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IP Journal of Diagnostic Pathology and Oncology

Journal homepage: https://www.jdpo.org/

Review Article

Penile and scrotal tumors revisited: Diagnostic and classification updates for pathologists

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Abstract

Penile and scrotal malignancies are uncommon tumors that demonstrate marked geographical variation in incidence. The 2022 fifth edition of the World Health Organization (WHO) classification of urinary and male genital tumors introduces substantial updates to the classification of penile neoplasms, building on the 2016 edition by emphasizing the etiological and histopathological distinctions between human papillomavirus (HPV)-associated and HPV-independent cancers. These updates provide clarity in both diagnosis and potential treatment pathways, especially for squamous cell carcinomas (SCC), which dominate malignancies in these regions. Notably, scrotal cancers are incorporated for the first time in this edition.

Based entirely on the WHO 2022 classification of urinary and male genital tumors and its associated reviews, this article provides a comprehensive overview of the major revisions, highlighting the histopathological refinements, characterization of precursor lesions, updated categories of invasive neoplasms, and their clinical significance in penile and scrotal malignancies.

Keywords: Penile cancers; Scrotal cancers; WHO 2022 classification of urinary and male genital tumors; TNM staging of penile cancers.

Received: 02-05-2025; **Accepted:** 29-05-2025; **Available Online**:

1. Introduction

Penile cancer is a rare malignancy in the developed world, with a prevalence of around 0.1 to 1 per 100,000 men in high-income nations.[1,2] The disease is more common in developing countries with geographical variation in prevalence. The estimated incidence of penile cancer in India is 0.8 per 100,000 men.[3] The most common malignant tumor of the penis is reported to be squamous cell carcinoma (SCC).[4]

Several risk factors for penile cancer have been identified, including lack of circumcision, phimosis, poor genital hygiene, chronic lichen sclerosus and long-standing balanoposthitis.[2,5] Human papillomavirus (HPV) is associated with nearly 40% of cases, while other factors include obesity, smoking, and exposure to psoralen UV-A phototherapy.[5]

2. General Changes in WHO 2022 Classification (5th edition)

In continuation with the approach of the 2016 edition, the new World Health Organization's (WHO) 2022 classification (5th Edition) of urinary and male genital tumors highlights the importance of distinguishing between human papillomavirus (HPV)-associated and HPV-independent squamous cell carcinomas (SCCs), both in invasive cancers and premalignant penile lesions which are designated as penile intraepithelial neoplasia (PeIN). It must be remembered that at present there are no established differences in respect to prognosis or treatment between HPV-associated and HPV-independent penile tumours.[2,4] However, some recent studies suggest that HPV-associated SCC may respond better to chemo-radiotherapy, which may be related to the lack of *TP53* mutation.[6,7]

It is recommended that the SCCs be classified into the HPV-associated and HPV-independent types. Although

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https://doi.org/10.18231/j.jdpo.2025.014

various methods such as PCR, in situ hybridization etc. are available, the block positivity of p16 immunohistochemistry (IHC) is being regarded as a reliable and practical test for the detection of HPV and subclassification of the penile SCCs. In centers where such tests are lacking, a diagnosis of Squamous cell carcinoma- NOS (not otherwise specified) is acceptable.[4] Among the penile neoplastic lesions, HPV-associated PeIN is acknowledged as the precursor lesion to invasive HPV-associated squamous cell carcinoma driven by HPV. HPV-independent differentiated PeIN is the precursor lesion of HPV-independent SCC. While the term 'differentiated' is used in the HPV-independent squamous lesions, the term 'undifferentiated PeIN' is discouraged in the HPV associated lesions.[2,4]

In accordance with all WHO tumor classifications of the 5th edition, the term "subtype" is now used instead of "variant." In contrast to the approach taken in the previous edition, a simplified histological classification of the subtypes of HPV-associated and HPV-independent penile SCCs has been presented.[4] Some of the previously described subtypes have been included as histological patterns under the SCC category, e.g. pseudohyperplastic and pseudoglandular carcinoma are grouped as patterns of usual type SCC, which itself is a subtype of HPV-independent SCC. Similarly, carcinoma cuniculatum is included as a pattern of verrucous carcinoma, which is again a subtype of HPV-independent SCC. Likewise, the various 'variants' of precursor lesions in the previous 2016 edition are termed as 'patterns' in this edition.[4]

Again, there is a mixed subtype in both the HPV associated and HPV independent SCC categories, which includes tumors with mixed histological patterns are present. It is recommended that the relative percentages of the patterns be mentioned in the report, although the prognostic significance of the relative percentages is yet to be determined.[4]

For histological grading of the SCCs, the WHO Classification of Tumors/International Society of Urological Pathology (WHO/ISUP) grading system of Grade 1 (well-differentiated), 2 (moderately differentiated), and 3 (poorly differentiated) may be used. The precursor lesions are however not graded as all are considered high-grade lesions.[4]

A major update is the inclusion of tumors of the scrotum in the new WHO classification scheme. For the first time, scrotal malignancies have been acknowledged in the WHO edition of tumors.

In recent studies[8,9] on scrotal cancers, SCC has emerged as the most frequent type. Other malignancies include extramammary Paget disease, basal cell carcinomas, sarcomas, melanomas, and adnexal skin tumors. Owing to the comparable spectrum of intraepithelial lesions and invasive carcinomas, the updated WHO classification applies uniform terminology to both penile and scrotal cancers in the current edition.[4]

3. Benign and Precursor Lesions of the Penis

One benign lesion and two precursor lesions for squamous cell carcinoma are included in the WHO 5th edition.
The benign lesion is Condyloma acuminatum, and the two precursor lesions are:

1. Penile intraepithelial neoplasia, HPV-associated (HPV-associated PeIN).
2. Differentiated penile intraepithelial neoplasia, HPV independent (Differentiated PeIN).

Condyloma acuminata, also known as genital or anogenital warts, are non-neoplastic tumor-like lesions usually occurring in the penis, scrotum, perineum, and anus. They are caused by HPV, mostly by low-risk genotypes 6 and 11. Histologically, they show acanthosis and papillomatosis with the formation of papillary structures along with surface parakeratosis and hyperkeratosis. Koilocytic atypia, the hallmark of this disease, represents the viral cytopathic effect of HPV and may not be prominent in some cases.[10]

The salient features and common patterns of the precursor lesions are enumerated in **Table 1**. [4]

HPV-associated PeIN is a premalignant lesion of penile squamous cell carcinoma, which is usually caused by the high-risk HPV 16/18 and is characterized by dysplastic squamous epithelium with an intact basement membrane.[1]

The terms like penile carcinoma in situ, Bowen disease, and erythroplasia of Queyrat, previously used to denote the premalignant/precursor lesions, are not recommended. However, the squamous intraepithelial lesion, in line with the cervical intraepithelial lesions, remains an acceptable term.[10]

HPV-associated PeIN appears as flat to slightly elevated macules/ papules/ plaques, with a moist, velvety, erythematous appearance on the glans, foreskin or the shaft of the penis. It may be pigmented and occasionally multifocal.[11]

The basaloid subtype (the term undifferentiated is less favored) is more common than the warty subtype (condylomatous/bowenoid). The basaloid PeIN is characterized by a monomorphic population of basaloid cells (small immature cells with high N:C ratio) showing high mitotic count and prominent apoptosis. On the other hand, the warty subtype shows spiky appearance with squamous maturation, atypical parakeratosis, pleomorphism and koilocytosis, and numerous mitotic counts.[2,10,12] The mixed subtype shows combined features of basaloid PeIN at the base and more differentiated cells with koilocytic changes (warty) at the surface.[10] Immunohistochemistry shows block positivity for p16.

The association of these high-risk HPV- driven lesions with penile SCC is significant. However, the actual prognosis remains unknown due to a lack of substantial data.

Differentiated PeIN, which is HPV-independent, tends to develop in slightly older men in a background of chronic lichen sclerosus (LS) or other causes of chronic inflammation/irritation/injury like phimosis, long-standing balanoposthitis etc. It is more common in countries with a high incidence of penile cancer and is often diagnosed along with invasive SCC.[2,13]

It preferentially affects the inner surface of the foreskin and may be solitary or multiple, appearing usually white or pink and plaque-like.[13]

A high prevalence of TP53 mutations is being reported in differentiated PeIN and HPV-independent penile SCC. [13]

Histologically, the differentiated PeIN is characterized by dysplastic squamous epithelium (with atypical hyperchromatic cells) primarily limited to the basal and parabasal cells within an otherwise well-differentiated epithelium with an intact basement membrane and surface maturation.

Hyperkeratosis, parakeratosis, spongiosis, dyskeratotic cells with prominent intercellular bridges, elongated and intercommunicating rete ridges, and even squamous pearls may be seen.[13] Histologic subtypes of differentiated PeIN are hyperplasia-like, classic and pleomorphic.[13,14] The clues for diagnosis include the transition of normal to hyperplastic squamous epithelium with nuclear changes confined to the basal and parabasal cells, lack of koilocytic atypia, and presence of lichen sclerosus in the background in some cases. The differentials, like hyperplastic squamous epithelium / pseudoepitheliomatous hyperplasia, can be excluded with a combined IHC panel of p53 and Ki67.

Ki-67 immunostaining in squamous hyperplasia is usually confined to sparse basal cells, whereas in differentiated PeIN, it often demonstrates a continuous pattern in atypical cells of the basal and occasionally suprabasal layers.[2,13-16]

Likewise, p53 expression in squamous hyperplasia is either absent or limited to scattered cells, whereas differentiated PeIN demonstrates variable p53 staining, ranging from negative to patchy basal or suprabasal positivity.[13]

Pleomorphic differentiated PeIN can be differentiated from HPV-associated PeIN by the lack of block positivity for p16.[13]

4. Invasive Penile Cancers

The WHO 2022 classification, as highlighted in **Table 2**,[4] is primarily based on the association with HPV. It is important to note that hematolymphoid, melanocytic, mesenchymal, and metastatic tumors—which can also affect other genital or urological organs—have been excluded from the classification of penile/scrotal tumors, and are now included under the broader classification of urinary and male genital tumors as subcategories.[4,15]

4.1. HPV-associated squamous cell carcinoma

HPV-associated squamous cell carcinomas (SCC) are invasive keratinizing carcinomas that usually present as large exophytic growths arising from the HPV-associated penile intraepithelial neoplasia of the penile mucosal or cutaneous compartments.[2]

High-risk HPVs are associated with about 33% of all penile cancer cases, with HPV 16 being the most common genotype, the others being HPV strains 18, 31, 33, 45, 51, 52, 53, and 58.[17]

They have a variety of pathological subtypes like basaloid carcinoma, warty carcinoma, clear cell carcinoma, lymphoepithelioma-like carcinoma (that also includes cases that are described as medullary carcinoma) and mixed (that includes warty-basaloid or other admixed subtypes).[2]

The common locations and salient features of these subtypes are highlighted in **Table 3**:[18-23] Warty carcinomas are usually associated with positivity for multiple HPV genotypes.[23,24] The association of HPV with the precursor lesions and invasive cancers highlight the possible benefits of HPV vaccination in males.[24]

4.2. HPV-independent squamous cell carcinoma

As per WHO 2022, HPV-independent squamous cell carcinoma (SCC) is defined as an invasive keratinizing carcinoma arising from penile mucosal or cutaneous compartments that is not associated with HPV infection. They encompass a variety of pathological subtypes viz usual type of SCC (including pseudohyperplastic patterns and pseudoglandular/acantholytic patterns), verrucous SCC (including carcinoma cuniculatum as a pattern), papillary SCC, sarcomatoid SCC and mixed.[25]

They develop in a setting of differentiated PeIN, induced by markers of chronic inflammation related to phimosis, poor hygiene, and lichen sclerosus.[2,16,25,26,27] Early circumcision has a protective role as a strong association has been found between the development of differentiated PeIN or penile SCC and the presence of a foreskin.[28] The localization, histomorphology, prognosis and other salient features of these various subtypes are highlighted in **Table 4**.[2,25,29-46]

Table 1: Precursor lesions of penis (based on WHO 2022 classification)[4]

Penile intraepithelial neoplasia, HPV-associated ***Common patterns:*** Basaloid (undifferentiated) Warty (condylomatous, bowenoid) Mixed PeIN (warty/basaloid) ***Less frequent patterns:*** Pagetoid and Clear cell	Accounts for 80% of all PeIN lesions Precursor or premalignant lesion of squamous cell carcinoma of penis **Not recommended terms:** penile carcinoma in situ, Bowen disease, erythroplasia of Queyrat Caused by high-risk HPV types Immunohistochemistry shows block p16 positivity
Differentiated penile intraepithelial neoplasia, HPV-independent ***Patterns:*** Hyperplasia-like Classic Pleomorphic	HPV-independent precursor or premalignant lesion of penile squamous cell carcinoma (SCC) Dysplastic changes are mostly confined to the basal and parabasal layers of the squamous epithelium. Remaining epithelium remains well-differentiated with preservation of the basement membrane Tends to develop in slightly older men in a background of chronic lichen sclerosus More common in countries where the incidence of penile cancer is high

Table 2: Invasive penile cancers (based on WHO 2022 classification)[4]

Types	**Subtypes**
HPV-associated squamous cell carcinoma	Basaloid squamous cell carcinoma Warty carcinoma Clear cell squamous cell carcinoma Lymphoepithelioma-like carcinoma [Poorly differentiated to undifferentiated carcinoma with prominent lymphoid stroma (including medullary carcinoma)] Mixed (to include warty-basaloid or other admixed subtypes)
HPV-independent squamous cell carcinoma	Squamous cell carcinoma, usual type (including pseudohyperplastic patterns and pseudoglandular patterns) Verrucous carcinoma (including carcinoma cuniculatum) Papillary squamous cell carcinoma Sarcomatoid squamous cell carcinoma Mixed
Squamous cell carcinoma NOS (invasive keratinizing carcinoma without special features, for which evaluation of p16 is not available)	
Adenosquamous carcinoma	
Mucoepidermoid carcinoma	

Table 3: Sites of occurrence and salient features of the various subtypes of HPV-associated squamous cell carcinoma of penis.[18-23]

Subtype	**Location**	**Morphology**	**Prognosis**
Basaloid SCC (undifferentiated)	Typically occur in the glans penis and foreskin, variably involving the coronal sulcus	Architecture: Nests, sheets, and islands of basaloid-appearing carcinoma. Cytology: Cells with scant cytoplasm. Vascular and perineural invasion are frequent findings Comedo-type necrosis or central abrupt keratinization. Brisk mitotic activity IHC: Strong block positivity for p16 (a surrogate marker for HPV)	Aggressive

Warty carcinoma (condylomatous, bowenoid)	Single or multiple anatomical sites e.g glans penis, coronal sulcus, and foreskin	**A**rchitecture: Papillary or warty exophytic surface with a deeply infiltrative front. Cytology: Atypical cells with koilocytotic atypia. Mixed warty and basaloid features can be seen. IHC: Strong p16 positivity, suggestive of HPV association.	Intermediate
Clear cell SCC	Manifests as a large tumor affecting the foreskin, coronal sulcus, or glans	Cytology: Large clear cells. Stains: PAS-positive, diastase-resistant cytoplasmic material. Necrosis: Comedo or geographic necrosis is often present. Extensive lymphatic and vascular invasion noted.	Aggressive
Lymphoepithelioma-like carcinoma	Predominantly located in the glans penis, although all compartments are involved	Pattern: Syncytial sheets of undifferentiated to poorly differentiated cells. Inflammation: Dense infiltrate of lymphocytes and plasma cells or eosinophils may obscure tumor cells.	Rare subtype. Prognosis depends on pathological stage, vascular, lymphatic, and perineural invasion; and inguinal lymph node metastasis
Medullary Carcinoma (included under Lymphoepithelioma-like carcinoma)		Architecture: Solid sheets, nests, or trabecular patterns of poorly differentiated/ anaplastic tumor cells. Inflammation: Prominent tumor-associated infiltrate of neutrophils, lymphocytes, plasma cells, and eosinophils. Frequent mitotic figures. Common tumor necrosis.	Rare subtype

Table 4: Sites of occurrence and salient features of the various subtypes of HPV-independent squamous cell carcinoma of penis.[2,25,29-46]

Subtype	**SCC, Usual Type (including pseudohyperplastic and pseudoglandular patterns)**	**Verrucous Carcinoma (including Carcinoma Cuniculatum)**	**Papillary SCC**	**Sarcomatoid SCC**
Localization	Glans (most common-48%); pseudohyperplastic – foreskin; pseudoglandular – glans, coronal sulcus, foreskin	Glans, coronal sulcus, foreskin	Glans ± other compartments	Glans ± coronal sulcus and foreskin
Average Age	~58 years (pseudoglandular ~50 years)	77 years (Carcinoma Cuniculatum)	63 years (range: 43–85 years)	59 years (Range: 28–81 years)
Epidemiology	Most common subtype (45–65% of penile SCCs)	3–7% of penile SCCs; 12–38% of verruciform tumors	5–15% of penile carcinomas; 27–53% of verruciform tumors	1–4% of penile carcinomas
Clinical Course	May present with high-grade lesion and deep invasion; early nodal metastasis in pseudoglandular type	Longstanding, slow-growing exophytic wart-like lesion	Exophytic, slow-growing, verruciform mass	Slow growth followed by rapid enlargement and ulceration
Gross Appearance	Erythematous, nodular, or ulcerated lesions; pseudoglandular – large, deeply invasive, irregular masses	Cobblestone/spiky, papillomatous surface; well demarcated; cuniculatum – sinus tract formation	Large, cauliflower-like, granular white-grey tumor with verruciform growth	Large, fungating or polypoid tumor with surface ulceration and haemorrhage

Histopathology	Invasive keratinizing SCC; patterns include pseudoglandular, pseudohyperplastic, multicentric etc.; pseudoglandular mimics adenoid cystic carcinoma	Very well differentiated SCC; broad pushing margins; central keratin plugs; cuniculatum – deep keratin-filled sinuses	Complex, jagged papillary structures featuring variable fibrovascular cores and keratin accumulations between adjacent papillae	Predominantly spindle cells; resembles sarcomas; may include rhabdoid or pleomorphic cells; requires IHC for diagnosis
Prognosis	Prognosis depends on grade and stage; pseudoglandular pattern has higher risk of deep invasion and nodal metastasis	Excellent prognosis; no metastases reported even with deep invasion	Good prognosis	Poor prognosis and aggressive behavior; frequent nodal as well as systemic metastasis and death within 1 year of diagnosis

Table 5: Prognostic stage groups in penile cancers as per AJCC 8th edition[56]

T Category	N Category	M Category	Stage Group
Tis	N0	M0	0is
Ta	N0	M0	0a
T1a	N0	M0	I
T1b	N0	M0	IIA
T2	N0	M0	IIA
T3	N0	M0	IIB
T1–T3	N1	M0	IIIA
T1–T3	N2	M0	IIIB
T4	Any N	M0	IV
Any T	N3	M0	IV
Any T	Any N	M1	IV

4.3. Squamous cell carcinoma NOS (SCC-NOS)

Squamous cell carcinoma NOS (SCC-NOS) is an invasive keratinizing carcinoma that lacks any distinctive histological features to classify it into a specific subtype, and is an acceptable alternative diagnosis where p16 immunohistochemistry and HPV testing are not available. Most of these tumors arise from the mucosal squamous epithelium lining the distal penis, particularly the glans and coronal sulcus,[47] and morphologically resemble conventional invasive keratinizing squamous cell carcinomas that are seen at other anatomical sites.

4.4. Adenosquamous and mucoepidermoid carcinomas of the penis

Adenosquamous and mucoepidermoid carcinomas of the penis represent forms of invasive SCC distinguished by areas of glandular or mucinous differentiation embedded within a predominantly squamous neoplasm, usually occurring in patients in the sixth decade.[48] While ASC typically exhibits both squamous and gland-forming components, MEC are solid tumors featuring mucin-producing cells without true gland formation.

However, both entities are placed under the rubric of ASC,[48,49,50] and the WHO essential criterion for diagnosis is SCC with gland formation and/or mucin-producing cells showing positivity for CK7, CEA, and mucin stains, while lacking p16 expression.[48]

Lymph node involvement has been reported in approximately 50% of patients with penile adenosquamous or mucoepidermoid carcinoma at the time of diagnosis, indicating a high potential for regional metastasis, despite the overall rarity of these tumours.[50]

4.5. Extramammary paget disease

Extramammary Paget disease (EMPD) is a rare intraepidermal adenocarcinoma which may affect the penis and/or scrotum. It may arise primarily within the skin (known as primary Paget disease) or occur secondarily due to intraepidermal spread from an underlying genitourinary or gastrointestinal tract malignancy (known as secondary Paget disease).[2]

Paget cells are large, round to oval cells with pale cytoplasm and atypical nuclei, present singly or in small clusters within the epidermis[51,52] and are positive for CK 7, CEA and EMA. Other IHC markers like GCDFP-15, HER2,

CK20, CDX2, PSA, or GATA3 may be used depending on the suspected primary site.

5. Grading and TNM Staging of Penile Cancers

Tumour differentiation (grading) and histological subtypes remain important prognostic parameters.

As mentioned earlier, for histological grading of the SCCs, the WHO/ISUP grading system of Grade 1 (well-differentiated), 2 (moderately differentiated), and 3 (poorly differentiated) may be used, which is based on the degree of pleomorphism, differentiation and keratinization of the tumor cells.[4]

Subtypes like warty SCC, verrucous carcinoma, including carcinoma cuniculatum, papillary SCC, etc, have a good prognosis as compared to basaloid SCC, sarcomatoid SCC, clear cell SCC and poorly differentiated SCC, which are aggressive tumours.

Due to the strong association between high-risk human papillomavirus (HPV) infection and certain histological subtypes of penile squamous cell carcinoma, particularly basaloid and warty variants, the prognostic impact of HPV status remains a topic of active investigation. While HPV-associated tumors may exhibit distinct molecular profiles and immune responses, current evidence on their influence on treatment response and overall survival is limited.

The TNM staging system—based on the primary tumor (T), regional lymph nodes (N), and distant metastasis (M)—is generally regarded as the most critical prognostic indicator across tumor types, and penile tumors are no exception to this principle.[53]

The last two editions of the AJCC cancer staging manuals (7th and 8th) have undergone some major changes in penile cancer staging.

Significant emphasis is placed on the factors such as lymphovascular invasion (LVI), perineural invasion (PNI), and extranodal extension (ENE), along with lymph node involvement, distant metastasis, and the extent of the primary tumor.

It is worth noting that the liver, lungs, and retroperitoneal nodes are among the most common sites of distant metastasis.[53,54,55]

The pathological TNM (pTNM) staging of penile cancers based on AJCC 8th edition is as follows:[53,56]

T -Primary Tumour

pTX: Primary tumour cannot be assessed
pT0: No evidence of primary tumour
pTis: Carcinoma in situ (Penile intraepithelial neoplasia)
pTa: Non-invasive localised squamous cell carcinoma (including verrucous carcinoma)
pT1: Tumour invades subepithelial connective tissue (*)

1. pT1a Tumour invades subepithelial connective tissue without lymphovascular invasion (LVI) or perineural invasion (PNI) and is not poorly differentiated (grade 3 or sarcomatoid)
2. pT1b Tumour invades subepithelial connective tissue with lymphovascular invasion (LVI) or perineural invasion (PNI) or is poorly differentiated (grade 3 or sarcomatoid)

pT2: Tumour invades corpus spongiosum (either glans or ventral shaft) ± invasion of the urethra
pT3: Tumour invades corpus cavernosum (including tunica albuginea) ± invasion of the urethra
pT4: Tumour invades other adjacent structures (i.e., scrotum, prostate, pubic bone)

Notes (*)

1. Glans: Tumour invading lamina propria
2. Foreskin: Tumour invading dermis, lamina propria *or* dartos fascia
3. Shaft: Tumour invading connective tissue between epidermis and corpora and regardless of location

N –Regional Lymph Nodes
pNX: Regional lymph nodes cannot be assessed
pN0: No regional lymph node metastasis
pN1: Metastasis in ≤ 2 unilateral inguinal lymph nodes; no extranodal extension (ENE)
pN2: Metastasis in ≥ 3 unilateral inguinal nodes or bilateral inguinal lymph nodes; no ENE
pN: Metastasis in pelvic lymph node(s) (unilateral or bilateral) *or* ENE of regional lymph node metastasis

M -Distant metastasis
M0: No distant metastasis
M1: Distant metastasis present

The AJCC prognostic stage groups for penile cancers based on the individual TNM staging are highlighted in **Table 5**.[56]

It may be noted that Stage 0 includes non-invasive lesions, such as carcinoma in situ (Tis) and non-invasive verrucous carcinoma (Ta). Stage I represents low-risk early invasive tumors, typically corresponding to T1a N0 M0, which lack lymphovascular/perineural invasion and are of low histological grade. Stage IIA indicates higher-risk local invasion, encompassing tumors such as T1b (high grade or with lymphovascular/perineural invasion) and T2 (invading corpus spongiosum), with no regional lymph node involvement (N0) or distant metastasis (M0). Stage IIB reflects deeper local invasion, involving tumors with invasion of the corpus cavernosum with/without involvement of urethra (T3), again without nodal or distant spread. Stage IIIA and IIIB are defined by regional lymph node involvement. Stage IIIA includes T1–T3 tumors with a single unilateral inguinal lymph node metastasis (N1), while Stage IIIB includes T1–T3 tumors with multiple or bilateral inguinal

lymph node metastases (N2). Finally, Stage IV encompasses locally advanced or systemic disease, including tumors invading adjacent structures (T4), those with pelvic lymph node involvement (N3), or those showing distant metastases (M1).

6. Cancers of Scrotum

Scrotal tumors possess a distinctive historical and histopathological context, notably being the first recognized occupational cancer, historically described in chimney sweepers. Sir Percival Pott, an English surgeon in the 18th century, was the first to describe an association between soot exposure in chimney sweepers and scrotal cancer, marking one of the earliest documented links between occupational exposure and cancer.

The 2022 edition of the WHO tumor classification marks the inclusion of scrotal malignancies for the first time.

The classification underscores that precursor squamous lesions and invasive squamous cell carcinoma (SCC) of the scrotum—being the most common primary malignancies at this site—should be classified in line with penile SCC, using similar terminologies.

As mentioned previously, other tumors like extramammary Paget disease can involve the scrotum just like the penis.

The 5th edition also includes a dedicated chapter on basal cell carcinoma of the scrotum (BCC-S). These are rare tumors of unknown etiology, arising from the basal cells of the interfollicular epidermis and/or hair follicle and exhibiting morphological features akin to basal cell carcinoma (BCC) at other cutaneous sites.[57] The tumor may sometimes exhibit an aggressive clinical course, warranting extended clinical surveillance for metastasis for 2–5 years after excision of the tumour.[58]

It is essential to differentiate BCC from basaloid SCC, as the latter displays more aggressive histological features, including frequent mitoses and comedonecrosis.[59]

7. Conclusion

Penile and scrotal cancers, while uncommon, often result in severe anatomical disfigurement and can cause deep emotional and psychological trauma in affected individuals.

The association of both intraepithelial lesions and invasive cancers with high-risk HPV is strong, and the 2022 WHO classification followed the paradigm of the 2016 WHO classification to subclassify penile tumors into HPV-associated and HPV-independent types. This is also consistent with the approach used in the classification of the tumors of female genital tract.

The AJCC 8th edition staging system for staging refines the system adopted in the 7th edition. Pathological staging—based on the anatomical extent of the primary tumor, regional lymph node involvement, and distant metastasis—along with tumor grade, histological subtype, and additional features such as lymphovascular invasion (LVI), perineural invasion (PNI), and extranodal extension (ENE), remains integral to prognostication. However, the prognostic significance of HPV status warrants further investigation

This edition of the WHO classification introduces scrotal cancers, highlighting the growing need for awareness and clinical focus for these rare tumors. The precursor lesions and the invasive SCC of the scrotum follow the same terminology as their penile counterparts and are similarly classified based on HPV infection.

8. Source of Funding

None.

9. Conflict of Interest

None.

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Cite this article: Chakrabarti I, Mazumder S. Penile and scrotal tumors revisited: Diagnostic and classification updates for pathologists. *IP J Diagn Pathol Oncol*. 2025;10(2):56-65.