# Penile premalignant lesions: terminology, classification and risk of malignant transformation

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**Abstract**

Over 95% of all malignant tumors of the penis represent squamous cell carcinoma. A significant proportion of these tumors develop on the basis of precancerous lesions, others appear in clinically unchanged mucosa. Early detection and treatment of lesions with a risk of malignant transformation can prevent the development of invasion. In this paper we present the terminology, available classifications and the risk of malignant transformation of precancerous lesions of the penis.

**Key words:** penis, premalignant lesions, penile squamous cell carcinoma.

## Introduction

Squamous cell carcinoma (SCC) represents over 95% of all malignant tumors of the penis [1]. The incidence of SCC of the penis varies in different regions of the world (from 1% to 15% of all male cancers) [2], while in countries with high rates of incidence it is usually diagnosed at an invasive stage [3]. In Poland, the incidence is 0.8/100 000 men [4]. The peak incidence stretches between 50 and 70 years of age. Therefore, age is a risk factor for this cancer. This is indicated by a rise in incidence: before 40 years of age it reaches 19% and before the age of 30 years – 7% [5]. The treatment of invasive forms is based on amputation procedures, which are significantly disabling. Early detection and treatment of precursor lesions for SCC plays an important role in the prevention of SCC as this allows organ function to be preserved [5-7]. Prevention of this cancer is complicated by the fact that only some of the tumours develop on the basis of clinically changed mucosa. Other cases develop in clinically intact mucosa or in connection with subclinical dysplasia [8].

## Transformation of intact epithelium in squamous cell carcinoma

The term "dysplasia" is used to define architectural disorder and atypia of epithelial cells. The criteria used in the assessment of dysplasia are shown in Table 1 [9].

Depending on the severity of dysplasia, atypical cells occupy more superficial layers of the epithelium starting from the basal layer [10]. Low-grade dysplasia (mild/low grade dysplasia) determines the changes involving only the lower third of the epithelium thickness. Moderate dysplasia corresponds to the attachment of 2/3 of the epithelium thickness, whereas a high-degree dysplasia (severe/high-grade dysplasia) can be diagnosed when superficial layers are involved (more than two thirds of the epithelium). Diagnosis of preinvasive cancer (carcinoma in situ) can be made if entire epithelium thickness is involved. Classification of penile intraepithelial neoplasia (PeIN), which is similar to the cervical intraepithelial neoplasia (CIN), includes three categories of changes. Intraepithelial neoplasia of grade 1 (PeIN 1) corresponds to low-grade dysplasia, intraepithelial neoplasia of grade 2 (PeIN 2) corresponds to moderate dysplasia. Intraepithelial neoplasia of grade 3 (PIN 3) includes both high-grade dysplasia and carcinoma *in situ*. The risk of progression to invasive cancer increases with the degree of PeIN. Thus, the risk is the highest in men with PeIN 3 and the lowest in PeIN 1. The concept of "low-grade intraepithelial changes (Low-Grade Squamous Intraepithelial Lesion; L-SIL)" includes PeIN 1. The term "high-degree intraepithelial changes (High-Grade Squamous

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**Table 1.** Criteria used in the assessment of dysplasia

| Architectural features | Cytological features |
|---|---|
| • Irregular epithelial stratification | • Abnormal variation in nuclear size (anisonucleosis) |
| • Loss of polarity of basal cells | • Abnormal variation in nuclear shape (nuclear pleomorphism) |
| • Drop-shaped rete ridges | • Abnormal variation in cell size (anisocytosis) |
| • Increased number of mitotic figures | • Abnormal variation in cell shape (cellular pleomorphism) |
| • Abnormally superficial mitoses | • Increased nuclear-cytoplasmic ratio |
| • Premature keratinization in single cells (dyskeratosis) | • Increased nuclear size |
| • Keratin pearls within rete pegs | • Atypical mitotic figures |
| | • Increased number and size of nucleoli |

Intraepithelial Lesion; H-SIL)" includes PeIN 2 and PeIN 3 (Table 2) [11].

## Classification of precancerous lesions of the penis

Basing on current literature, entities with more or less documented risk of transformation in SCC are described as "premalignant lesions", "pre-existing lesions", "precancerous lesions" or "precursor lesions" [5, 6, 10, 11]. The World Health Organization proposed using the term "precursor lesions" and those changes include PeIN 3, Bowen's disease (BD), erythroplasia of Queyrat (EQ) and extramammary form of Paget's disease (Table 3) [12].

This classification shows pathological variants. It is well known that the clinical picture of PIN3 presents three entities: EQ, BD and bowenoid papulosis (BP). A question arises why EQ and BD were considered as separate and why BP was not included at all.

The International Working Group "2009 International Consultation on Urologic Disease Consensus Publishing Group" [13] proposed using the term "premalignant lesions" to identify changes that have a risk of neoplastic transformation. They classified changes associated with human papilloma virus infection (human papilloma virus – HPV) and changes associated with chronic inflammation (Table 4).

This classification represents clinical and pathological division and, from a practical point of view, is more useful than the pathological classification proposed by the WHO. However, this division also has some drawbacks:
• includes both clinical and pathological terms;
• does not take into account two entities associated with chronic inflammation like lichen planus (LP) and Zoon balanitis (ZB), although in the literature we have found

**Table 2.** Correlation between dysplasia, PeIN and SIL

| Dysplasia | Penile intraepithelial neoplasia (PeIN) | Squamous intraepithelial lesion (SIL) |
|---|---|---|
| Mild | PeIN 1 | L-SIL |
| Moderate | PeIN 2 | H-SIL |
| Severe | PeIN 3 | |
| Carcinoma *in situ* | | |

**Table 3.** Pathological classification of tumors of the penis according to WHO

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|---|
| **I. Malignant epithelial tumors of the penis** |
| Squamous cell carcinoma |
| Basaloid carcinoma |
| Warty (condylomatous) carcinoma |
| Verrucous carcinoma |
| Papillary carcinoma, NOS |
| Sarcomatous carcinoma |
| Mixed carcinomas |
| Adenosquamous carcinoma |
| Merkel cell carcinoma |
| Small cell carcinoma of neuroendocrine type |
| Sebaceous carcinoma |
| Clear cell carcinoma |
| Basal cell carcinoma |
| **II. Precursor lesions** |
| Intraepithelial neoplasia grade III |
| Bowen's disease |
| Erythroplasia of Queyrat |
| Paget's disease |
| **III. Melanocytic tumours** |
| Melanocytic nevi |
| Melanoma |
| **IV. Mesenchymal tumours** |
| **V. Hematopoietic tumours** |
| **VI. Secondary tumours** |

**Table 4.** Division of precancerous lesions of the penis by the International Working Group "2009 International Consultation on Urologic Disease Consensus Group Publishing"

| Lesions related to HPV infection | Lesions related to chronic inflammation |
|---|---|
| Buschke-Lowenstein giant condyloma | Lichen sclerosus |
| Bowenoid papulosis | Penile horn |
| Erythroplasia of Queyrat | Leukoplakia |
| Bowen's disease | Pseudoepitheliomatous, keratotic and micaceous balanitis (PKMB) |

**Table 5.** Division of precancerous lesions of the penis according to EAU

| | |
|---|---|
| **Changes occasionally coexisting with SCC** | Penile horn |
| | Bowenoid papulosis |
| | Lichen sclerosus |
| **Changes in the high risk of SCC (30%)** | Erythroplasia of Queyrat |
| | Bowen's disease |

reports on the development of squamous cell carcinoma (*in situ* or invasive) on their basis [14, 15];
- among entities associated with HPV infection only Buschke-Lowenstein giant condylomata were included, while other clinical manifestations of HPV infection, for example flat genital warts, which can also coexist with dysplasia, were omitted [16];
- leukoplakia is listed among entities associated with chronic inflammation, but there are no data in the literature about its malignant transformation on the penis.

Another classification of penile premalignant lesions appeared in the latest recommendations of the European Association of Urology (Table 5) [1].

The authors classified lesions rarely concomitant with SCC and lesions with a high risk of cancer development. The first group included penile horn, bowenoid papulosis and lichen sclerosus. The second group consisted of erythroplasia of Queyrat and Bowen's disease. It remains unclear why it does not include Buschke-Lowenstein giant condyloma and PKMB.

While discussing the processes leading to cancer progression, the precancerous lesions and precancerous conditions should be separated. The first term applies to specific local pathology, which is characterized by an increased risk of developing cancer. The second term has a broader meaning and identifies the state with an increased risk of cancer development. In the presence of precancerous condition (e.g. ulcer colitis – UC) it is desirable to establish the risk of malignant transformation by assessing the presence of precancerous lesions (e.g. the degree of dysplasia in UC). Considering the unclear separation of precancerous lesions and conditions, the WHO Working Group proposes introducing the term "potentially malignant disorders; PMD" [17]. It should include all types of clinical manifestations (precancers) increasing the risk of cancer. In conclusion, the terminology and the division of lesions of the penis with a risk of malignant transformation require further arrangement.

## The risk of developing of squamous cell carcinoma on the basis of precancerous lesions

Among changes associated with human papilloma virus infection, there are two entities with the highest risk of malignant transformation: Buschke-Lowenstein giant condyloma and erythroplasia of Queyrat. The frequency of SCC development in these units is 30% [18, 19]. More rarely the transformation into invasive SCC is observed on the basis of Bowen's disease and bowenoid papulosis. In those cases, the risk does not exceed 5% [20, 21].

Among entities associated with chronic inflammation, SCC occurs in 100% of patients with PKMB and in 30% of patients with penile horn [22, 23]. A significantly lower risk of developing cancer, which varies from 2% to 5%, was observed in patients with lichen sclerosus [24, 25]. In ZB, LP and leukoplakia, the risk of malignant transformation is unknown. So far, only few cases of the SCC development on the basis of ZB and LP were described [14, 15]. There are no data assessing the percentage of patients with leukoplakia developing SCC.

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