WHO Classifications of Gynecologic Tumors (5th ed. 2020)

--- A Concise Review for Clinicians

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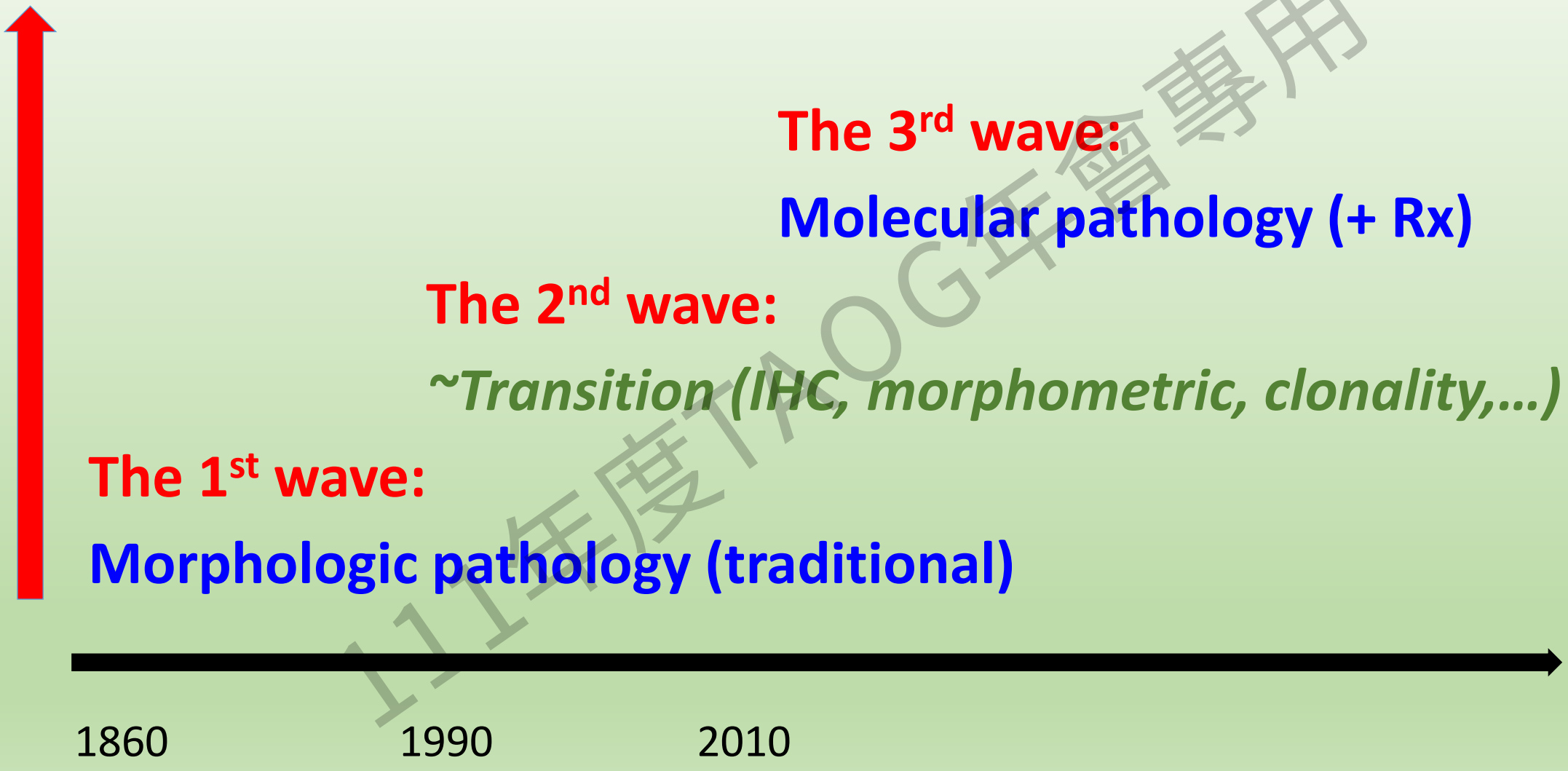
WHO Classifications of Gynecologic Tumors (5th ed., 2020)

- Prepared by **191** authors and editors
- Contributors from around the world
- More than **3100** references
- More than 850 high-quality images

- 4th ed. 2014 (GYN)
- 2nd/3rd ed. 1994/2003 (GYN & Breast)



Endometrial hyperplasia

WHO 1994

- Simple hyperplasia 1%
- Complex hyperplasia 3%

- Simple hyperplasia with atypia 8%
- Complex hyperplasia with atypia 29%

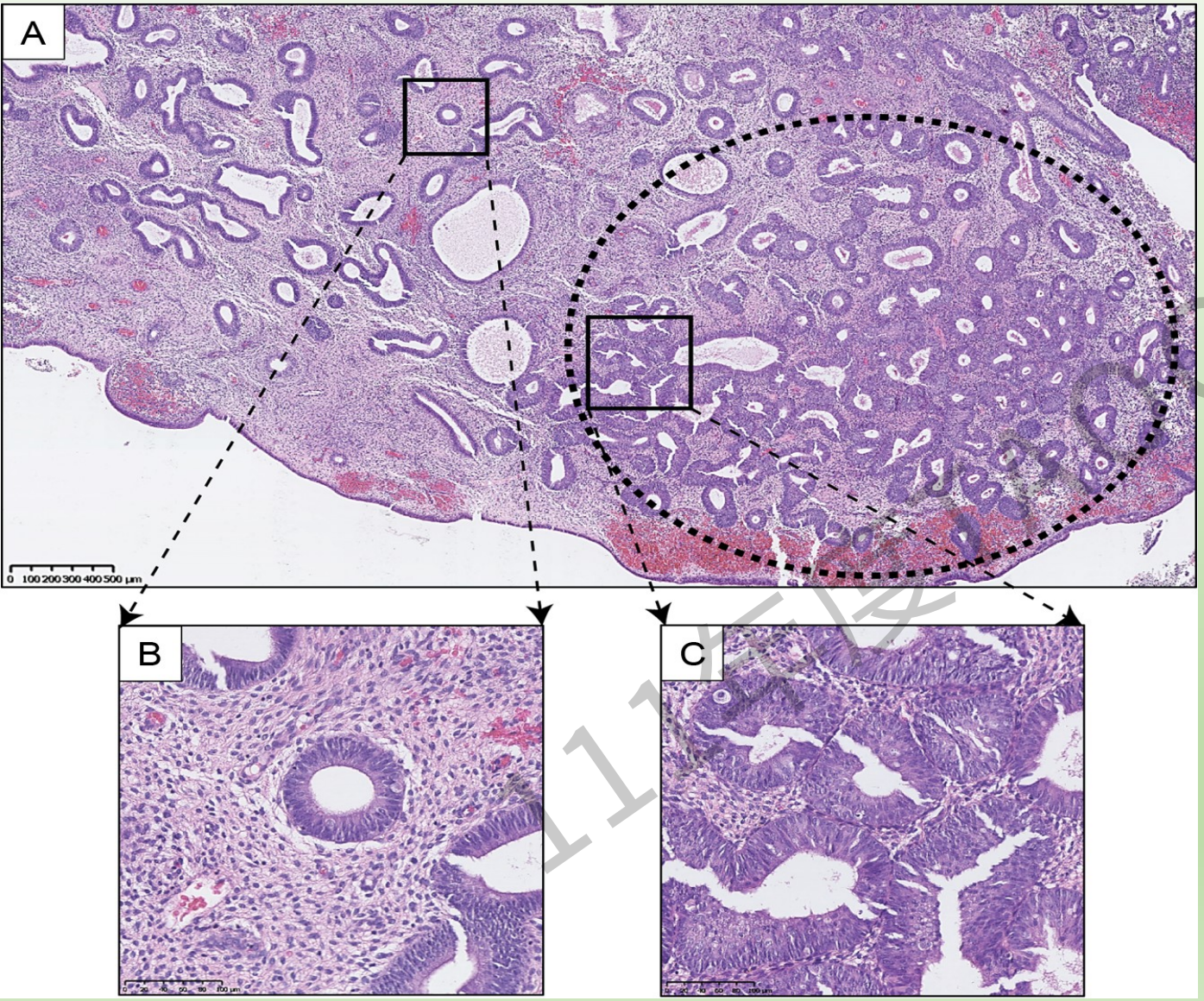
[non-atypia/atypia: 10%/40% →CA]

WHO 2014/2020

- **Hyperplasia without atypia**

- **Atypical hyperplasia / EIN**
  (endometrial intraepithelial neoplasm)

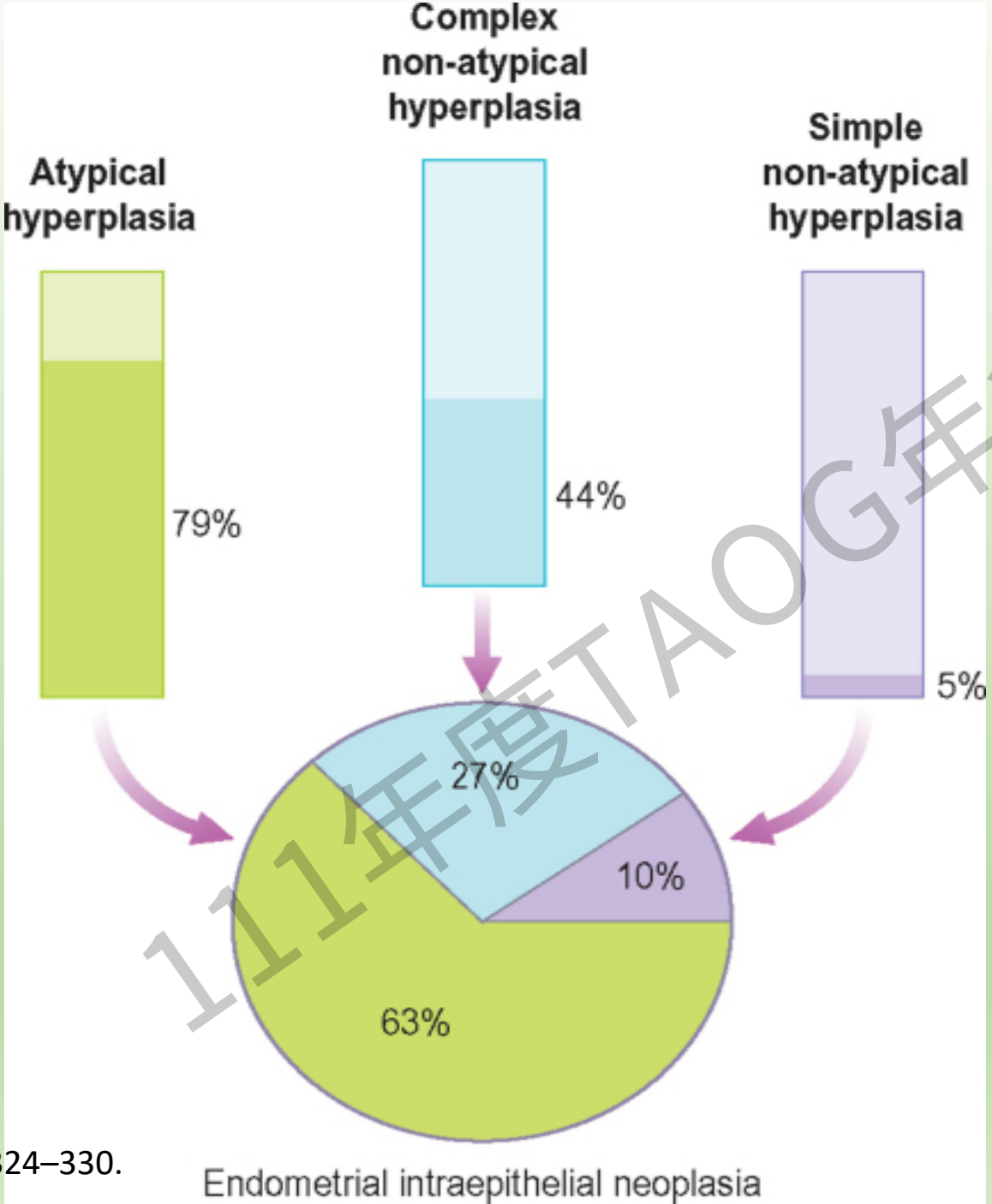
Endometrial Intraepithelial Neoplasia (EIN)



- **Size >1 mm**
- **Glands : stroma > 1 : 1**
- **Cytology change**
  (Glandular epithelium cytologically distinct from background endometrium)

Based on :

- morphometric studies
- molecular genetic studies of colonality



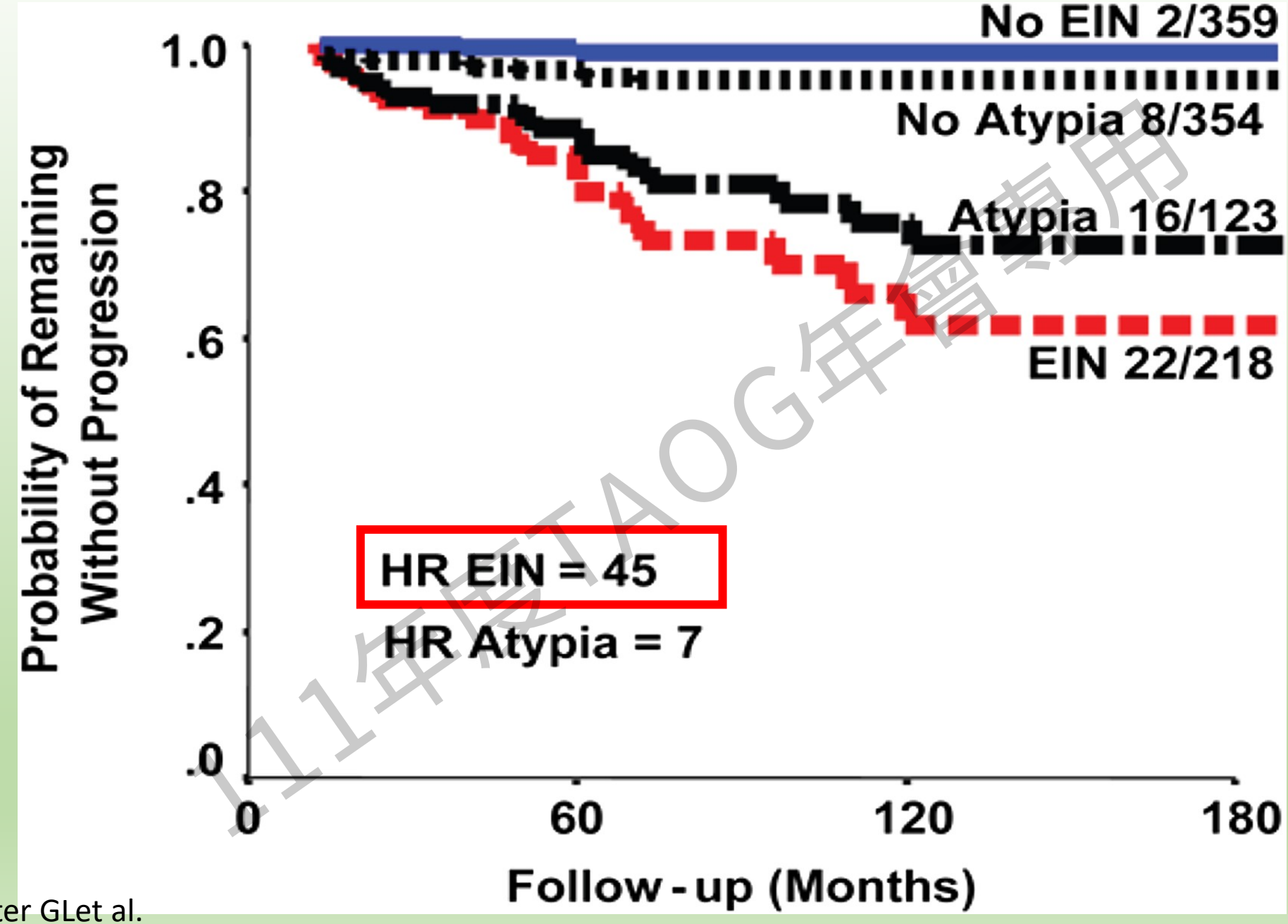
39% of EIN pts had cancer diagnosed within the 1st yr,

EIN: 28% → CA in 20 yrs

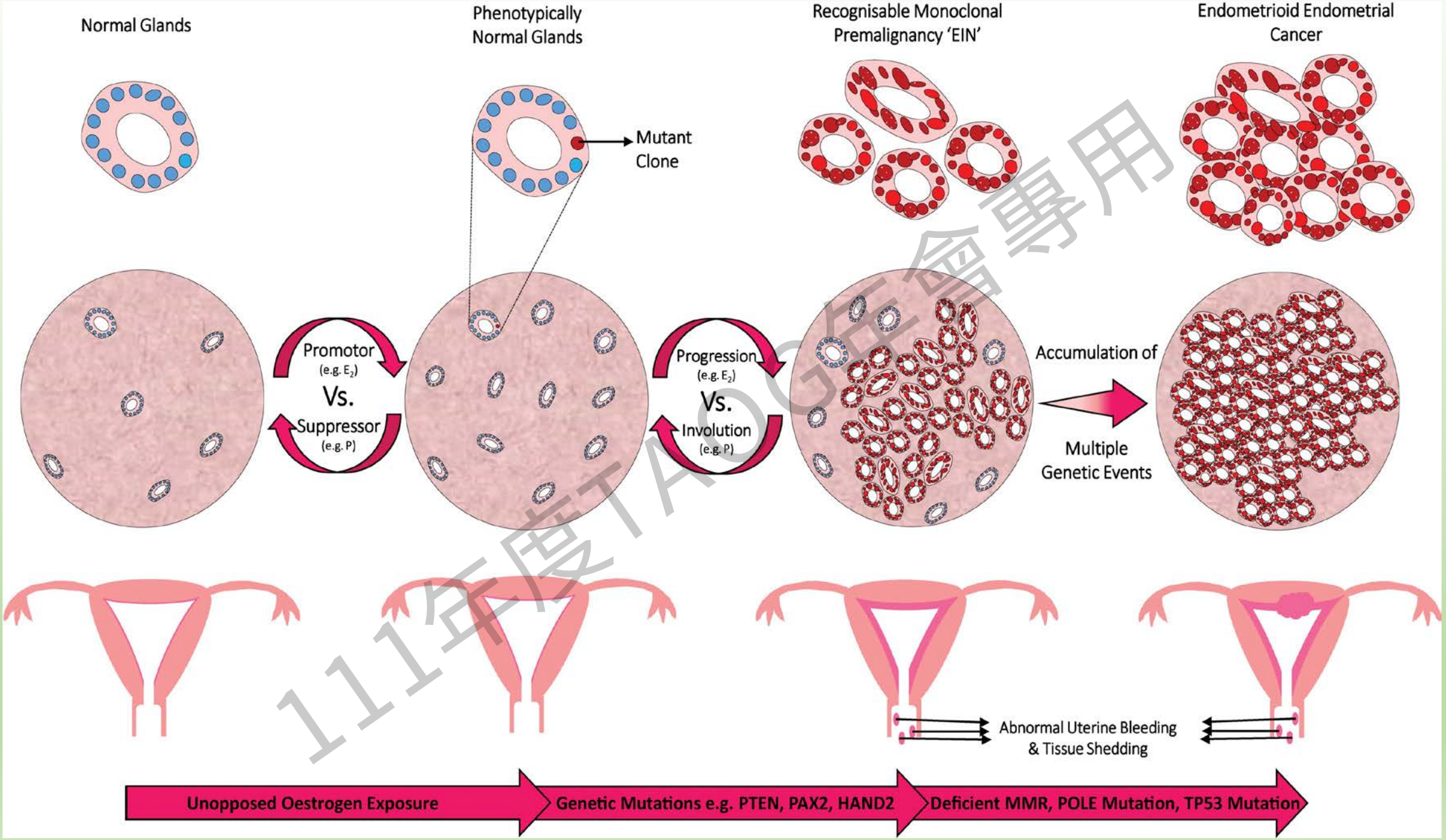
vs

4.6% for non-AH/EIN

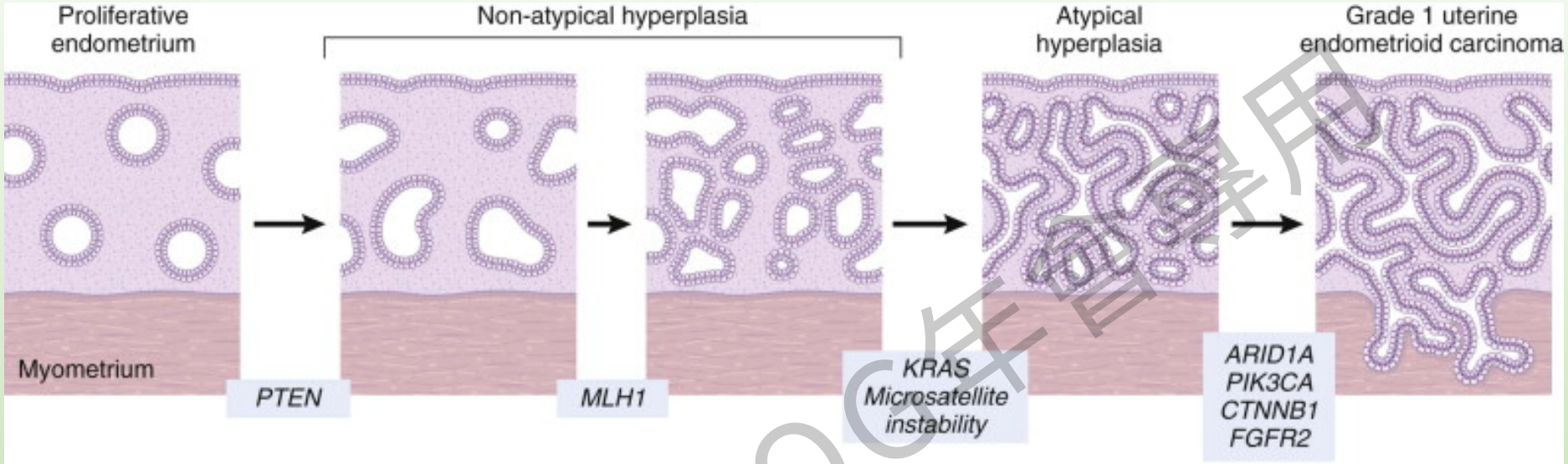
Hecht JL,…, Mutter GL.
Mod Pathol 2005; 18:324–330.

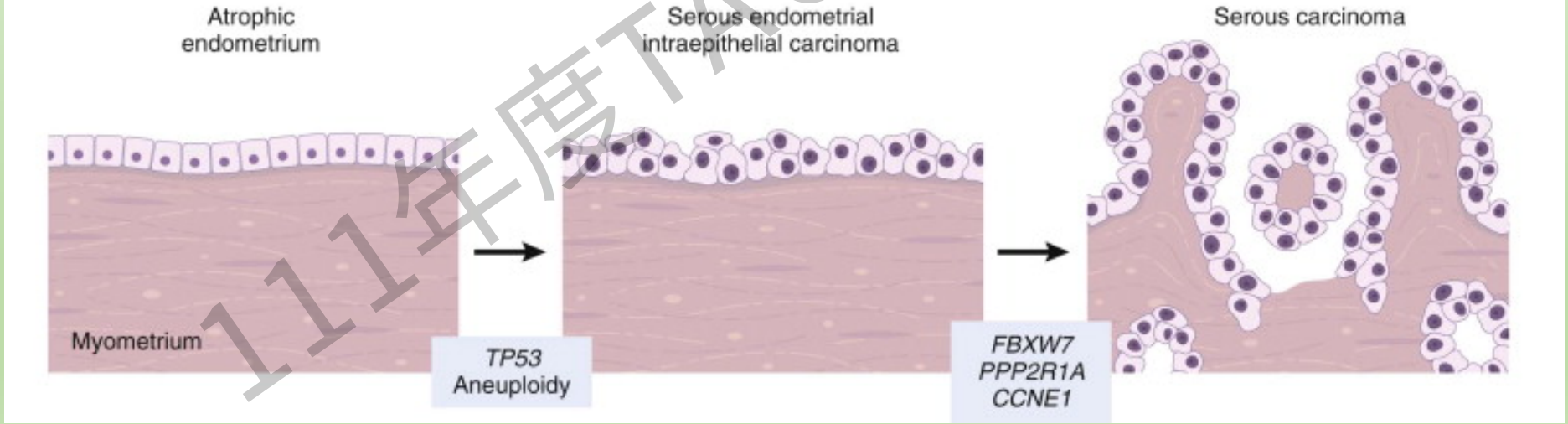


Baak JPA, Mutter GLet al.
Cancer 2005;103:2304–2312.



Type 1: endometrioid CA, FIGO G1~G2 (low-grade) / G3 (high-grade)





Type 2: non-endometrioid (serous CA), FIGO G3

Endometrial carcinoma

2014

- Endometrioid CA
  - Squamous differentiation
  - Villoglandular
  - Secretory
- Mucinous CA
- Serous CA
- Clear cell CA
- Undifferentiated CA

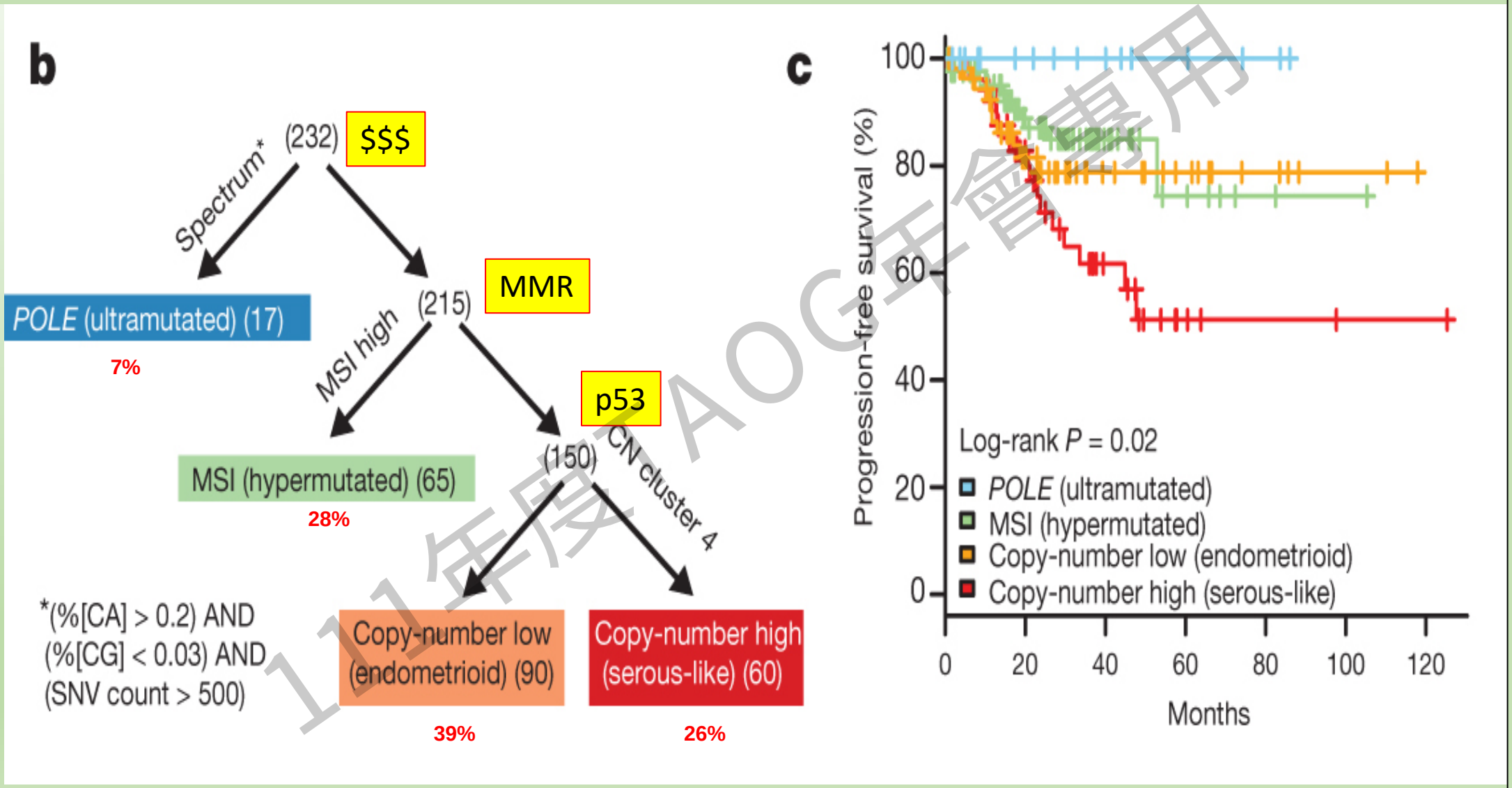
2020

- Endometrioid ADC NOS
  - **POLE-ultramutated**
  - **Mismatch repair-deficient**
  - **P53-mutant**
  - **No specific molecular profile (NSMP)**
- Mucinous CA, gastric/GI type
- Serous CA
- Clear cell CA
- Undifferentiated CA
- Mesonephric/mesonephric-like CA

Pathogenesis of Endometrial Ca

- Ultramutated/POLE tumors
  - mutations in DNA polymerase ε (POLE)
  - <10%; The highest somatic point mutation of human cancer.
- Hypermutated/MSI (microsatellite instability) tumors
  - mutations in or epigenetic silencing of mismatch repair genes
  - 20%; Lynch syndrome (HNPCC)
- Copy number low/MSS (microsatellite stable) tumors
  - associated with endometrioid morphology
- Copy number high/serous-like tumors
  - aggressive tumors with serous or high-grade endometrioid morphology that are often associated with *TP53* mutations
  - 50% of PD CA with TP53 mutation

The Cancer Genome Atlas (TCGA) molecular classification
Mutation spectra across endometrial carcinomas



G Getz *et al. Nature* **497**, 67-73 (2013)

nature

Table 3. Histological types within the four TCGA molecular classes as seen in a community and tertiary hospital-based cohort[52] and high-risk patients enrolled in the PORTEC-3 trial[51]

Histological type of EC		POLEmut	MMRd	NSMP	p53abn	Total
Number (%) of cases, Vancouver data (community and tertiary hospital-based data; all risk groups)						
Endometrioid, low-grade	(6.5%)	38 (*69*)	186 (*75*)	349 (*90*)	11 (*6*)	**584 (68)**
Endometrioid, high-grade	(11.3%)	11 (*20*)	45 (*18*)	22 (*6*)	19 (*11*)	**97 (11)**
Serous		0 (*0*)	6 (*2*)	3 (*1*)	90 (*51*)	**99 (11)**
Clear cell		0 (*0*)	0 (*0*)	5 (*1*)	6 (*3*)	**11 (1)**
Undifferentiated/dedifferentiated		1 (*2*)	4 (*2*)	1 (*<1*)	2 (*1*)	**8 (1)**
Mixed		5 (*9*)	4 (*2*)	5 (*1*)	15 (*9*)	**29 (3)**
Carcinosarcoma		0 (*0*)	0 (*0*)	2 (*1*)	29 (*17*)	**31 (4)**
Other		0 (*0*)	2 (*1*)	0 (*0*)	3 (*2*)	**5 (1)**
Total		55 (6)	247 (29)	387 (45)	175 (20)	864 (100)

Thompson E, Huvila J, Leung S *et al*. Refining pathologic interpretation of endometrial carcinomas: lessons learned from a nationwide study in a new era of molecular classification. *Int. J. Gynecol. Cancer* 2020; **30**; A3–A4.

McCluggage WG, et al. Histopathology 2022, 80(5), 762

Table 3. Histological types within the four TCGA molecular classes as seen in a community and tertiary hospital-based cohort[52] and high-risk patients enrolled in the PORTEC-3 trial[51]

Histological type of EC		POLEmut	MMRd	NSMP	p53abn	Total
Number (%) of cases, PORTEC-3 data (high-risk cases)						
Endometrioid, low-grade		4 (*8*)	59 (*43*)	94 (*73*)	4 (*4*)	**161 (39)**
Endometrioid, high-grade	(25.6%)	29 (*57*)	47 (*34*)	16 (*12*)	21 (*23*)	**113 (28)**
Serous	(9.2%)	6 (*12*)	7 (*5*)	6 (*5*)	46 (*49*)	**65 (16)**
Clear cell	(15.3%)	6 (*12*)	12 (*9*)	9 (*7*)	12 (*13*)	**39 (10)**
Undifferentiated/dedifferentiated*		–	–	–	–	–
Mixed		3 (*6*)	7 (*5*)	3 (*2*)	6 (*6*)	**19 (5)**
Carcinosarcoma†		–	–	–	–	–
Other		3 (*6*)	5 (*4*)	1 (*1*)	4 (*4*)	**13 (3)**
Total		51 (12)	137 (33)	129 (32)	93 (23)	410 (100)

Leon-Castillo A, de Boer SM, Powell ME *et al.* Molecular classification of the PORTEC-3 trial for high-risk endometrial cancer: impact on prognosis and benefit from adjuvant therapy. *J. Clin. Oncol.* 2020; **38**; 3388–3397.

McCluggage WG, et al. Histopathology 2022, 80(5), 762

Uterine corpus tumors

2014

- **Mixed epithelial & mesenchymal tumors**
  - Adenomyoma
  - Atypical polypoid adenomyoma
  - ~~**Adnofibroma**~~
  - Adenosarcoma
  - Carcinosarcoma

2020

- **Mixed epithelial & mesenchymal tumors**
  - Adenomyoma
  - Atypical polypoid adenomyoma
  - Adenosarcoma

- **Epithelial tumors**
  - **Carcinosarcoma**

Endometrial stromal tumors

2014 / 2020

- Endometrial stromal nodule(ESN)
- Endometrial stromal sarcoma, low grade (LG-ESS)
- Endometrial stromal sarcoma, high grade (HG-ESS)**
- Undifferentiated uterine sarcoma [SMARCA4 mutation]

Endometrial stromal tumors (WHO-2020)

	CD10	ER	PR	CyclinD1	BCOR	Desmin	SMA	Caldesmon
ESN	+ D	+ D	+ D	-/+ F	-/+ F	-/+ F/D	+ D	+ F/D
LG-ESS	+ D	+ D	+ D	-/+ F	-/+ F	-/+ F/D	+ D	+ F/D
YWHAE-NUT2A/B HG-ESS Low-grade areas	+ D	+ D	+ D	-/+ F	-/+ F	-	-	-
YWHAE-NUT2A/B HG-ESS High-grade areas	-	-	-	+ D	+ D	-	-	-
ZC3H7B-BCOR HG-ESS	+ D	-/+ F	-/+ F	+ D	-/+ F/D	-	-/+ F	-/+ F
BCOR ITD HG-ESS	+ F/D	-	-	+ D	+ F/D	-/+ F	-	-

Cervix (FIGO 2019 & AJCC v9)

- **T1a: stromal invasion ≦5mm** ~~**& horizontal spread ≦7mm**~~
- **T1b: stromal invasion >5mm**~~**or horizontal spread >7mm**~~

- T1b1: ~~clinical lesion ≦4cm~~ **≦2cm in size**
- T1b2: ~~clinical lesion >4cm~~ **>2cm & ≦4cm in size**
- **T1b3**: clinical lesion >4cm

Squamous Cell Tumors (WHO-2020)

Cervix & Vagina

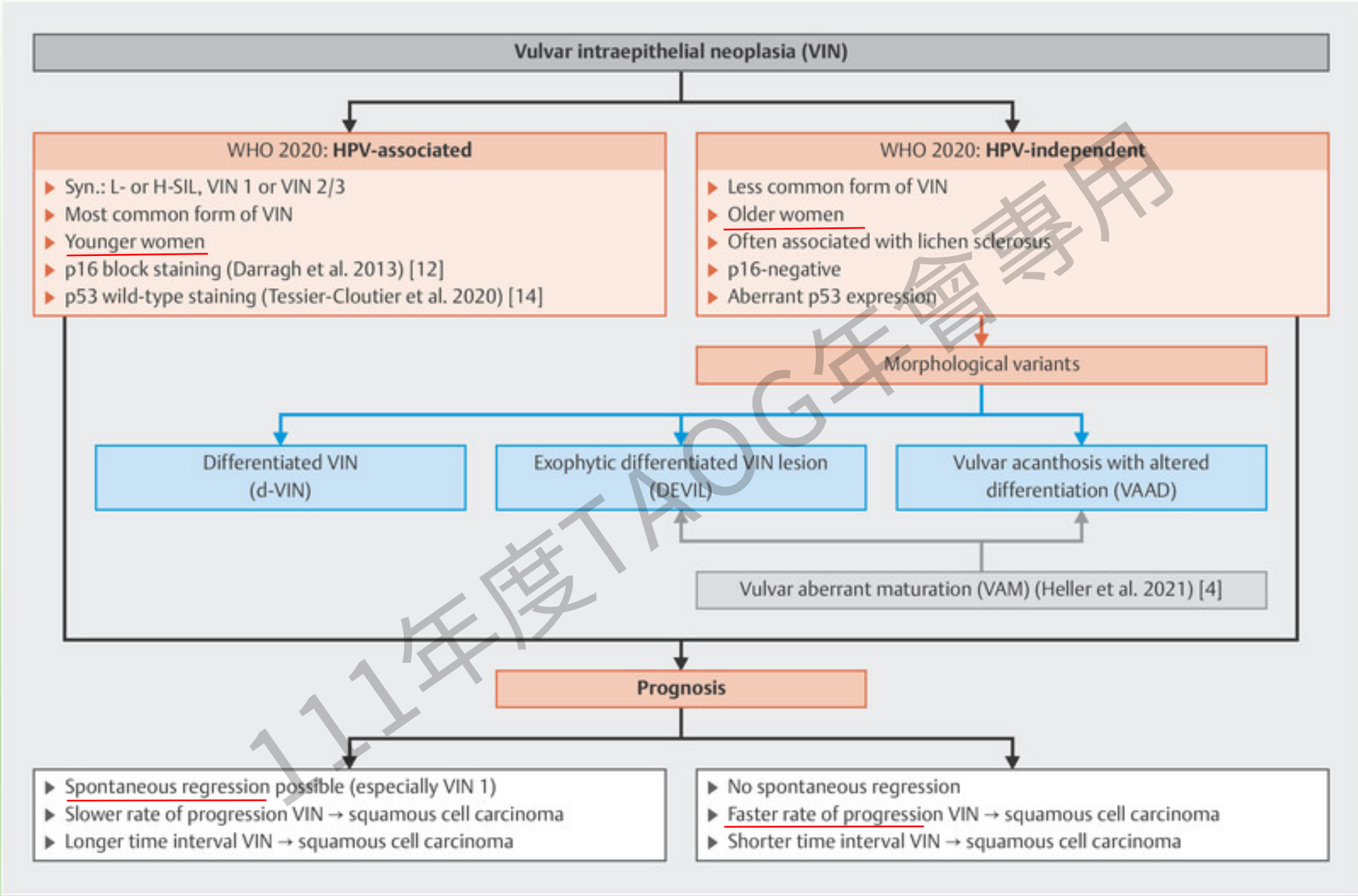
- LSIL (CIN1, VAIN1)
- HSIL (CIN2/3, VAIN2/3)
  - **HPV(+)**

- Squamous cell carcinoma (**SCC**)
- SCC, HPV-associated
- SCC, HPV-independent **(cx5-7%/vag26%)**
- SCC, NOS

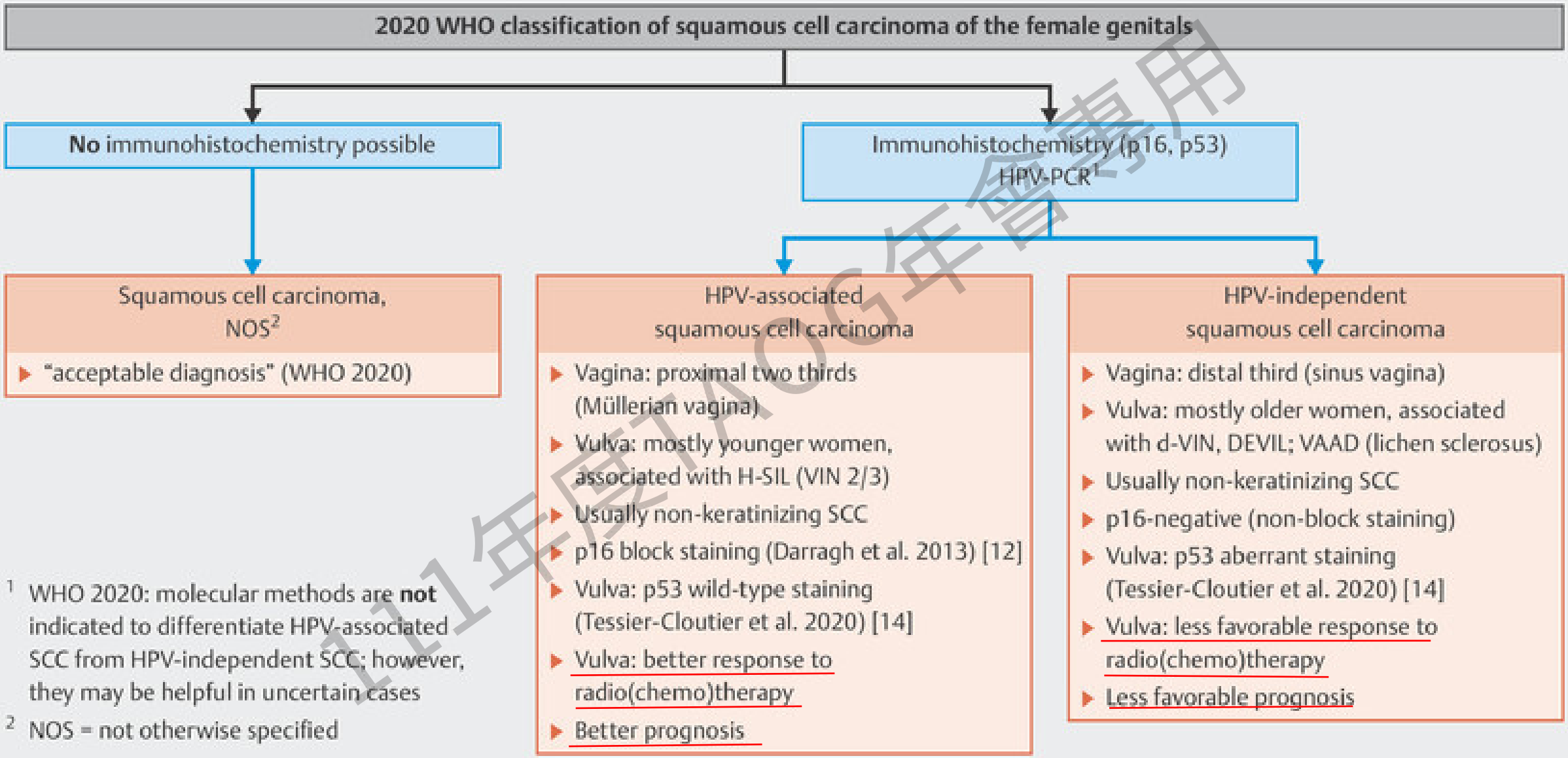
Vulva

- VIN, HPV-associated (LSIL/HSIL) (p16+)
- VIN, HPV-independent (p16-)
  - Differentiated VIN **(dVIN)** (p53+)
  - Differentiated exophytic VIN **(DEVIL)** (p53-)
  - Vulvar acanthosis with altered diff.**(VAAD)** (p53-)

- SCC, HPV-associated
- SCC, HPV-independent **(25-80%) or (2/3)** [p53+(80%)]
- SCC, NOS



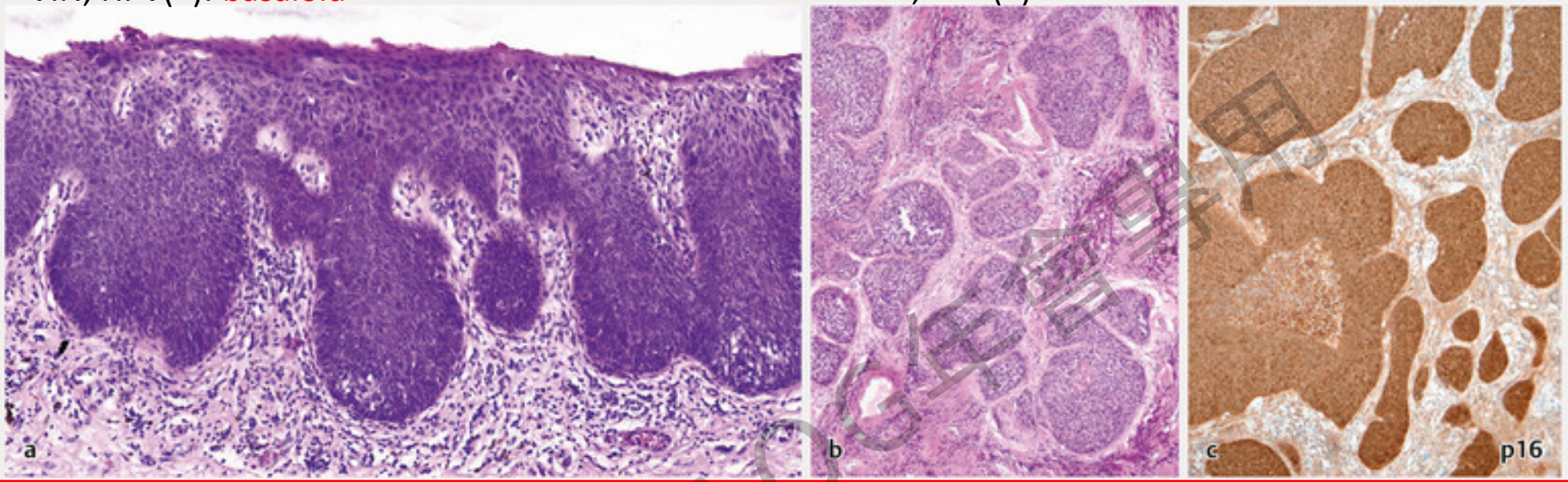
Höhn AK, Brambs CE, Hiller GGR, May D, Schmoeckel E, Horn LC. *Geburtshilfe Frauenheilkd*. 2021;81(10):1145-1153.

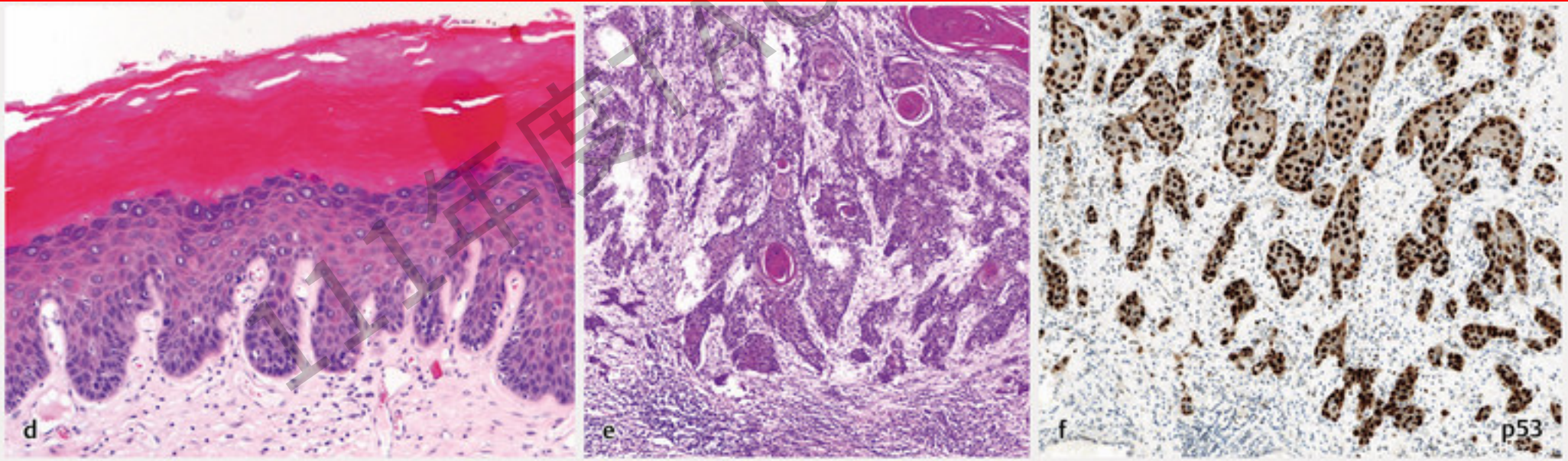


Höhn AK, Brambs CE, Hiller GGR, May D, Schmoeckel E, Horn LC. *Geburtshilfe Frauenheilkd*. 2021;81(10):1145-1153.

VIN, HPV(+): basaloid

SCC, HPV(+): basaloid





VIN,HPV(-): differentiated

SCC,HPV(-), keratinizing

Höhn AK, Brambs CE, Hiller GGR, May D, Schmoeckel E, Horn LC. *Geburtshilfe Frauenheilkd*. 2021;81(10):1145-1153.

Cervical SCC

Types → “Patterns”

WHO 2014	WHO 2020
Squamous cell carcinoma, usual type	Squamous cell carcinoma, HPV-associated
Keratinising type	Squamous cell carcinoma, HPV-independent
Non-keratinising type	Squamous cell carcinoma, NOS
Papillary type	
Basaloid type	
Warty type	
Verrrucous type	
Squamotransitional type	
Lymphoepithelioma-like type	

HPV, Human papillomavirus; NOS, not otherwise specified.

Glandular tumors (cervix)

2014

- **Adenocarcinoma in situ (AIS)**

- **Adenocarcinoma (ADC)**
  - Endocx ADC, usual type
  - Mucinous CA,NOS
    - Gastric, intestinal, signet-ring cell
  - Mesonephric CA
  - Clear cell CA
  - Villoglandular CA
  - Endometrioid CA
  - Serous CA

2020

- AIS NOS
- AIS, HPV-associated
- AIS, HPV-independent

- ADC NOS
- ADC, HPV-associated
- ADC, HPV-independent
  - **Gastric, clear cell, mesonephric, NOS**

- Endometrioid ADC NOS

Glandular tumors (cervix)

2014

- **AIS**

- **ADC**
  - Endocx ADC, usual type
  - Mucinous CA,NOS
    - **Gastric**, intestinal, signet-ring cell
  - **Clear cell CA**
  - **Mesonephric CA**
  - Villoglandular CA
  - Endometrioid CA [HPV(+)]**(5%) (X)**
  - ~~Serous CA~~ **(X)**

2020

- AIS NOS
- AIS, HPV-associated
- AIS, HPV-independent

- ADC NOS
- ADC, HPV-associated [85%]
- ADC, HPV-independent [15%]
  - **Gastric (10-15%), clear cell (3-4%), mesonephric (<1%), NOS**

- **Endometrioid ADC NOS** [HPV(-)] **(<1%)**

ADC, HPV-associated (cervix) (WHO-2020)

- **Usual type** (~75%)
  - Papillary (including villoglandular)/ micropapillary growth
    - Villoglandular variant
- **Mucinous type** (~10%)
  - Mucinous NOS ADC
  - Intestinal ADC
  - Signet-ring cell ADC
  - **Stratified mucin-producing CA** (i-SMILE)

Glandular tumors **(vagina)**

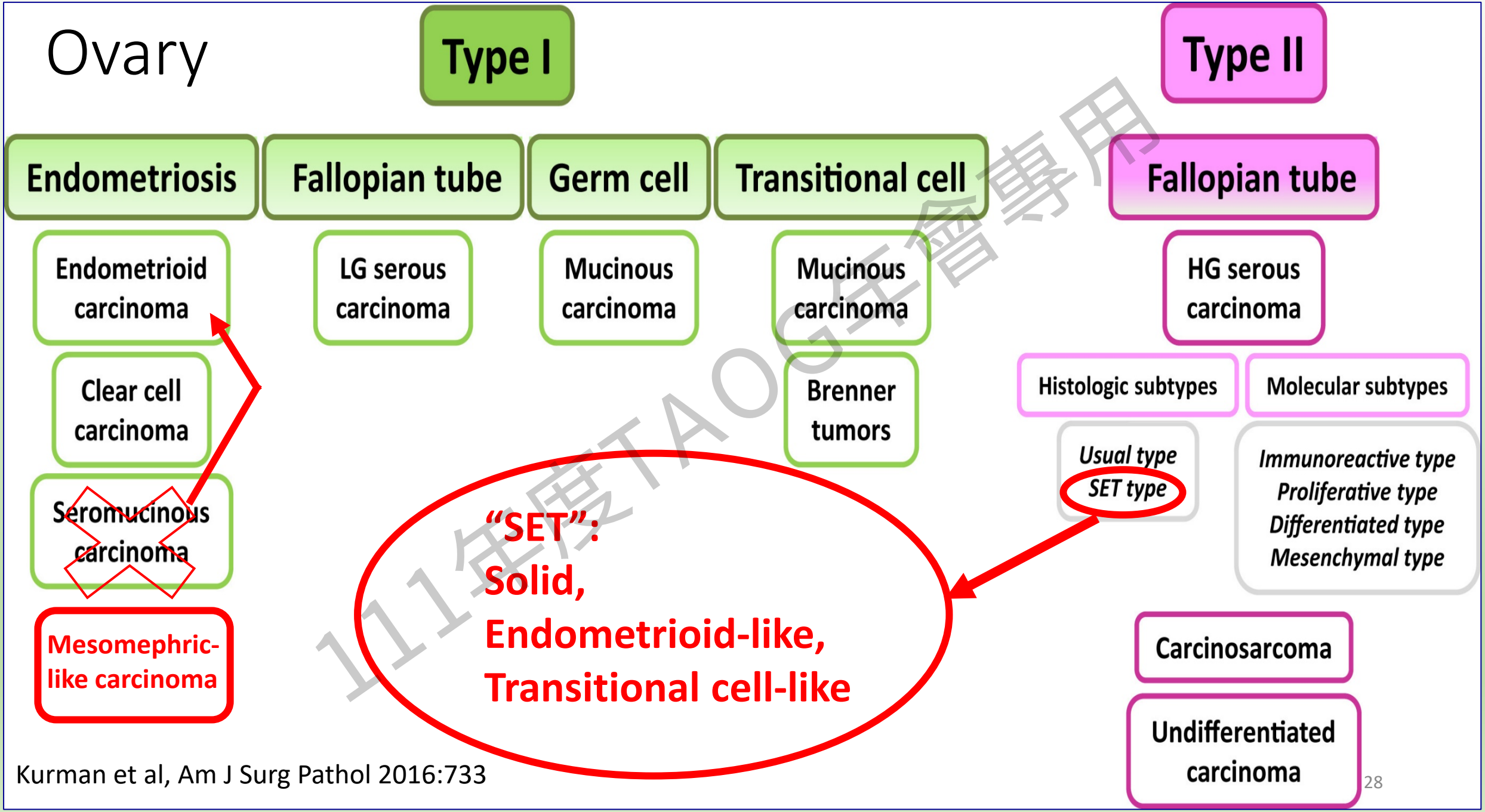
2014

- ADC
  - Endometrioid CA
  - Clear cell CA
  - Mucinous CA,NOS
  - Mesonephric CA

2020

- ADC, NOS
- ADC, HPV-associated
- **Endometrioid ADC NOS**
- Clear cell ADC NOS
- Mucinous CA, gastric NOS
- Mucinous ADC (intestinal type)
- Mesonephric ADC

Ovary



Kurman et al, Am J Surg Pathol 2016:733

Ovary: Serous Tumors

2014

- Serous cystadenoma with focal epithelial hyperplasia (<10%)

- Serous borderline tumor(SBT)-micropapillary variant/ Non-invasive low-grade serous carcinoma(LGSC)
- SBT with microinvasion(<5mm)
- ~~SBT with microinvasive carcinoma~~

2020

- Serous cystadenoma with focal epithelial hyperplasia (<10%)
  - Except for **surface involvement** → associated with recurrence
- SBT, micropapillary/cribriform subtype
- SBT with microinvasion(<5mm)
- **Microinvasive LGSC** (<5mm)

Ovary: Seromucinous Tumors

2014

- Seromucinous cystadenoma
- Seromucinous borderline tumor/Atypical proliferative seromucinous tumor
- ~~Seromucinous carcinoma~~

2020

- Seromucinous cystadenoma
- Seromucinous borderline tumor

→subtype of endometrioid CA (with mucinous differentiation)

Ovary

2014

- Undifferentiated CA

2020

- Undifferentiated CA:
  - ✓Lack of a specific line of differentiation
- **Dedifferentiated CA**:
  - an **undiff. CA** + a **differentiated** component
    - ✓Endometrioid CA (commonly) or serous CA (rarely)
    - ✓A specific type mixed CA

Mixed Carcinomas (≥ 2 different histological types)

2014

- Endometrium:
- **5 %** of a 2nd histological type

2020

Endometrium:

- **Any %** of high-grade CA
- At least one is serous or clear cell
  - Uncommon (10%)

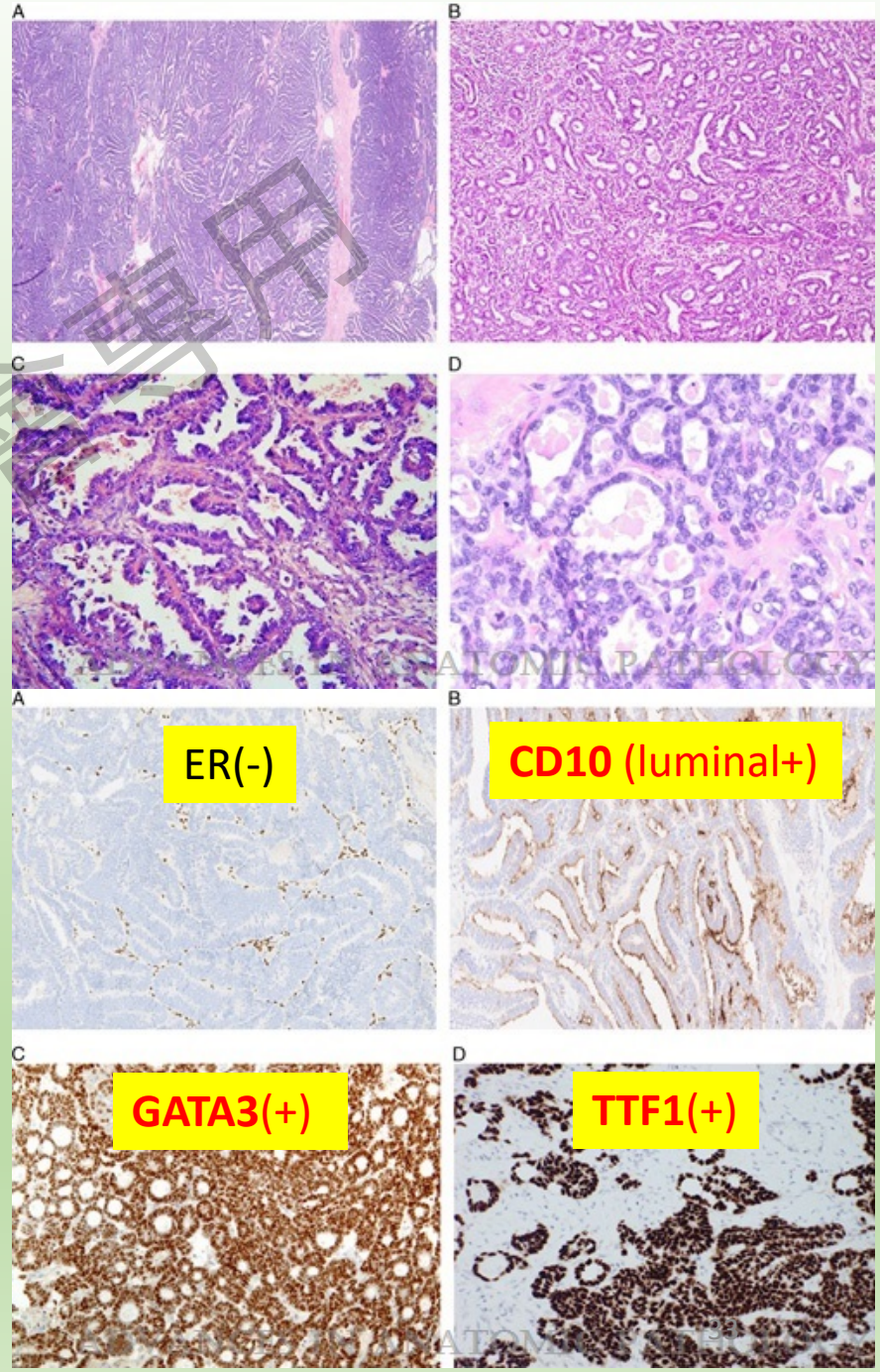
- Ovary:
- **Any %** of a 2nd histological type
  - Rare (<1%)

Mesonephric CA (MA)
Mesonephric-like CA (MLA)

- Vagina & Cervix: **MA** [ADC, HPV(-)]

- **Endometrium & Ovary: MLA**
  - Rare
  - ***KRAS*** & ***PIK3CA*** mutation
  - Associated **endometriosis (Müllerian origin)**
  - **Aggressive!!**

Adv Anat Pathol 2022;29(4):208-216



Synchronous endometrioid CAs of endometrium & ovary

1. **Both tumors are low-grade**
2. **<50% myometrial invasion**
3. **No involvement of any other site**
4. **Extensive LVSI not present**

Clonally related. ***BUT:***

Excellent outcome → "indolent metastasis"

→ managed as independent synchronous tumors.

Table 1.01 Criteria for assigning primary site in extrauterine HGSC

Primary site	Criteria for diagnosis
Fallopian tube	STIC present *or* Mucosal HGSC present *or* Part or entire length of tube inseparable from tubo-ovarian mass
Ovary	Both fallopian tubes separate from ovarian mass *and* No STIC or mucosal HGSC in either tube
Tubo-ovarian	Fallopian tubes and ovaries not available for complete examination *and* Pathological findings consistent with extrauterine HGSC
Peritoneal	Both tubes and both ovaries fully examined *and* No gross or microscopic evidence of STIC or HGSC in tubes or ovaries

Mod Pathol. 2015;28(8):1101-22
Gynecol Oncol. 2016;141(2):195-8
Int J Gynecol Pathol. 2016;35(3):230-7
Histopathology. 2014;65(2):149-54
Pathology 2015;47(5):423-31

W Glenn McCluggage

Naveena Singh

Neuroendocrine neoplasms (NENs)

2014

- Low-grade NE tumor (NET)
  - Carcinoid tumor
  - Atypical carcinoid tumor
- High-grade NE carcinoma (NEC)
  - Small cell NEC
  - Large cell NEC

2020

- NET NOS
  - NET, grade 1
  - NET, grade 2

  (excluded “ovarian carcinoid”)
- Small cell NEC
- Large cell NEC
- Combined small/large cell NEC

  (non-NE carcinoma admixed with NEC)

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Molecular events in adnexal sex-cord-stromal & other neoplasms

Tumour type	Molecular event
Adult granulosa cell tumour	Somatic *FOXL2* mutations
Sertoli–Leydig cell tumour	Somatic or germline *DICER1* mutations
Juvenile granulosa cell tumour	*AKT1* duplications and somatic mutations
Microcytic stromal tumour	*CTNNB1* or *APC* mutations
Sclerosing stromal tumour	*FHL2*::*GLI2* fusion
Sex cord tumour with annular tubules	*STK11* mutations
STK11 adnexal tumour	*STK11* mutations
Small-cell carcinoma of the ovary of the hypercalcaemic type	Somatic or germline *SMARCA4* mutations

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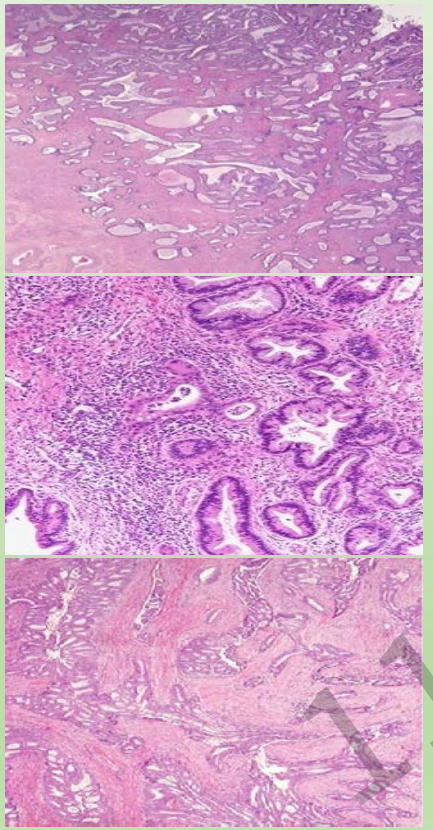
ADC, HPV-associated (cervix) (WHO-2020)



Silva system

- Pattern A (non-destructive)
- Pattern B (early/focal destructive)
- Pattern C (diffusely destructive)

	LN (+)	Recurrence	DOD
A	0 %	0 %	0 %
B	4 %	1 %	0 %
C	24 %	22 %	9 %