Precancerous Lesions of the Cervix, Vulva and Vagina According to the 2014 WHO Classification of Tumors of the Female Genital Tract

Systematik der präinvasiven Läsionen von Zervix, Vulva und Vagina nach der WHO-Klassifikation 2014 „Tumours of the Female Genital Tract“

1 Precancerous lesions (dysplasias) of the cervix

1.1 Historical terminology

Based on studies carried out by Schauenstein, Schottländer and Kermauer in the early decades of the 20th century, the term “carcinoma in situ” (CIS) was introduced into general medical terminology by Broders in 1932 to describe precancerous lesions of the squamous epithelium. This was a revolutionary step, as most of the medical community at the time doubted the existence of a preinvasive stage for invasive carcinoma. The term “dysplasia” goes back to Reagan, who first used it in 1953 to describe all atypical and abnormal differentiations of the squamous epithelium which were less pronounced than those occurring in CIS. In 1963 Koss presented the theory, since disproved, that all cervical dysplasias, irrespective of their degree of severity (i.e., including even mild and moderate dysplasia), could progress to invasion, although the incidence of progression differed. The CIN terminology, which divides the lesions into 3 main groups and is still widely used today, was introduced by Richart in 1968. He used it to describe a continuous progression from mild (CIN 1) to moderate dysplasia (CIN 2) and finally to severe dysplasia or carcinoma in situ (CIN 3). At a workshop held in Bethesda (Maryland) in 1990, Richart transferred the already existing dual nomenclature used in cervical cytology which differentiated low-grade from high-grade lesions into 3 main groups and is still widely used today.

The current WHO classification of precancerous lesions of cervical squamous epithelium is based on new findings on HPV-related carcinogenesis; the key assumption in this context is that two early genes of HPV (E6 and E7) trigger neoplastic transformation of the squamous epithelium. This capacity to induce neoplastic transformation requires a specific expression pattern of E6 and E7, which only occurs in a small percentage of HPV infections. These types are referred to as transforming HPV infections [1]. Transforming infections are usually associated with HPV high-risk genotypes. After constant expression of E6 and E7 oncogenes the oncoproteins encoded by E6 and E7 bind to to cell cycle proteins, leading to loss of cell cycle control. Mutations gradually accumulate and cells become genetically unstable. Morphological findings are moderate or severe dysplasia of the cervical squamous epithelium (CIN 2 or CIN 3), which are summarized in the WHO classification as HSIL. At this stage disruption of the cell cycle led to an accumulation of tumor suppressor gene p16 which...
Preinvasive lesions of rare subtypes of adenocarcinoma of the cervix (e.g., clear cell, serous, endometrioid, mesonephric, gastric-type, and minimal deviation adenocarcinoma) are insufficiently characterized and are therefore not classified separately [3].

1.3 Current joint classification of HPV-associated squamous intraepithelial lesions of the cervix, vulva and vagina, WHO 2014 (Table 1)

As the pathogenesis of HPV-related cancers in the squamous epithelium of the cervix, vulva and vagina is comparable, the current WHO terminology uses the previously mentioned diagnostic categories LSIL and HSIL to classify HPV-associated lesions in all three organs [2, 5, 6]. (Table 1): LSIL therefore includes all lesions (koilocytic changes, flat condyloma, mild dysplasia) resulting from permissive (productive) HPV infection of the squamous epithelium of the cervix, vulva or vagina. Pointed condylomas are classified in the 2014 WHO classification among benign lesions of the squamous epithelium as variants of LSIL. HSIL includes moderate and severe HPV-associated dysplasias of the cervix, vulva and vagina (Table 1).

LSIL of the cervix, vulva and vagina have a high rate of spontaneous remission and only a low risk of progression to invasive carcinoma. HSIL of the cervix, vulva and vagina have a significant risk of progression to invasive carcinoma. The diagnostic categories CIN 1, VIN 1 (usual type) and VAIN I can also be continued to be used synonymously for LSIL, just as CIN 2, CIN 3, VIN 2 (usual type), VIN 3 (usual type), VAIN 2 and VAIN 3 can be used synonymously for HSIL. In clinical practice, adding the individual diagnostic criteria in brackets would be very useful (e.g., HSIL [CIN 2], LSIL [condyloma], etc.), and the authors would recommend doing so because of the differences in clinical course (i.e., different progression and regression rates of CIN 2 and CIN 3).

2 Preinvasive Lesions of the Vulva

2.1 Historical terminology

In 1965 Kaufman and Gardner grouped premalignant changes of the vulva into three groups: erythroplasia of Queyrat, Bowen’s disease and carcinoma simplex, first described by Abell in 1965. Since 1976 the International Society for the Study of Vulvar Disease (ISVVD) uses the terms mild dysplasia (VIN 1), moderate

---

Table 1. Terminology for HPV-associated precancerous lesions of the squamous epithelium of the cervix, vulva and vagina.

<table>
<thead>
<tr>
<th>2014 WHO classification</th>
<th>2003 WHO classification</th>
<th>Synonyms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-grade squamous intraepithelial lesion (LSIL)</td>
<td>CIN 1 V1 (usual type) VAIN 1</td>
<td>mild dysplasia condyloma koilocytic atypia koilocytosis</td>
</tr>
<tr>
<td>High-grade squamous intraepithelial lesion (HSIL)</td>
<td>CIN 2 V2 (usual type) VAIN 2 CIN 3 V3 (usual type)</td>
<td>moderate dysplasia severe dysplasia carcinoma in situ Bowen’s disease Bowenoid dysplasia</td>
</tr>
</tbody>
</table>

---

Table 2. Terminology for HPV-associated glandular intraepithelial lesions of the cervical columnar epithelium.

<table>
<thead>
<tr>
<th>2014 WHO classification</th>
<th>Old terminology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma in situ (AIS) Syn: high grade cervical glandular intraepithelial neoplasia (HG-CGIN)*</td>
<td>endocervical glandular dysplasia (EGD)</td>
</tr>
</tbody>
</table>

* In contrast to squamous epithelial lesions, low-grade lesions of the cervical columnar epithelium are not classified.

---

Table 3. Terminology for HPV-negative squamous intraepithelial lesions of the vulva.

<table>
<thead>
<tr>
<th>2014 WHO classification</th>
<th>Synonyms</th>
</tr>
</thead>
<tbody>
<tr>
<td>differentiated VIN (dVIN) VIN, differentiated type CIS, simplex type</td>
<td></td>
</tr>
</tbody>
</table>
dysplasia (VIN 2) and severe dysplasia (VIN 3). In 2004 the ISVVD introduced a two-part classification system, classifying lesions into HPV-positive usual-type VIN (formerly VIN 2/3) or HPV-negative differentiated VIN (dVIN)/simplex-type carcinoma in situ (CIS) [1].

2.2  Current 2014 WHO classification (Tables 1 and 3)

The WHO currently classifies vulvar lesions into two fundamentally different lesions of the squamous epithelium according to the different pathogenesis of the vulvar cancer (HPV-induced or HPV-negative): SIL and differentiated VIN (dVIN). SIL covers all HPV-associated intraepithelial lesions. In analogy to cervical and vaginal classifications, these vulvar lesions are differentiated into LSIL and HSIL. In contrast, dVIN refers to HPV-negative lesions which generally develop in the context of dermatoses (lichen sclerosus and lichen planus). In contrast to HPV-associated lesions (SIL), dVIN is not graded according to severity. Biologically dVIN corresponds to an in situ carcinoma, independently of histological differentiation. On immunohistochemical examination, dVIN typically does not overexpress p16INK4A. Around half of dVIN show a positive immunohistochemical reaction for p53 antibodies [5].

At colposcopy the changes found with HPV-induced precancerous vulvar lesions largely correspond to those found in the cervix and vagina. The signs of dVIN on colposcopy are still insufficiently described; most commonly they correspond to those reported for leukoplakia or, in rarer cases, erythroplakia [1]. While vulvar LSIL has a high rate of spontaneous remission, vulvar HSIL and dVIN have a significant risk of progression to invasive carcinoma (see also 1.3). Compared to HPV-induced precancerous lesions, dVIN tend to progress faster to invasive carcinoma, in some cases within less than 1 year [1,5].

Genital Paget’s disease is another preinvasive epithelial vulvar lesion. Melanoma in situ is a non-epithelial preinvasive lesion [1,5].

3  Current Classification of Preinvasive Vaginal Lesions, WHO 2014 (Table 1)

Preinvasive lesions of the vaginal squamous epithelium are generally associated with HPV and, as such, are currently differentiated by the WHO into LSIL and HSIL (see also 1.3). At colposcopy vaginal LSIL generally correspond to type 1 changes (minor changes), while HSIL usually present as type 2 changes (major changes). In rare cases, vaginal cancers develop independently of HPV, e.g. subsequent to lichen planus. The mechanism of HPV-independent cancers in the vaginal squamous epithelium is still insufficiently studied but is assumed to correspond to the development in the vulva. However, to date the WHO has not identified diagnostic criteria analogous to dVIN [1,6].

Acknowledgements

The authors would like to thank Dr. V. Küppers and Dr. J. Quaas of the Study Group for Cervical Pathology and Colposcopy of the German Society for Gynecology and Obstetrics for their critical review of the manuscript.

Conflict of Interest

None.

Affiliations

1 Arbeitsgemeinschaft für Kolposkopie in der Österreichischen Gesellschaft für Gynäkologie und Geburtshilfe*
2 Institut für Pathologie und Verein Interessengemeinschaft für Vulvaerkrankungen, ZVR 174112632, Medizinische Universität Graz, Österreich*
3 Arbeitsgemeinschaft Gynäkologische Onkologie der Österreichischen Gesellschaft für Gynäkologie und Geburtshilfe*
4 Arbeitsgemeinschaft Gynäkologische Onkologie der Deutschen Gesellschaft für Gynäkologie und Geburtshilfe, Kommission Zervix**
5 Arbeitsgemeinschaft Gynäkologische Onkologie der Deutschen Gesellschaft für Gynäkologie und Geburtshilfe, Kommission Zervix und Vulva**
6 Arbeitsgemeinschaft Gynäkologische Onkologie der Deutschen Gesellschaft für Gynäkologie und Geburtshilfe, Kommission Vulva und Vagina**
7 Arbeitsgemeinschaft Zervixpathologie und Kolposkopie e. V. in der Deutschen Gesellschaft für Gynäkologie und Geburtshilfe**
8 Arbeitsgemeinschaft Gynäkologische Onkologie der Deutschen Gesellschaft für Gynäkologie und Geburtshilfe, Kommission Uterus**

References