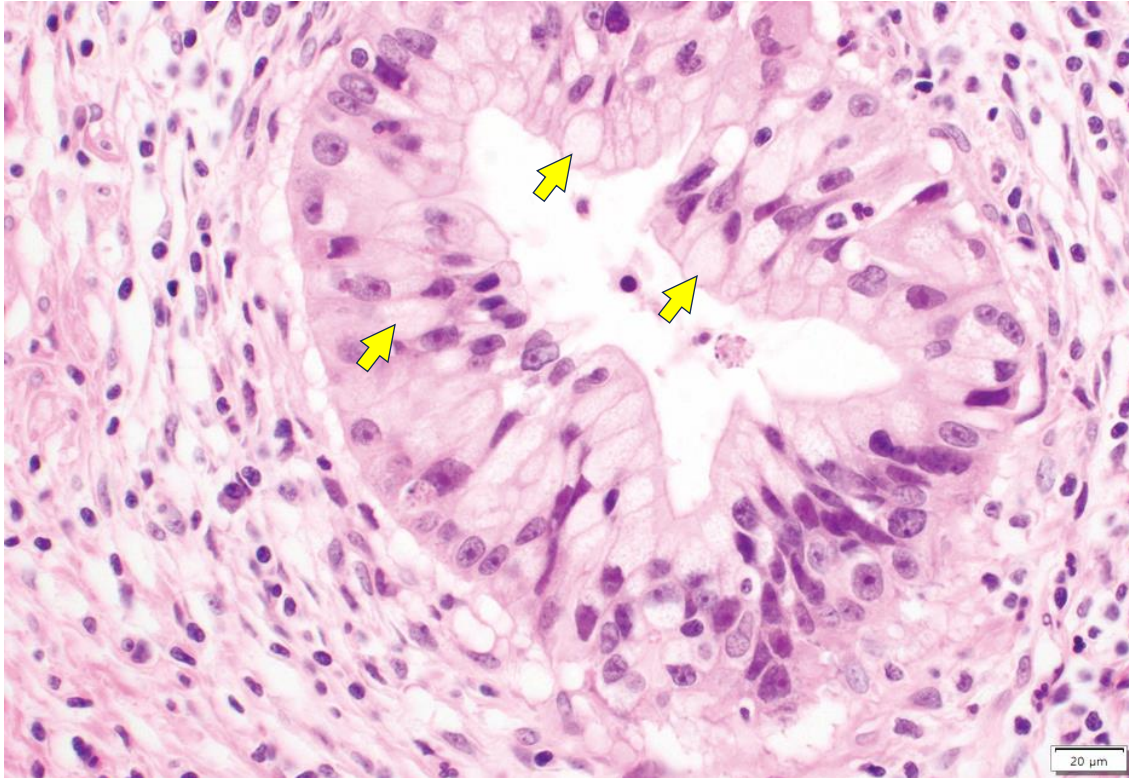
HPV-independent EAC

- Gastric type
- Clear cell type
- Mesonephric type

HPV-independent gastric-type EAC

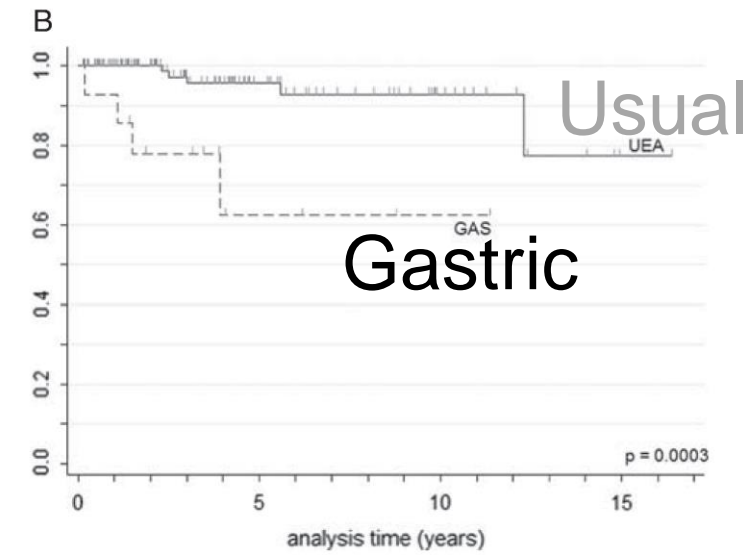
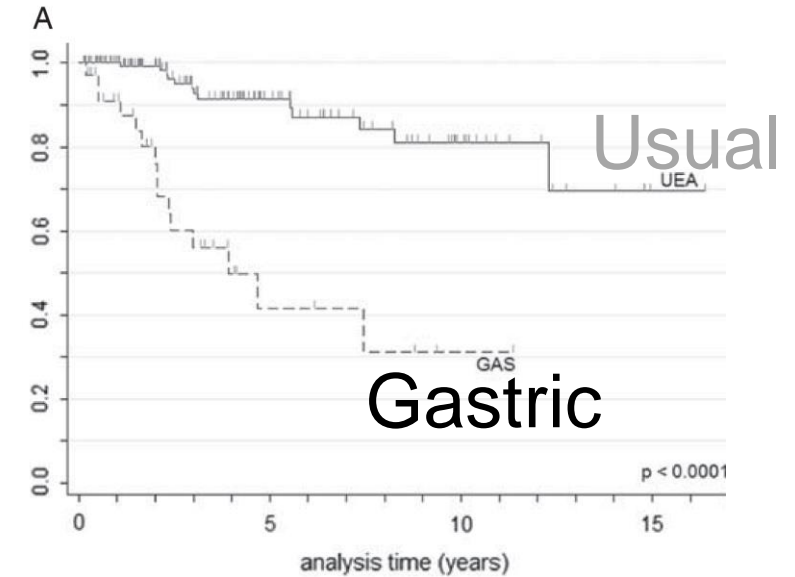
- Second most common EAC type (10-15%)
- Extremely aggressive clinical behavior
 - Unrelated to HPV infection
 - Much more than HPV-associated usual-type EAC
 - Poor response to conventional chemotherapy
- Gastric morphology
 - Abundant, mucin-containing cytoplasm
 - Resembling gastric and pancreatobiliary adenocarcinoma

HPV-independent gastric-type EAC



HPV-independent gastric-type EAC

- Significantly worse DSS than
 - HPV-associated usual-type EAC
- 5- and 10-year DSS for all stage
 - Gastric type: 42% and 31%
 - Usual type: 91% and 81%
- 5- and 10-year DSS for stage I
 - Gastric type: 62% and 62%
 - Usual type: 99% and 93%

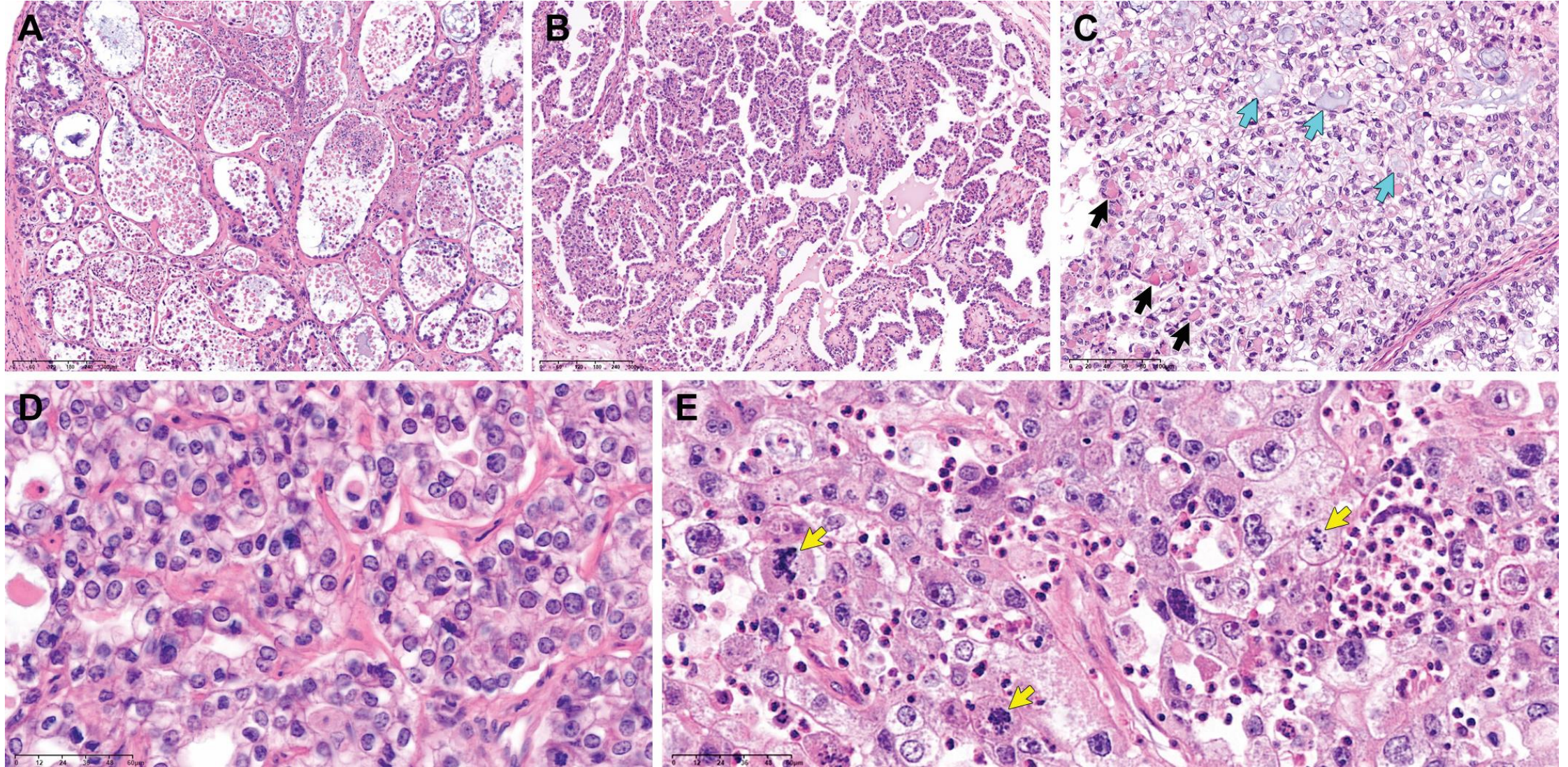


- Peutz-Jeghers syndrome
 - Autosomal dominant
 - Loss-of-function mutation in *STK11/LKB1* gene
 - Mucocutaneous pigmentation or melanosis
 - Hamartomatous polyps of the gastrointestinal tract
 - History of intussusception in a child or young adult
- Association with gastric-type EAC

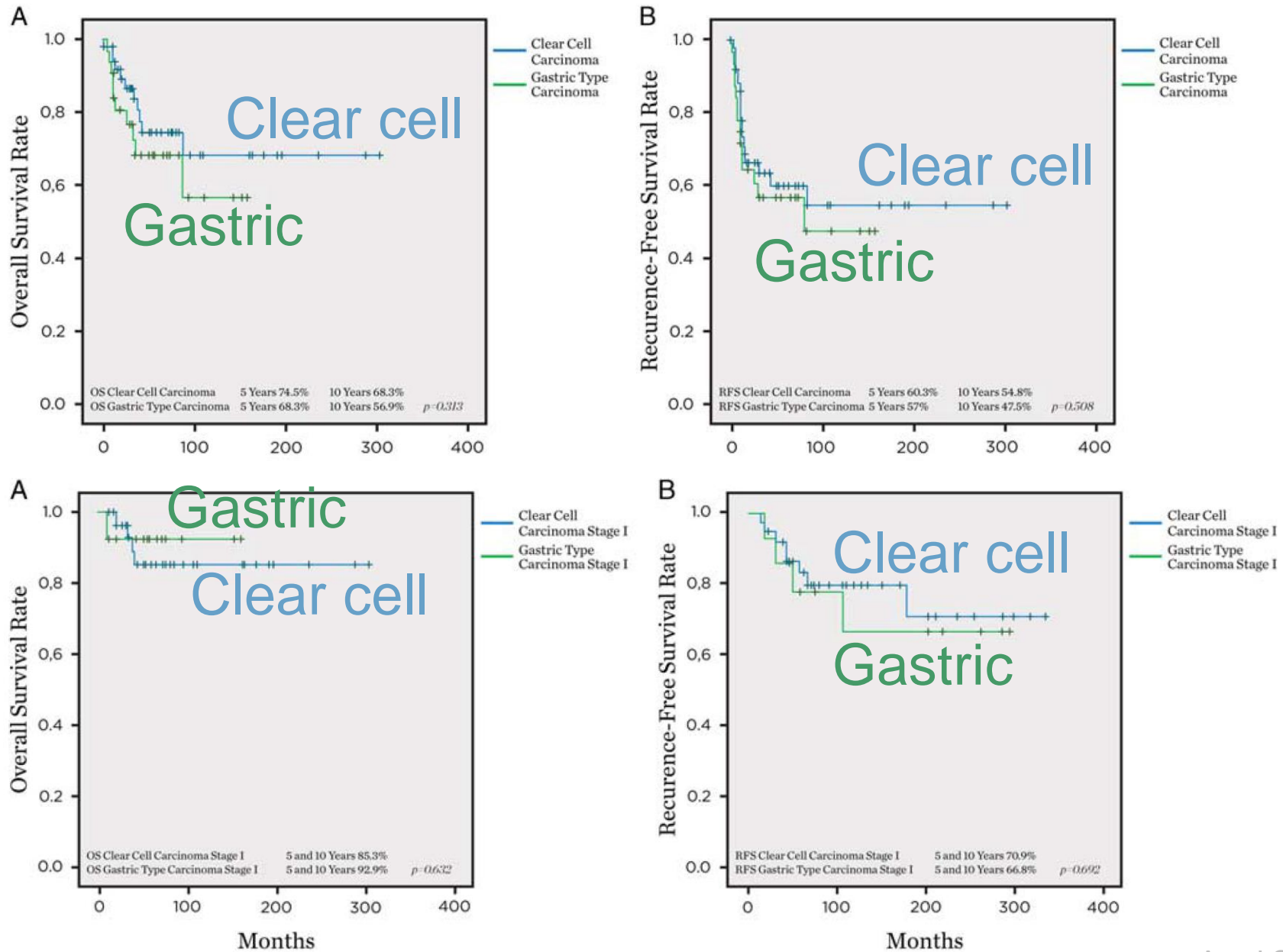
HPV-independent clear cell-type EAC

- <5% of all cervical carcinoma cases
- Bimodal age distribution (around 20 and 42 years)
- Sporadic (non-DES-exposed)
 - Predominantly endocervix
- Diethylstilbestrol (DES) exposure *in utero*
 - A peak in 19 years
 - Vaginal upper one-third or exocervix

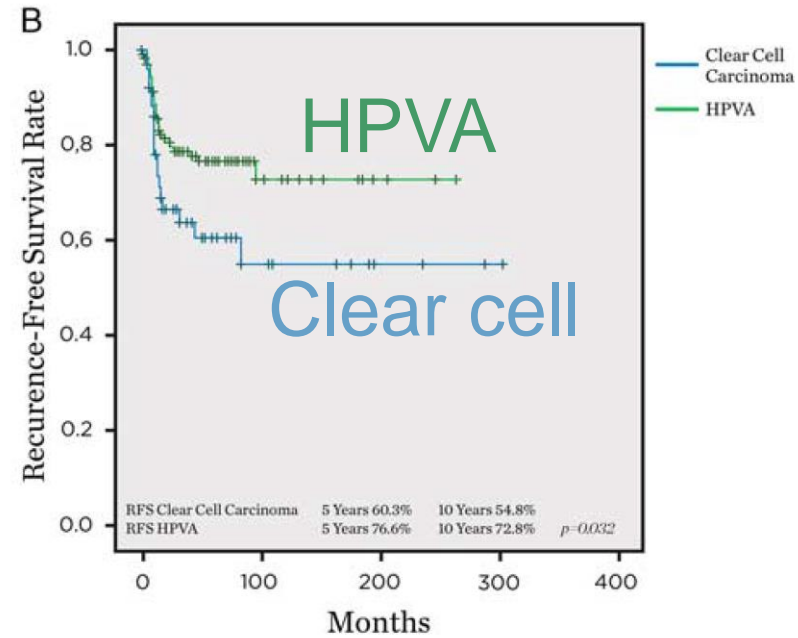
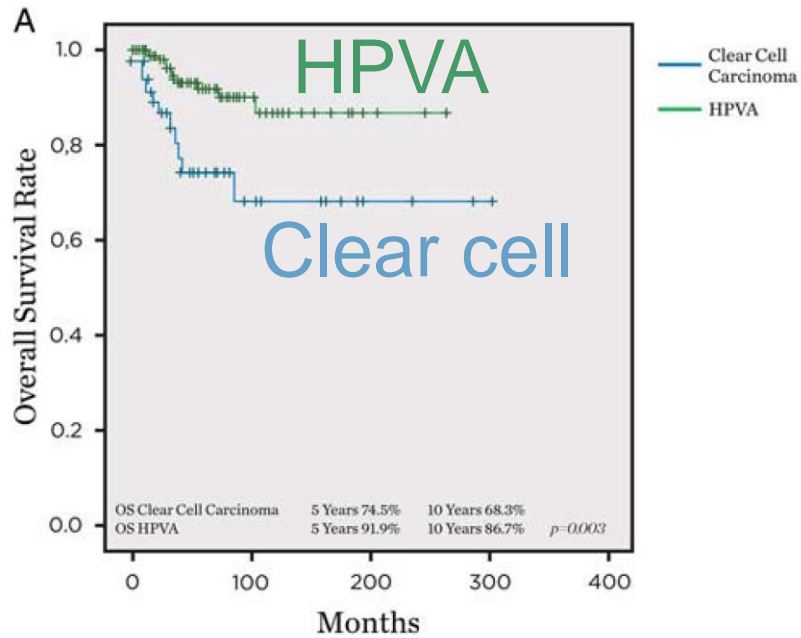
HPV-independent clear cell-type EAC



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HPV-independent clear cell-type EAC

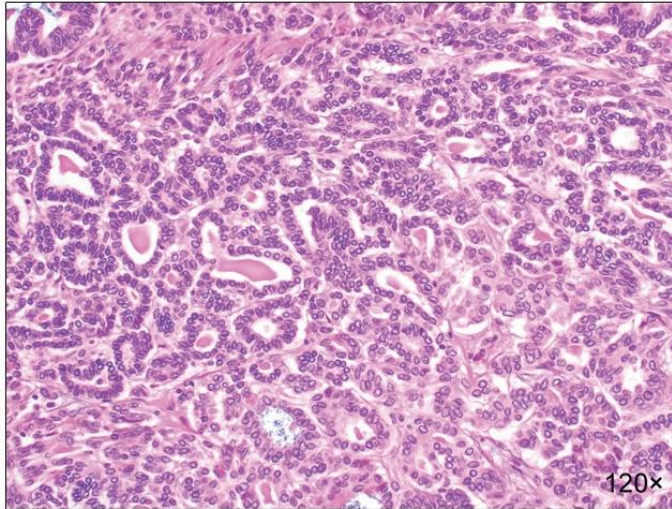


HPV-independent mesonephric-type EAC

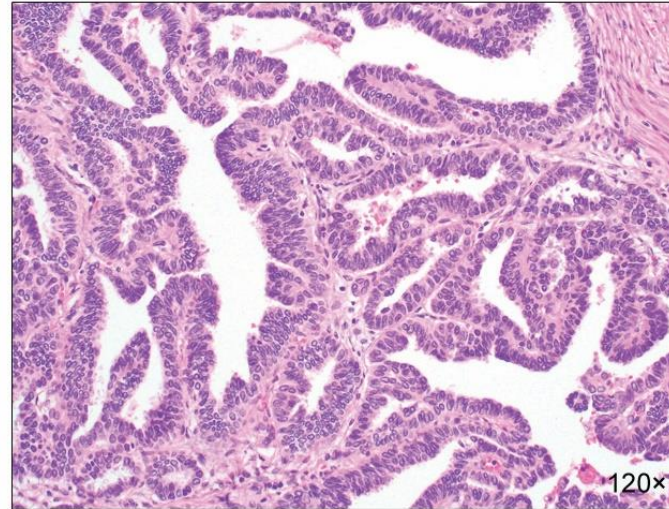
- <1% of all EAC cases
- Derived from Wolffian (mesonephric) remnants
- Morphological heterogeneity
 - Architectural diversity
 - Resembling other types of EAC
 - Posing diagnostic challenges

HPV-independent mesonephric-type EAC

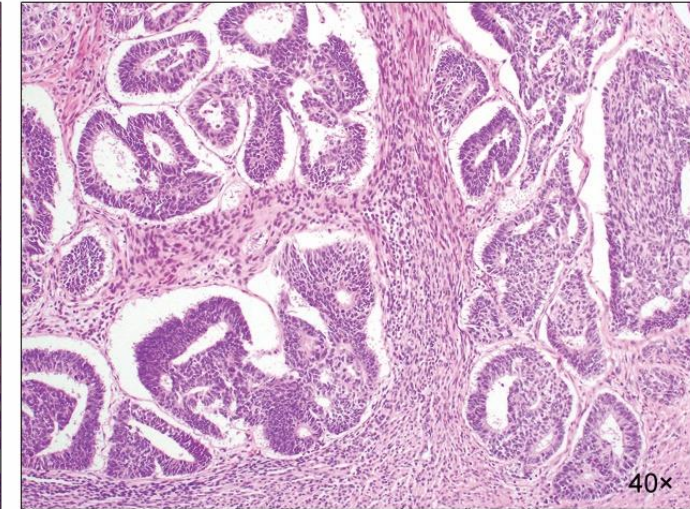
Tubular



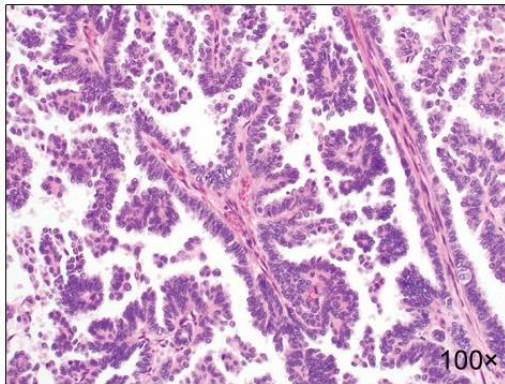
Ductal



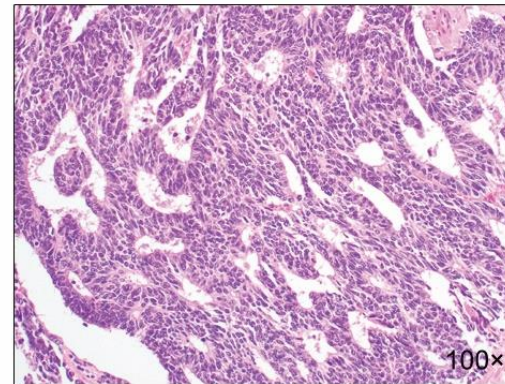
Endometrioid-like



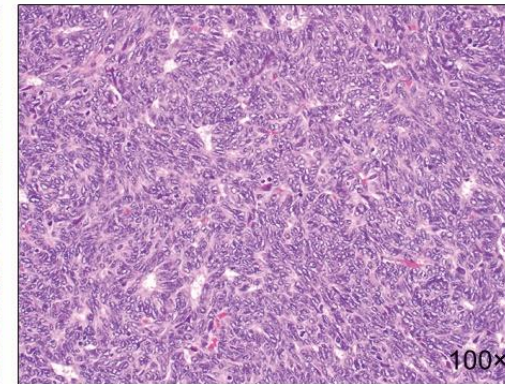
Papillary



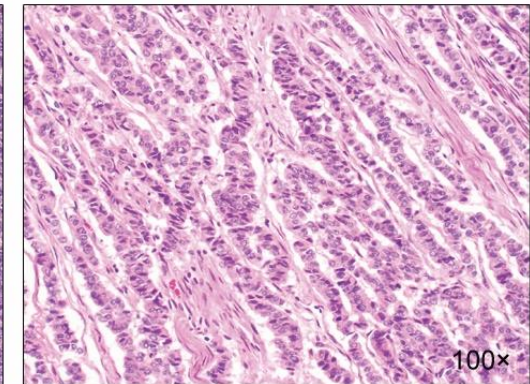
Cribriform



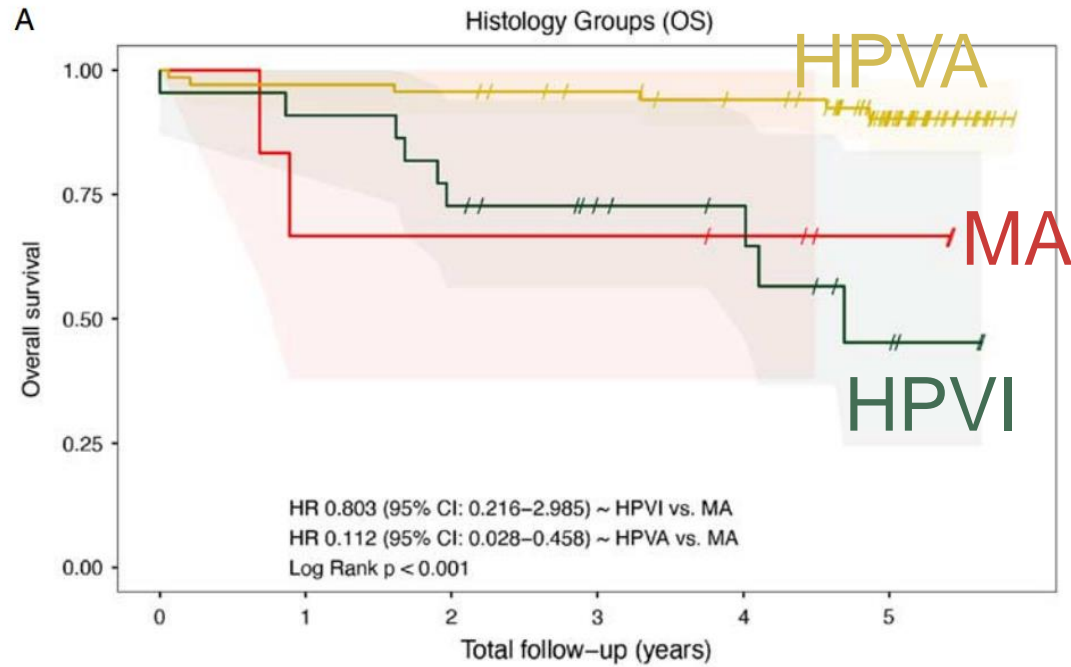
Solid



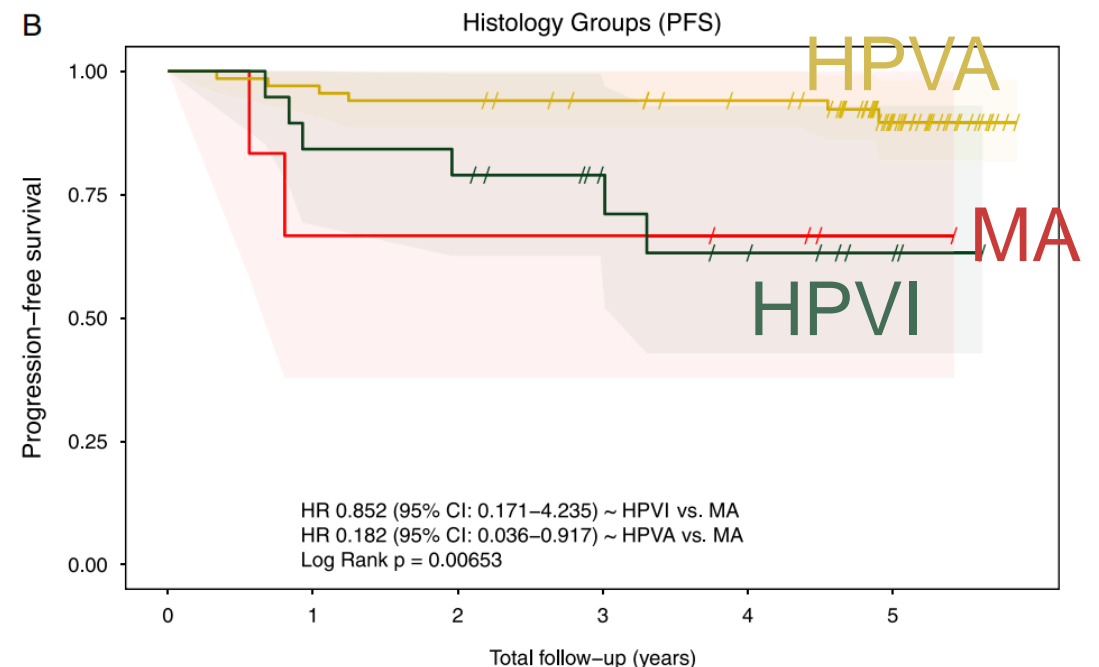
Sex cord-like



HPV-independent mesonephric-type EAC



	0	1	2	3	4	5
HPVI	22	20	16	11	9	4
HPVA	69	67	66	62	58	31
MA	6	4	4	4	3	1



	0	1	2	3	4	5
HPVI	19	16	15	10	7	3
HPVA	67	65	63	59	55	26
MA	6	4	4	4	3	1

Numbers at risk

- Distinct clinicopathological features
 - Rare but aggressive behavior
 - Often misdiagnosed due to morphological diversity
- Lung metastases
 - Early-stage disease
 - Despite appropriate treatment

- Updated EAC classification
 - 2018 IECC and 2020 WHO Classification
- HPV-independent EAC
 - Gastric, clear cell, and mesonephric types
 - Aggressive behavior and worse patient outcome

Thank you for listening.

HPV-independent Endocervical Adenocarcinoma

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