Thieme

2020 WHO Classification of Female Genital Tumors

WHO-Klassifikation 2020 für Tumoren des unteren weiblichen Genitales

Authors

Anne Kathrin Höhn[1], Christine E. Brambs[2], Grit Gesine Ruth Hiller[1], Doris May[3], Elisa Schmoeckel[3], Lars-Christian Horn[1]

Affiliations

1 Arbeitsgruppe Mamma, Gynäko- & Perinatalpathologie, Institut für Pathologie, Universitätsklinikum Leipzig AöR, Leipzig
2 Frauenklinik, Kantonsspital, Luzern, Schweiz
3 Pathologisches Institut der Ludwig-Maximilians-Universität München, München

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Correspondence

Dr. med. Anne Kathrin Höhn
Arbeitsgruppe Mamma-, Gynäko- & Perinatalpathologie, Institut für Pathologie, Universitätsklinikum Leipzig AöR
Liebigstraße 26, 04103 Leipzig, Deutschland
annekathrin.hoehn@medizin.uni-leipzig.de

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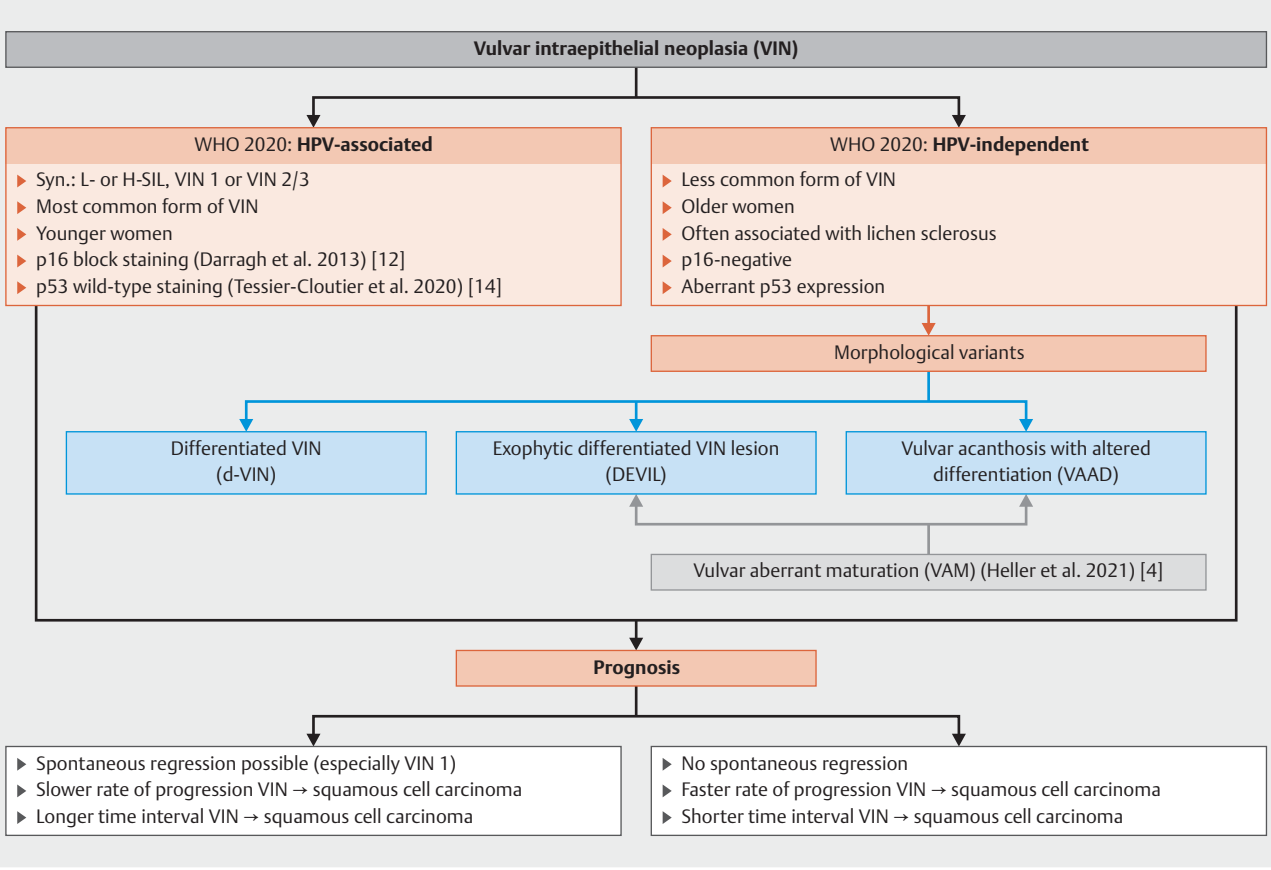
ABSTRACT

The 2020 WHO classification is focused on the distinction between HPV-associated and HPV-independent squamous cell carcinoma of the lower female genital organs. Differentiating according to HPV association does not replace the process of grading; however, the WHO classification does not recommend any specific grading system. VIN are also differentiated according to whether they are HPV(p16)-associated. HPV-independent adenocarcinoma (AC) of the cervix uteri has an unfavorable prognosis. Immunohistochemical p16 expression is considered to be a surrogate marker for HPV association. HPV-associated AC of the cervix uteri is determined using the prognostically relevant Silva pattern.

ZUSAMMENFASSUNG

In der WHO-Klassifikation 2020 steht die Unterscheidung von HPV-assoziierten und HPV-unabhängigen Plattenepithelkarzinomen des unteren weiblichen Genitales im Vordergrund. Die Unterscheidung der HPV-Assoziation ersetzt das Grading nicht, für welches jedoch kein Gradingsystem empfohlen wird. Auch bei der VIN erfolgt die Trennung nach HPV-(p16-)Assoziation. HPV-unabhängige Adenokarzinome (AC) der Cervix uteri sind prognostisch ungünstiger. Als Surrogatmarker für eine HPV-Assoziation gilt der immunhistochemische Nachweis von p16. Beim HPV-assoziierten AC der Cervix uteri erfolgt die prognostisch relevante Angabe des sog. Silva-Patterns.



▶ **Fig. 1** Clinicopathological characteristics of the 2020 WHO classification of vulvar precancerous lesions [1–4, 12, 14].

Introduction

The WHO Classification of Female Genital Tumors is the fourth volume in the fifth edition of the WHO series on the classification of human tumors, and was fundamentally revised in 2020 due to new histomorphological data and, in particular, molecular pathology data. In comparison with the 2013 edition, the scope of the work has doubled in length. The WHO classification is now primarily constructed on the basis of new (molecular) pathology data. However, data of therapeutic and diagnostic relevance, insofar as they are available, are certainly also incorporated. The WHO Blue Books represent an important foundation for a globally uniform diagnostic standard. In Germany, the guidelines of the AWMF (Association of the Scientific Medical Societies) recommend using the current WHO classification for the pathological findings report. The obligation to use the diagnostic histopathological standards and terminology according to the current WHO classification is described in all of the guidelines relating to gynecological malignancies with the verb “should”, this being the highest level of recommendation. While the WHO classification sets out terminology and criteria for diagnosis, the TNM classification of malignant tumors as well as the FIGO classification (Fédération Internationale de Gynécologie et d’Obstétrique) are used for staging, i.e., determining the extent and spread of the gynecological tumors.

The following article summarizes the significant changes of clinical relevance in the current WHO classification for tumors of the female genitals in a way that is relevant in practice.

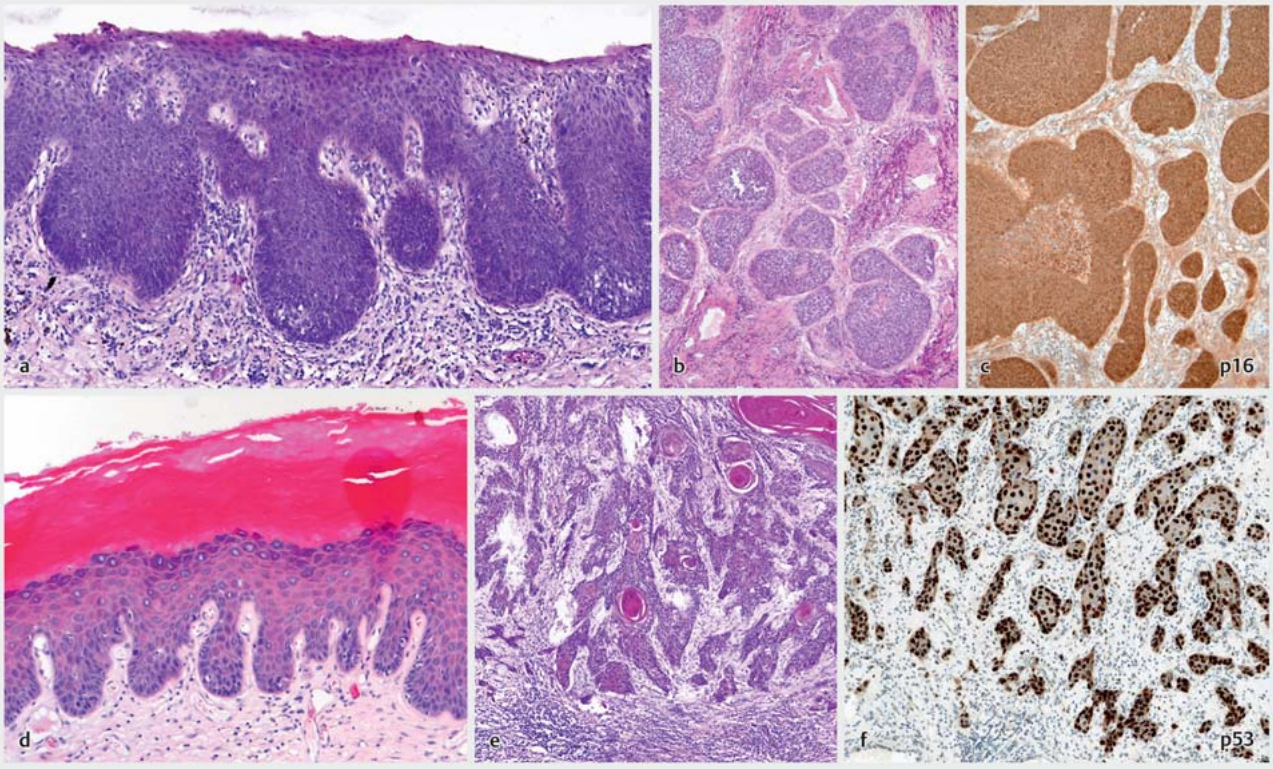
Vulvar Tumors

With reference to **vulvar intraepithelial neoplasias** (VIN), the distinction between HPV-associated and HPV-negative neoplasia has been retained. In terms of nomenclature, HPV-associated VIN corresponds to low (VIN 1) and high-grade SIL (VIN 2 and 3; ▶ **Figs. 1** and **2**).

In cases of VIN where no HPV is detected, the term **HPV-independent VIN** has been introduced [1, 2]; ▶ **Fig. 1** showing a variable morphology:

- The differentiated VIN with its horizontal spread (d-VIN) is a precursor lesion that is allocated to a more aggressive,
- the differentiated exophytic VIN lesion **(DEVIL)** to a less aggressive (keratinizing) squamous cell carcinoma and the
- vulvar acanthosis with altered differentiation **(VAAD)** is allocated to verrucous carcinoma as a precursor/risk lesion [2, 3].

Within this context, it is important to note that different types of lesions may coincide with each other [1, 2, 4]. Due to morphological similarities or overlaps [3], DEVIL and VAAD are also covered by the umbrella term of aberrant maturation of the vulvar squa-



▶ **Fig. 2** Precancerous lesions (VIN) and vulvar carcinoma. **a** HPV-associated VIN (usual VIN; u-VIN), **b** and **c** non-keratinizing, HPV-associated squamous cell carcinoma of the vulva with a plump pattern of invasion and p16 positivity (so-called block staining; see text), **d** HPV-independent VIN (d-VIN), **e** and **f** keratinizing squamous cell carcinoma of the vulva with a netlike pattern of invasion and aberrant p53 expression (see text).

mous epithelium (vulvar aberrant maturation; VAM; [4]) (▶ **Fig. 1**), a term that is not included in the WHO classification.

Despite the fact that this distinction as yet lacks diagnostic and therapeutic relevance [5, 6], the new WHO classification differentiates between HPV-associated and HPV-independent squamous cell carcinoma due to their different pathogenesis (▶ **Figs. 1** and **2**), and the WHO recommends supplying this information in the findings report. The ratio of HPV-independent to HPV-associated squamous cell carcinoma is stated to be between 0.60 and 0.83 [7].

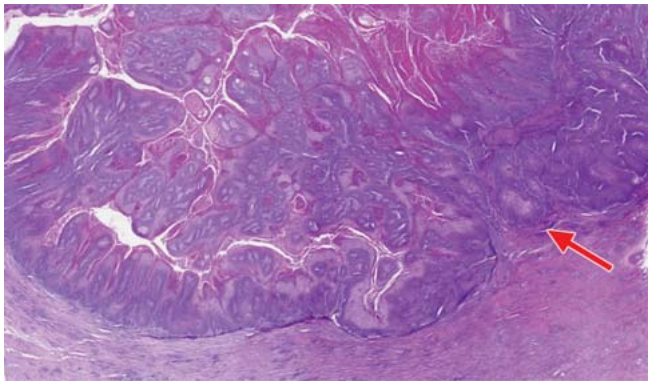
Irrespective of clinicopathological differences (▶ **Table 1**), the HE-morphology does not allow for reliable differentiation between HPV-associated and HPV-independent (p53-associated) squamous cell carcinoma [2, 4], as it has an error rate of 20–30% [8, 9]. The third pathogenetic concept postulated by Nooij et al. [10] (see below; ▶ **Table 1**; [5, 11]) is not included in the new WHO classification as the current data are still insufficient.

Immunohistochemistry showing strong nuclear and cytoplasmic p16 reactivity (so-called block staining; [12]; ▶ **Fig. 2c**) points towards HPV association and is defined as a "reliable (although not perfect)" surrogate marker by the WHO (WHO 2020, [4, 13]). Analysis using p53 immunohistochemistry may help to more accurately diagnose VIN and vulvar squamous cell carcinoma [4] (▶ **Fig. 2f**), as staining patterns have been defined that correlate well with underlying mutations [7, 14].

Should it not be possible to classify the tumor based on p16 immunohistochemistry (and/or molecular HPV detection) or the presence of p53, the WHO deems the description **squamous cell carcinoma NOS** to be "acceptable" (▶ **Fig. 5**). The WHO explicitly points out that molecular analyses (i.e., HPV detection in situ) are not indicated for diagnostic evaluation.

Patients with p16-positive squamous cell carcinoma who have received radio(chemo)therapy show a higher response rate that is statistically significant compared with patients with p53-associated carcinoma [15 – 18].

In these patient groups with very different therapeutic approaches, it has now been acknowledged that p16-positive carcinomas have a better prognosis compared with those that are p53-positive [5, 6, 11, 19]. The study by McAlpine et al. [20] points out that patients with p53-positive tumors benefit from a more radical surgical approach. Initial molecular studies show that vulvar carcinoma with a p53 mutation and an additional PIK3CA comutation have a particularly unfavorable prognosis [7]. There also clearly exists a third pathogenetic group of $p16^-/p53^-$tumors, which ranks prognostically between the p16-positive and the p53-aberrant vulvar carcinoma [5, 11] (▶ **Table 1**). Whether or not the prognostically favorable low-grade squamous cell carcinoma with verrucous morphology represents one morphological end of the $p16^-/p53^-$ tumor spectrum [7] is still unclear.



▶ **Fig. 3** Verrucous carcinoma of the vulva: exophytic verrucous growth of well-differentiated squamous cell epithelium with superficial parakeratosis and a sharp demarcation, with only focal infiltration (arrow), from the subjacent stroma.

The WHO classification does not include **grading** specifications. In the view of the authors, HPV association (i.e., p16 block positivity; [12]) does not (yet) replace the grading process. Should a grading be necessary for documentation or for the DRG system, this can be done based on the extent of keratinization, analogous to the approach used thus far.

It is unclear why **verrucous carcinoma** (▶ **Fig. 3**) is no longer listed in the WHO classification; it is, however, mentioned in more recent reviews [2,4]. Molecular analyses also regard this tumor type separately [7]. Based on verified HRAS and PIK3CA mutations, VAAD is thought to be a precursor lesion of verrucous carcinoma [3].

The WHO classification explicitly mentions the possibility of immunohistochemical HER2 detection for **Morbus Paget**. A meta-analysis of 713 patients demonstrated that HER2 expression was present in 30% of cases, and steroid hormone receptor positivity for ER, PR and AR was present in 13%, 8% and 40% respectively [21]. These may serve as a basis for possible therapeutic targets.

Vaginal Tumors

When it comes to the **vaginal intraepithelial neoplasia** (VaIN; ▶ **Fig. 4a**) and **adenocarcinoma**, there have been no changes.

For squamous cell carcinoma of the vagina, the detection of HPV is currently of no therapeutic relevance [22]. Nevertheless, the WHO recommends making this distinction for these tumor types as well (▶ **Fig. 5**).

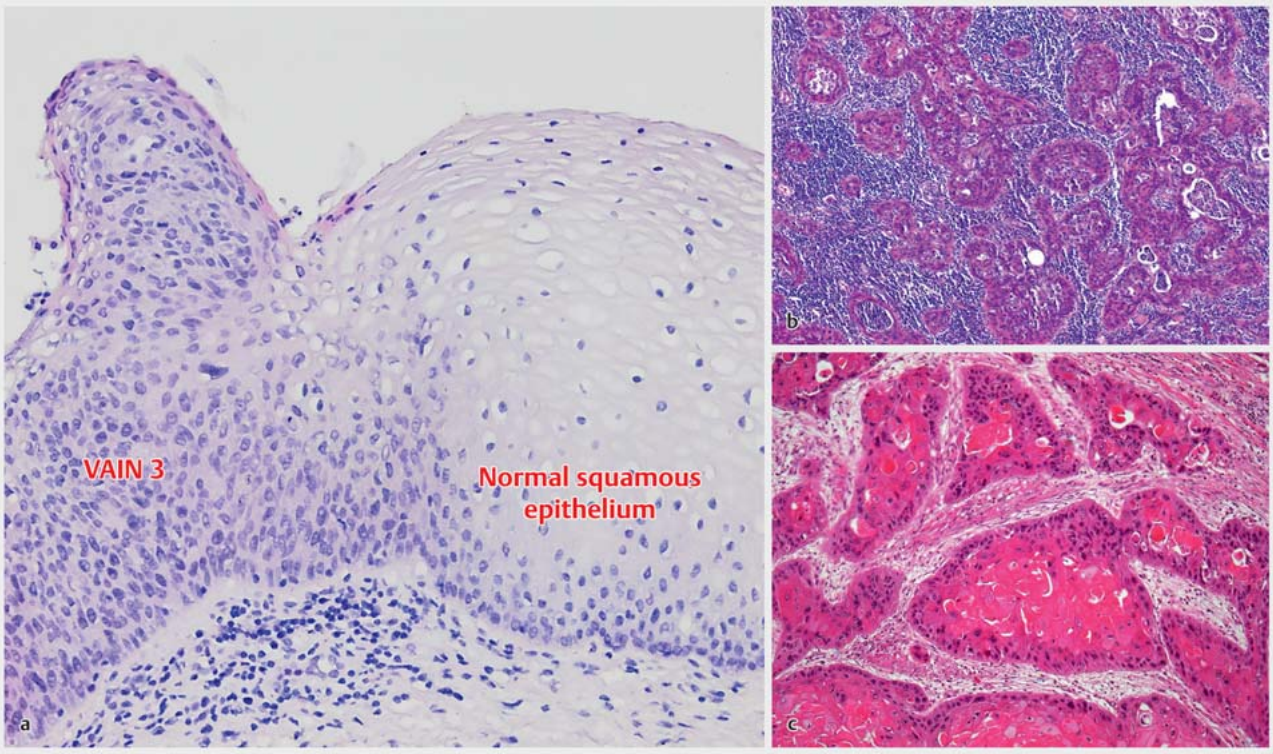
In general, the majority of vaginal squamous cell carcinomas are HPV-associated, especially those with a non-keratinizing morphology (▶ **Fig. 4b**) and tumor location in the upper or intermediate third (so-called Müllerian vagina). Distal squamous cell carcinomas are known as introitus carcinoma and stem from the urogenital sinus (so-called sinus vagina; [23,24]). Lacking HPV association, these are often keratinizing squamous cell carcinomas (▶ **Fig. 4c**).

For vaginal carcinomas too, the WHO points out that molecular analyses (i.e., HPV detection in situ) are not indicated for the diagnostic evaluation.

The WHO classification does not include **grading** specifications. In the view of the authors, HPV association (i.e., p16 block positivity; [12]) does not (yet) replace the grading process. Should a grading be necessary for documentation or for the DRG system,

▶ **Table 1** Pathogenetically based clinicopathological characteristics of vulvar squamous cell carcinoma [2,4–6,10,11,20,42].

	HPV-associated	HPV-independent	Uncertain
	$p16^+/p53^-$	$p16^-/p53^+$	$p16^-/p53^-$
Frequency	40%	50–60%	20%
Age	40–60 years of age	50–70 years of age	60–70 years of age
Precancerous lesion	VIN 2/3 (H-SIL)	HPV-independent VIN (d-VIN,? VAAD,? DEVIL)	? (d-VIN-/VAAD-like?)
Etiopathogenesis	High-risk HPV infection	p53 alteration	? (NOTCH-1/HRAS/ PIK3CA mutation?)
Biomarker expression	p16 positive (block staining)	p53-aberrant staining pattern	p16 negative/p53 wt
Histology (Heller et al. 2020)	Non-keratinizing (ca. 66%)	Keratinizing (80–90%)	Keratinizing/ non-keratinizing
Inguinal lymph node metastases	30%	40%	30%
Radio(chemo)sensitivity	Usually sensitive	Less sensitive	Possibly less sensitive
Prognosis	Better	Poorer	Intermediate
▪ Local recurrence (Nooij et al. 2017) [10]	5.3%	22.6%	16.3%
▪ 2-year DFS (Woelber et al. 2021) [11]	64%	47%	60%
▪ 5-year DSS (Barlow et al. 2020) [5]	89%	75%	83%
▪ Overall survival (Woelber et al. 2021) [11]	82%	70%	75%



▶ **Fig. 4** Precancerous lesions and carcinoma of the vagina. **a** HPV-associated precancerous lesion of the vagina (VAIN 3), **b** keratinizing squamous cell carcinoma of the vagina with slight peritumoral desmoplasia and absence of peritumoral inflammation, **c** non-keratinizing squamous cell carcinoma of the vagina with a high degree of peritumoral inflammation.

2020 WHO classification of squamous cell carcinoma of the female genitals

No immunohistochemistry possible

Squamous cell carcinoma, NOS[2]

- "acceptable diagnosis" (WHO 2020)

Immunohistochemistry (p16, p53) HPV-PCR[1]

HPV-associated squamous cell carcinoma

- Vagina: proximal two thirds (Müllerian vagina)
- Vulva: mostly younger women, associated with H-SIL (VIN 2/3)
- Usually non-keratinizing SCC
- p16 block staining (Darragh et al. 2013) [12]
- Vulva: p53 wild-type staining (Tessier-Cloutier et al. 2020) [14]
- Vulva: better response to radio(chemo)therapy
- Better prognosis

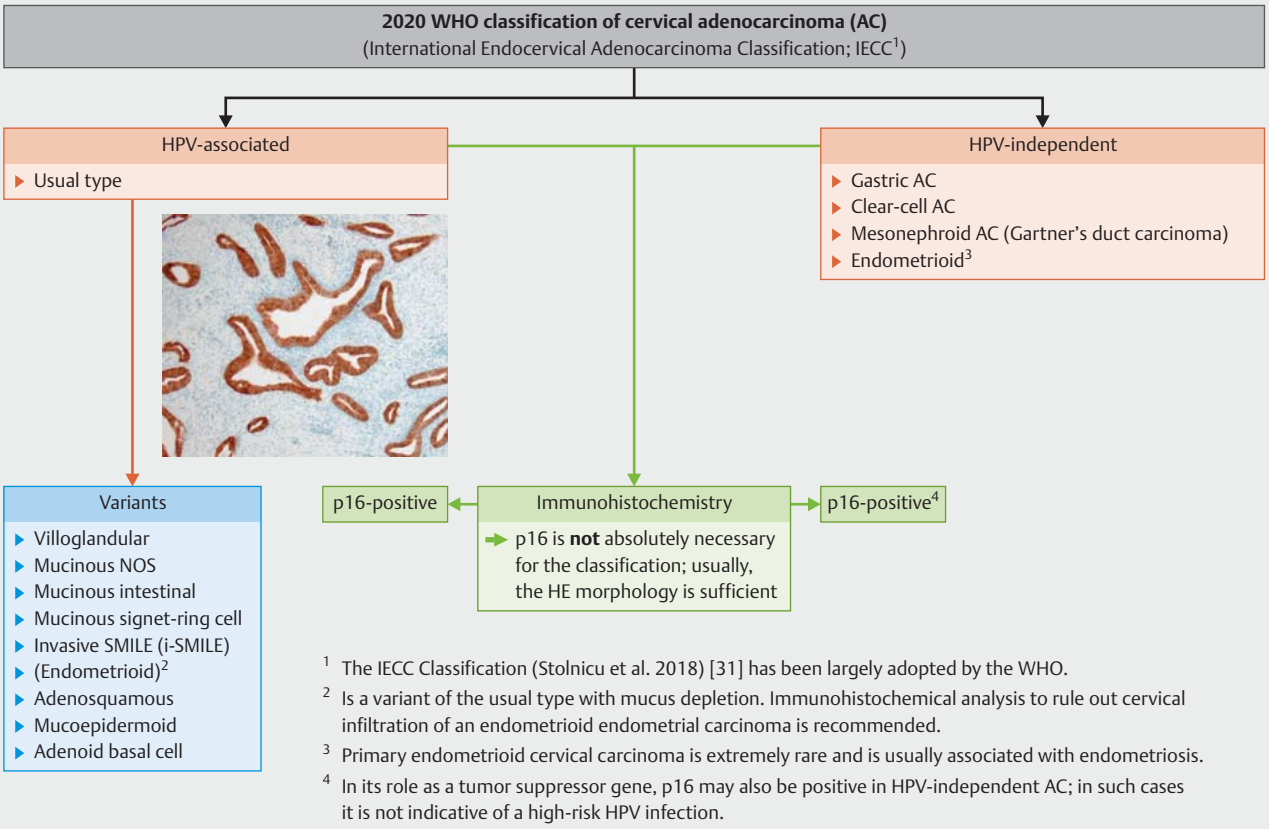
HPV-independent squamous cell carcinoma

- Vagina: distal third (sinus vagina)
- Vulva: mostly older women, associated with d-VIN, DEVIL; VAAD (lichen sclerosus)
- Usually non-keratinizing SCC
- p16-negative (non-block staining)
- Vulva: p53 aberrant staining (Tessier-Cloutier et al. 2020) [14]
- Vulva: less favorable response to radio(chemo)therapy
- Less favorable prognosis

[1] WHO 2020: molecular methods are **not** indicated to differentiate HPV-associated SCC from HPV-independent SCC; however, they may be helpful in uncertain cases

[2] NOS = not otherwise specified

▶ **Fig. 5** Clinicopathological characteristics of the 2020 WHO classification of squamous cell carcinoma of the female genitals [1, 5, 6, 8, 9, 11 – 14, 17, 18, 20, 24, 27, 44].



▶ **Fig. 6** Classification of adenocarcinoma of the cervix uteri in accordance with the 2020 WHO classification [1, 28, 29, 31, 32, 37]. Small image: strong p16 positivity of a usual-type AC.

this can be done based on the extent of keratinization, analogous to the approach used thus far.

Tumors of the Cervix Uteri

For **squamous cell cervical intraepithelial neoplasia** (CIN), there have been no changes.

When it comes to **adenocarcinoma in situ (AIS)**, a distinction is made between various HPV-associated variants and the non-HPV-associated **gastric AIS (g-AIS). SMILE (stratified mucin-producing intraepithelial lesion)** as a subtype of AIS is no longer listed as an independent entity.

Epithelial precancerous lesions and carcinoma of the cervix uteri are predominantly HPV-associated [25].

To ensure a uniform nomenclature, the WHO has classified these squamous cell carcinomas in a manner analogous to the vulvar and vaginal carcinomas (▶ **Fig. 5**).

For the very rare HPV-negative squamous cell carcinoma [26, 27] there is no known precancerous lesion.

Similarly for **squamous cell carcinoma of the cervix uteri**, the HE-morphology alone does not allow differentiation between the two forms; for this reason the WHO recommends performing p16 immunohistochemistry but also accepts the diagnosis of squamous cell carcinoma NOS (▶ **Fig. 5**), as there are no existing therapeutic or prognostic differences. With regard to **grading**, the WHO classification states that there is no established grading system. In the view of the authors, HPV association (i.e., p16 block positivity; [12]) does not (yet) replace the grading process. Should a grading be necessary for documentation or for the DRG system, this can be done based on the extent of keratinization, analogous to the approach used thus far.

For **adenocarcinoma (AC) of the cervix uteri**, a similar distinction is made with regard to the high-risk HPV association. HPV-negative AC has a significantly less favorable prognosis [28–30].

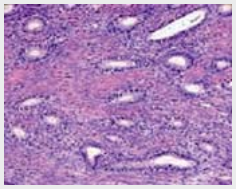
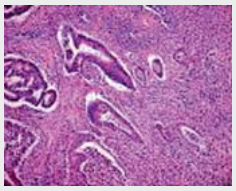
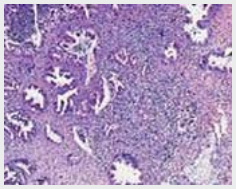
Therefore, the previous diagnostic category of **AC-NOS** no longer exists in the new edition of the WHO classification.

The same applies for (primary) **serous AC of the cervix uteri**, which are almost exclusively endometrial or isthmic endometrial carcinomas with cervical involvement [29, 31].

The WHO classification has adopted the "International Endocervical Adenocarcinoma Classification" (IECC; [28, 29]) (▶ **Fig. 6**), which was also included in the S3-Guideline for cervical carcinoma reviewed in 2021 [32].

An HPV analysis is not necessary for the diagnosis [1]. If "block-type" reactivity is detected [1] (▶ **Fig. 6**), p16 is a reliable surrogate marker for HPV association. In very rare cases, p16 hypermethylation may lead to a (false) negative immunohistochemistry [33], an error that is estimated to occur for CIN 3 in approx. 5% of

▶ **Table 2** Frequency and prognostic relevance of the Silva pattern for HPV-associated adenocarcinoma of the cervix uteri [43].

	Frequency	Pelvic lymph node metastasis	FIGO Stage I	FIGO Stage II–IV	Recurrence rate
Pattern A 	20.7%	0%	100%	0%	0%
Pattern B 	25.6%	4.4%	100%	0%	1.1%
Pattern C 	53.7%	23.8%	83%	17%	23.7%

cases [4, 34]. The choice of a suitable p16 clone is also very important for the reliable detection of p16 [35]. The p16 reactivity in old paraffin blocks or insufficiently fixed tissues is deemed unreliable [31, 36]. It is also important to note that HPV-independent AC (i.e., gastric AC) may also demonstrate p16 positivity [37]. The p16 immunohistochemistry must be interpreted within the context of the HE morphology.

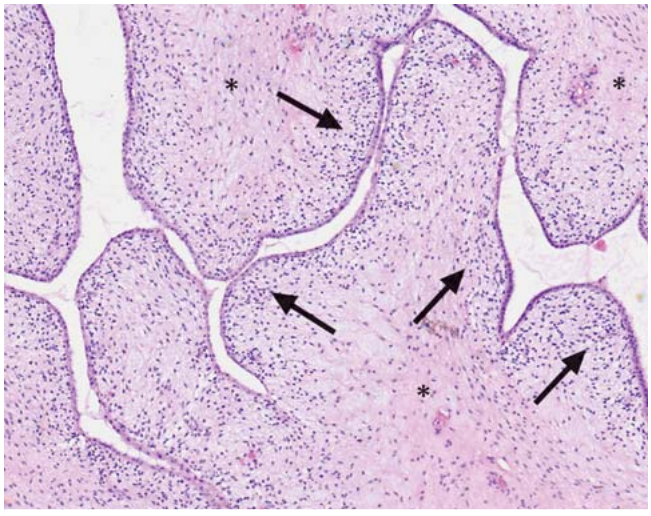
The so-called **Silva pattern**, a prognostically relevant classification of (HPV-associated) AC based on architectural criteria, has been newly adopted into WHO classification (▶ **Table 2**).

It distinguishes between the prognostically more favorable pattern A carcinoma with non-destructive invasion and the pattern B and C carcinoma with destructive invasion. Distinguishing between pattern A-AC and AIS based on HE morphology can be difficult (k = 0.23; [38]).

In almost all cases, **endometrioid AC** of the endocervix represents a mucin-depleted variant of HPV-associated AC. Immunohistochemistry should be used to distinguish between benign lesions and endometrioid endometrial carcinoma with cervical infiltration.

Epithelial-mesenchymal Tumors

Adenofibromas of the cervix uteri that were previously listed in the WHO classification are now considered in fact to be benign endometrial or cervical polyps with an unusual morphology [39, 40], or alternatively adenosarcoma with "low-grade stromal morphology" (▶ **Fig. 7**). Immunohistochemical analyses are helpful for differential diagnosis in these cases [41].



▶ **Fig. 7** Adenosarcoma of the Uterus: foliaceous tumor growth with very cell-poor stroma (*) showing discrete accentuation of the cell density underneath the superficial epithelium (arrows) with a bland cytology.

Conflict of Interest

The authors declare that they have no conflict of interest.

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